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Table of Contents

A Field Trial on the Efficacy and Safety of Powdered Ipil-ipil (Leucaena leucophala) Seeds as a Mass Deworming Agent in the Treatment of Intestinal Helminths (Ascaris lumbricoides, Trichuris trichiura) among School Children in Bagong Nayon, Antipolo City

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Introduction

INTESTINAL PARASITISM IS A common and widespread problem among children in the Philippines. The most common types are Ascariasis and Trichuriasis, the prevalence rates of which could be as high as 70-90%[1,2]. Uncontrolled parasitism compounds the malnutrition problem already prevalent in poorer communities. Because of the need to treat the affected children, mass deworming programs have been frequently carried out in poor communities. The magnitude of the problem, the prohibitive cost of using branded deworming agents and the increasing awareness of the value of indigenous medical plants have prompted the need to explore and provide scientific rationale for the use of these medicinal plants as sound and efficient alternative deworming agent. The DOH's Traditional Medicine has promoted the use of medicinal plants scientifically proven to be effective[3]. It has also encouraged the conduct of scientific investigations that could vouch the effects of these medicinal plants.

Leucaena leucophala (Ipil-ipil) seed has been endorsed for its antihelminthic property[4,5]. Since the 1980's basic toxicologic and pharmacologic studies were conducted by Estrada and Kintanar[6]. Clinical trials conducted by Maramba[7], Fuentes[8] and Rodriguez[9] generated varied degrees of effectiveness. Efficiency rates against Ascaris lumbricoides obtained from these studies ranged from 29.6%[7] to as high as 82%[8] and between 4% to 28% for Trichuris trichiura[7].

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This study was conducted to determine the efficacy and safety of powdered Ipil-ipil seeds as a mass deworming agent in the treatment of Ascariasis and Trichuriasis by measuring and comparing changes in the prevalence rates and mean ova counts in the study populations. This study further tested the hypothesis related to differences in the incidence of adverse effects of this herbal preparation between the intervention and control populations.

Materials and Methods

Study Design and Study population

This study is a field trial of the quasi-experimental design. Bagong Nayon II in Antipolo City, Philippines, was purposely chosen as the accessible study population. It is a homogenous community of low income families and has a high prevalence of intestinal parasitism.

The two public schools serving this community were preselected as the intervention and control populations. Three sections from each grade level were chosen at random and all students from these sections were eligible to participate. Two hundred thirty seven (237) students from the intervention and 440 from the control schools were given parental consent to join the study. Different cross sections of these consenting population served as the actual subjects at baseline (149 and 201) and after delivery of the intervention (183 and 186) for both the intervention and control populations respectively. Based on the sample size

computations, the minimum number of subject required per group is 200, thus response rates of 72% and 92% for the intervention and control groups respectively were posted at baseline. Post-intervention response rates were 100% and 93% for the intervention and control populations respectively.

Data Collection

Baseline demographic data and a short history as to the occurrence of hiccups, abdominal pain, and diarrhea were obtained from the actual population by trained interviewers. Diarrhea was defined operationally as the passing out of watery/soft, formed or unformed stools at least once prior to the interview. Operational definitions of some other important variables are included in the Appendix.

Baseline stool specimens were likewise collected from the same subjects and examined for the presence and counts of Ascaris and Trichuris ova. These same procedures were repeated within 3 days to one week after delivery of the intervention. All stool specimens submitted by the sample population were prepared and examined using the Kato-Katz technique by only one trained medical technologist. This technologist was not cognizant of the status of the stools he was examining. The number of Ascaris and Trichuris ova for every gram of stool specimen were noted and recorded.

The intervention consisted of the administration of single dose powdered Ipil-ipil seeds in capsule form (dose of 600 mg for 6-9 years and 1200 mg for 10 years and older) for subjects in the intervention group. On the other hand, health education regarding the prevention and control of intestinal parasitism was conducted for the control group. Both the parents and the students were invited to attend a two to three hour interactive session with the research team. Because of the need to treat infected subjects, the control group were likewise given the Ipil-ipil preparation as a mass deworming agent two to three weeks after collecting the post-education stool specimen. A third stool specimen was collected from a cross section of the control population and examined within 3 days to 1 week after the administration of Ipil-ipil capsules (results and analysis are presented in another paper).

Analysis

The prevalence rates of Ascariasis and Trichuriasis, mean ova counts and incidence of adverse effects were determined at baseline and after delivery of intervention for both study groups. Percentage change (defined as baseline minus post intervention rate or mean values divided by baseline value) of these outcome measures were composed within groups and between the intervention and control populations. T-tests were used to determine the statistical significance of the changes in mean ova counts within groups and also between the study groups. The net difference (baseline minus post intervention percentage change) in prevalence rates, and the absolute difference in the incidence rate of adverse rate of adverse effects between the study groups were also subjected to Chi square test.

Baseline ova counts of the study groups were stratified according to degrees of infestation. The proportion of subjects in each category were determined. This stratification is based on the following: Very light Ascaris infestation refers to those having ova counts from 1 to 9,999; light infestation for ova counts from 10,000 to 49,000; moderate for counts between 50,000 to 99,999; and heavy for counts of 100,000 or more (10).

Results

The actual sample population consisted of seven hundred nineteen elementary school children, 332 of whom came from the intervention population and 387 from the control population. The characteristics of the subjects are shown in Table 1.

Table 1. Selected Characteristics of the Sample Population

Characteristics	Intervention (N=149)	Control (N=183)
Age in Years (Mean)	9.43 (SD = 1.76)	9.03 (SD = 1.96)
Gender		
Male	47.9%	43.9%
Female	52.1%	56.1%
Baseline Measures		
PR Ascariasis	28.2%	27.4%
PR Trichuriasis	51.04%	56.2%
Mean Ascariasis Ova Ct	2.707 (SD=11.568)	3.485 (SD=10.214)
Mean Trichuriasis Ova Ct	169 (SD=391)	567 (SD=143)

Table 2 shows the prevalence rates of Ascaris and Trichuriasis before and after the administration of the interventions as well as the percentage change within groups and the corresponding net changes observed between the study groups. The prevalence rate of Ascariasis posted a 10% reduction after the administration of Ipil-ipil capsules. The control group likewise posted a greater decline in prevalence rate (16%) after the health education activities. Similar reductions in the prevalence rate of Trichuriasis are observed for both the study groups, the control group exhibiting higher percentage of prevalence reduction (20%) than the intervention group (1.0%).

Table 2. Prevalence Rates (in %) of Ascariasis and Trichuriasis at Baseline after Intervention including % PR Changes and Net Changes

	Intervention(N=149)			Control (N=183)			
	Baseline	Post-Int	% PRC*	Baseline	Post-Int	%PRC*	Net**
Asca	28.2	25.0	-10.0	27.4	23.0	-16.0	6.0%
Trichu	51.0	50.0	-1.0	56.2	45.0	-19.0	18.0

Ascaris baseline count x2 = 0.032 (p>0.75)
Ascaris post intervention x2 = 0.046(p>0.75)
Trichuris baseline count x2 = 0.006 (p>0.75)
Trichuris post invervention x2 = 0.021 (p>0.75)
**%PRC = (Prevalence Rate at Baseline-Prevalence Rate Post Intevervention)/ Prevalance at Baseline*
***Net Change = % PRC in Intervention Group-%PRC in Control Group*

Changes in mean Ascaris ova counts are shown in Table 3. A rise in the mean ova count of +24% is registered by the intervention group while the control group showed a reduction of -14%. This has resulted to a net change or difference of 38% for both groups.

Table 3. Mean Ascaris Ova Counts at Baseline, Post-Intervention and Net Changes in % within and between the Study Groups

	Intervention (N=149)	Control (N=183)
Baseline	2,707 (±11,568)	3.485 (±10,214)
Post-Intervention	3,359 (±14,425)	2,975.68 (±10,011)
Absolute Difference in Mean	+652	-510
%Change*	+24%	-14%
NET CHANGE**	38%	

intervention group t = 0.37 (p>0.05) *control group t = 0.64 (p>0.05)*
**%Change = (Mean at baseline-Mean Post Intervention)/Mean at baseline*
***Net Change = %Change Intervention Group - %Change Control Group*

Results related to Trichuris ova counts showed a similar pattern. The control group registered a reduction in mean ova count (-27%). The intervention group however showed a significant rise in the Trichuris ova count of 147% (Table 4).

Table 4. Mean Trichuris Ova Counts at Baseline, Post-Intervention and Net Changes within Groups and between Groups

Characteristics	Intervention (N=149)	Control (N=183)
Baseline	169 (±391)	567 (±1433)
Post-Intervention	418 (±1208)	411 (±1202)
Absolute Difference in Mean	+249	-156
%Change*	+147%	-27%
NET CHANGE**	174%	

intervention group t = 0.92 (p>0.05) *control group t = 0.30 (p>0.05)*
**%Change = (Mean at baseline-Mean Post Intervention)/Mean at baseline*
***Net Change = %Change Intervention Group - %Change Control Group*

Based on the ova counts, the intensity of helminth infestation was estimated and these are presented in Table 5.

Table 5. Prevalence Rate (%) by Degree of Ascaris Infestation

	Intervention (N=149)		Control (N=183)	
	No.	%	No.	%
Very Light	32	21.91	27	14.75
Light	8	5.36	14	7.65
Moderate	1	0.67	1	0.54
Heavy	1	0.67	3	1.63
TOTAL	42	28.2%	45	27.4%

Different values are used to stratify the degree of Trichuris infestation. Ova count ranging from 1 to 999 signify a very light intensity of infestation; counts from 1,000 to 4,999 are classigied as having light infestation; 5,000 to 9,999 as moderate; and those with 10,000 or more ova counts as heavily infested (Table 6).

Table 6. Prevalence Rate (%) by Degree of Trichuris Infestation

	Intervention (N=149)		Control (N=183)	
	No.	%	No.	%
Very Light	72	48.32	80	43.71
Light	4	2.68	19	10.38
Moderate	0	-	0	-
Heavy	0	-	1	0.54
TOTAL	76	51%	113	56.2%

Difference in the incidence of adverse reactions are presented in Table 7. There is a significant increase in the incidence of the selected adverse effects after the administration of Ipil-ipil capsules to subjects in the intervention group. Compared to those in the control group, a reduction in the occurrence of these manifestations were noted.

Table 7. Baseline and Post-Intervention Incidence Rates of Selected Adverse Effects, Attributable Risk Difference in the Study Groups

	Intervention (N=149)			Control (N=183)		
Adverse Effects	Baseline	Post-Int	ARD*	Baseline	Post-Int	ARD*
Hiccups	3.1%	23.3%	20.2%	5.1%	0%	5.1%
Abd Pain	4.1	23.0	18.9	22.7	1.6	21.1
Diarrhea	4.1	18.4	14.3	7.7	1.1	6.6

Chi squares p<0.000 for all adverse effects

**ARD = Incidence rate at baseline - Incidence rate Post-Intervention*

Discussion

Effective control of Ascariasis and Trichuriasis have been attained using a combination of control measures like health education on hygiene, personal disposal of human wastes and mass treatment of high risk groups. Considering the documented 30% to 82% efficacy rates of Ipil-ipil in previous clinical trials, this study embarked on proving its worth as an effective mass treatment of high risk groups in communities.

Except for the significant difference in the incidence of adverse effects prior to and after the administration of the intervention measures, and the difference observed between the intervention and control groups, the other outcome measures expressed as percentage and net changes (difference in prevalence rates and mean ova counts) were all not statistically significant.

This study demonstrated reductions in the prevalence rates of both Ascariasis and Trichuriasis of 10 percent and 1 percent respectively ($p>.05$) among those given Ipil-ipil seed preparation. This percentage reductions are two to three times lower than the reported lower value efficiency rate of 29.6% (7). The control group posted greater reductions for both helminthic infections.

The more impressive decline in the outcome measures observed in the control group reinforces the value of health education as an important pillar in the control and prevention of diseases.

Like other studies, several biases were encountered and these could have influenced the results of this study. Purposive selection of the study communities and the inclusion into the sample population only of subjects who voluntarily submitted stool specimens may have resulted to selection bias. Technical and logistic problems have prompted the investigators to obtain measurements from cross sections of the consenting population at baseline and after delivery of the interventions. Thus, the subjects at baseline may not be necessarily those included in the post-intervention measurements.

The significant reductions in Ascariasis prevalence rate (10%) in the intervention group could be due to a real, low efficiency rate of this single dose Ipil-ipil seed preparation as a mass deworming agent. No published studies have documented greater than 82% efficiency. The rates obtained from previous varied from a low a 29% to as high as 80%. With the 10% reduction in prevalence rate observed in this study, a minimal reduction in the number of subjects harboring these geohelminths could not significantly reduce the count of children who may continue to indiscriminately pollute the environment and contribute to further transmission of this helminthiasis. The fact that the mean ova counts increased by 24 percent after intervention is an added indication of its inability to eliminate the helminths totally.

In spite of a rather small sample used in the analysis regarding the occurrence of adverse effects, statistically significant within groups and between groups differences were observed. The attributable risk difference which is measured as the absolute difference in the incidence of hiccups, abdominal pain, and diarrhea before and after the administration of the Ipil-ipil preparation were all statistically significant. All of these showed a rise in the incidence rates which may well be associated with the preparation. The control group which received health education, however posted significant reductions. The occurrence of soft stools among subjects receiving the Ipil-ipil preparation confirms previous findings which showed 93 percent soft stool incidence rate[7].

Continued search for indigenous medicinal plants with anti-helminthic properties should be pursued. Health education coupled with the use of readily available and safe herbal preparations may yet be the quickest means of controlling and preventing the sustained problem of intestinal parasitism in depressed communities.

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Retinal Nerve Fiber Layer Thickness within the Area of Apparently Normal Field in Normal-Tension Glaucoma with Hemifield Defect†

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Abstract

Purpose: *To evaluate changes in nerve fiber layer (NFL) thickness in areas with apparently normal retinal sensitivity in eyes with normal-tension glaucoma (NTG) with hemifield dominant visual field defects.*

Methods: *The prospective clinical study consisted of 17 eyes from 17 patients with NTG in whom superior or inferior hemifield dominant defects based on the Humphrey visual field of central 30 degree were present, and 10 normal eyes from 10 control subjects matched in age and refractive error. The retinal NFL thickness was evaluated with a scanning laser polarimeter. Mean NFL thickness measurements in the defined ring in four quadrants (superior, inferior, nasal, and temporal) were obtained. To facilitate visual field and NFL thickness correspondence, the total deviation (TD) plot of the visual field was divided into four 90 degree quadrants, using Wirtschafter's scheme to match the four quadrants examined by laser polarimetry.*

Results: *The mean NFL thickness in the unaffected quadrant, i.e., the quadrant within the area corresponding to the hemifield with apparently normal visual field in eyes with NTG, was significantly thinner than the average NFL thickness of the superior and inferior quadrants in the normal eyes. In eyes with NTG, the NFL thickness in the affected quadrant also was significantly thinner than that in the unaffected quadrant. In the unaffected quadrant, visual field TD (the sum of the TD values within this quadrant) showed a significant correlation with the ratio of NFL thickness in the unaffected quadrant to that in the nasal quadrant.*

Conclusion: *Early changes in the retinal nerve fiber layer may already exist even in the unaffected area of the visual field in eyes with NTG with hemifield dominant visual field defects.*

Key Words: *Retinal nerve fiber layer thickness- Normal-tension glaucoma-Scanning laser polarimeter- hemifield defects.*

Introduction

EARLY VISUAL FIELD CHANGES in glaucoma are usually localized to a single hemifield.[1] In particular, a number of patients with normal-tension glaucoma (NTG) present clinically with visual field defects confined to one hemifield[2,3]; the other side appears normal. However, whether such areas with "normal" visual field, as determined by perimetry, are truly unaffected or not is unknown. Nerve fiber layer (NFL) changes have been known to precede manifestation of visual field damage.[4-8] Therefore, there may be detectable morphologic abnormalities in the retinal NFL even in areas corresponding to the normal visual field in glaucomatous eyes with only a hemifield-dominant defect.

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The advent of scanning laser polarimetry has introduced an objective means of evaluating NFL thickness. It has been demonstrated that quantitative measurements using scanning laser polarimetry have good reproducibility[9-11] and correspond to known properties of the retinal NFL, as follows: 1.) Peripapillary NFL is thickest in the superior and inferior arcuate regions; 2.) Peripapillary nerve fibers thin with increasing distance from the optic nerve head; 3.) The number of peripapillary nerve fibers decreases with increasing age; and 4.) Major arterioles and venules are embedded in the NFL, hence the NFL is thinner above the blood vessels than in adjacent areas.[12] Using NFL thickness measured by scanning laser polarimetry, it is possible to discriminate between glaucomatous eyes and normal eyes with a high degree of accuracy.[13]

In this study, we used scanning laser polarimetry to evaluate whether there are changes in NFL thickness in areas of apparently normal visual field in eyes with NTG with hemifield visual field defects.

Subjects and Methods

Selection of Study Subjects

From October 1996 to February 1998, we prospectively evaluated 118 candidates with NTG for the study, and enrolled 22 patients at the glaucoma clinic of Gifu University Hospital. For inclusion, patients had to have a follow-up period of at least 6 months or longer. They also had to have at least one eye that met the following criteria for hemifield defects as detected in two consecutive fields by Humphrey field analyzer (Zeiss-Humphrey, San Leandro, CA) using program central 30-2, standard, full-threshold strategy: 1) Three or more adjacent points with $p < 0.05$ in a total deviation (TD) probability map, or two or more test points with $p < 0.02$ or smaller in a TD probability map on a superior or an inferior hemifield; 2) At least one of such points was located within a superior (45°-135°) or an inferior (225°-315°) quadrant of the visual field divided using Wirtschafter's scheme (Figure 1); 3) The hemifield of the other side had no such probability symbols on both the TD and pattern deviation maps (Figure 2); 4.) A Glaucoma Hemifield Test (GHT) result that was outside normal limits; and 5.) Fixation loss less than 20% and false positive and negative rates less than 15%.

Figure 1 Wirtschafter's scheme of dividing visual field test point areas into the corresponding optic disc sectors.[15]

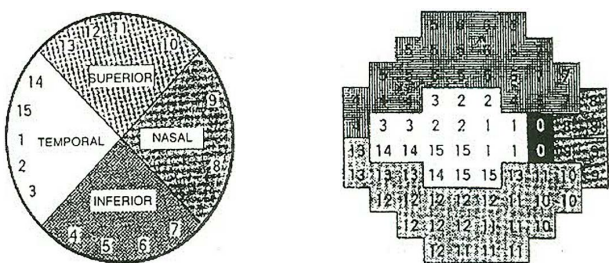
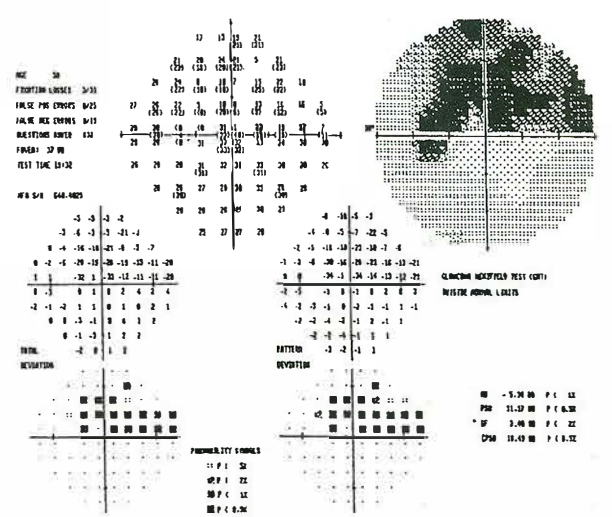


Figure 2 Total deviation and pattern deviation maps of the visual field in a patient enrolled in the study. No significant probability scores were observed in the unaffected quadrant.



Patients also had to have an intraocular pressure (IOP) of 21 mmHg or less based on measurements obtained at 2 hour intervals over 24 hours in both eyes by Goldmann applanation tonometry, and normal anterior chamber angles

on slit-lamp biomicroscopy and gonioscopy in both eyes. Additional inclusion criteria included glaucomatous disc abnormalities defined subjectively at ophthalmoscopic examination by two investigators (GT and YK) according to the following criteria: focal or generalized narrowing or disappearance of neuroretinal rim with enlarged amount of cupping or pallor, or eccentric cupping or pallor (i.e., cupping enlarged more either superiorly or inferiorly than horizontally within the disc, corresponding to the visual field defects); and that pallor did not extent over the cupping border.

Patients with a history of laser surgery or intraocular surgery in either eye, a history of systemic B-blocker or systemic or local corticosteroid therapy, or intracranial abnormalities or lesions on otolaryngologic or neurologic examination (including computed tomographic scans)[14] were excluded.

Patients also had to have a corrected visual acuity greater than 20/30, a visual field test performed within 3 months of NFL thickness measurements, and a good NFL image obtained by scanning laser polarimetry (mean image with an average deviation of less than 8 μm).

Fifteen healthy volunteers also participated in this study. All control subjects had best corrected visual acuity of 20/30. Normal appearance of the optic nerve head in both eyes was confirmed by ophthalmoscopic examination, and no other significant ocular diseases except for mild cataract were found by routine ophthalmologic evaluation, including slit-lamp biomicroscopy and ophthalmoscopy. No control subject had a history of high IOP or ocular trauma.

All control subjects underwent visual field testing with a Humphrey field analyzer using program central 24-2, standard, full-threshold strategy to confirm the presence of normal visual fields. A visual field was defined as normal when the GHT results was within normal limits and the field did not meet the following criteria for visual field defects: 1) three of more adjacent points with $p< 0.05$ in a total deviation probability map;2) two or more adjacent points with $p<0.02$ in a total deviation probability map; or 3) a difference of > 10 dB across the nasal horizontal meridian at two or more adjacent points. In normal eyes, IOP was measured using a Goldmann applanation tonometer to confirm that the measurements were < 21 mmHg.

The study protocol was approved by the Ethical Review Committee of Gifu University, and tenets of the Declaration of Helsinki were followed. Written consent was obtained from all patients after the study was thoroughly explained to them.

Subject Characteristics

After matching patients with NTG and control subjects by age and refractive error, we enrolled 17 eyes from 17 patients with NTG and 10 eyes from 10 control subjects in this study. If both eyes met inclusion criteria, one eye was randomly selected. Of the 17 patients with NTG, 9 were men and 8 were women. Patient age ranged from 36 to 75 years (mean ± SD 54.0 ±11.6 years). Eyes with NTG had a mean ± SD refractive error of -1.66 ± 3.19 (Table 1).

The 10 control subjects included 6 men and 4 women ranging in age from 39 to 60 years (mean 51.2 ± 6.0 years). These normal eyes had a mean refractive error of -2.18 ± 2.49 (Table 1).

Table 1. Background Data for Patients with Normal-Tension Galucoma (NTG) and Control Subjects

	Patients with NTG (n = 17)	Control Subjects (n = 10)
Age (yrs)	54.0±11.6 (36.75)	51.2±6.0 (39-60)
Refraction (D)	-1.66±3.19(-7.00-2.50)	-2.18±2.49(5-.50-1.25)
Mean Deviation (dB)	-5.87±2.96(-12.28—0.45)	-0.40±1.12(-2.84-0.57)
Total Deviation (dB)		
Unaffected quadrant	-2.41±52.10(-102-139)	—
Affected quadrant	-292.24±190.47 (-693—52)	—

Values are presented as mean ± standard deviation (range)

Measurement of Nerve Fiber Layer

All participants from both groups were examined by one examiner (RDCR) with a Nerve Fiber Analyzer (NFA) II scanning laser polarimeter (Laser Diagnostic Technologies, San Diego, CA). Three consecutive NFA images in a field 15° x 15° were taken to obtain a mean image with an average deviation of less than 8 um. This mean image was used to determine the peripapillary NFL thickness. An ellipse, best fitted to the inner margin of the peripapillary scleral ring, was placed to enable NFL thickness measurements in a ring area 5 pixels in width and 1.5 disc diameters from the center of the optic disc. Previous studies have shown this to be the area of greatest reproducibility[9]. Mean NFL thickness measurements were obtained in this defined ring in four quadrants (superior, 45°-135°; inferior, 225°-315°; nasal, 135°-225°; and temporal, 315° - 45°).

In evaluating the difference between NFL thickness in normal eyes and NFL thickness in eyes with NTG, the average of the superior and inferior quadrant of the normal eyes was computed. This was then compared with the NFL thickness of the unaffected quadrant (the quadrant within the area corresponding to the hemifield with apparently normal visual field) in the eyes with NTG. We also obtained the ratio of NFL thickness in each quadrant to NFL thickness in the nasal quadrant. We used the nasal quadrant to calculate relative NFL thickness ratios to standardize measurements and reduce the influence of optic disc size and variability of intensity adjustments by the examiner. Also, the nasal quadrant is known to have good repeatability and remains stable even with increasing age.[10] Participants underwent all examinations within 3 months of consultation and visual field testing.

Correspondence of Visual field and Nerve Fiber Layer Thickness

To facilitate visual field and NFL thickness correpondence in the patients with NTG, the TD plot map was divided into four 90° quadrants using Wirtschafter's scheme to match the four quadrants examined by scanning laser polarimetry.[15] The sum of the TD values in the superior and inferior quadrants was calculated. The quadrant that was within the hemifield defect was designated as the affected quadrant, and the opposite quadrant was the unaffecte ' quadrant.

Statistical Analysis

Statistical analysis of NFL measurements and TD was performed using the Wilcoxon signed rank test to evaluate the difference between paired two groups, and the Spearmann rank correlation test to evaluate the relationship between the two groups. The Mann-Whitney U test was then used to evaluate the difference in NFL thickness between eyes with NTG and normal eyes. Statistical significance was indicated by a p value < 0.05.

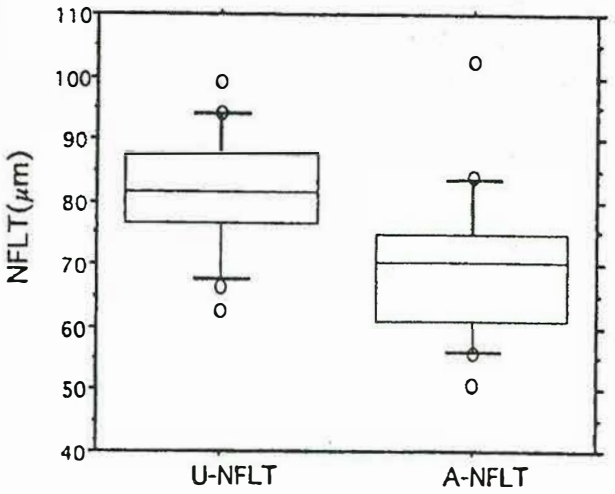
Results

Results are given as mean ± standard deviation, unless otherwise indicated.

Eyes with Glaucoma

Of the 17 eyes with NTG, 10 had a superior hemifield defect and 7 had an inferior hemifield defect. Mean NFL thickness in the unaffected quadrants was 81.55 ± 9.61 um, with a range of 62.60 to 99.30 um. Mean NFL thickness in the affected quadrant (the quadrant within the area corresponding to the hemifield with visual field defects) was 69.78 ± 12.43 um with a range of 50.70 to 102.50 um. There was a statistically significant difference in NFL thickness between the unaffected and affected quadrants (Wilcoxon signed rank test, p = 0.0099; Figure 3). Mean NFL thickness in the nasal quadrant was 60.65 ± 10.85 um, with a range of 47.70 to 87.20 um. The mean ratio of NFL thickness in the unaffected quadrant to that in the nasal quadrant was 1.374 ± 0.228. Mean ratio of NFL thickness in the affected quadrant to that in the nasal quadrant was 1.158 ± 0.141. This difference was also statistically significant (Wilcoxon signed rank test, p = 0.0106).

Figure 3 Box plot of nerve fiber layer thickness measurements of the affected and unaffected quadrants (Wilcoxon signed rank test, p=0.0099). In the box plot, the bottom and top bar represent the tenth and ninetieth percentiles, respectively. The box represents the twenty fifth, fiftieth, and seventy fifth percentiles. U-NFLT, affected quadrant nerve fiber layer thickness; A-NFLT, affected quadrant nerve fiber layer thickness.



In the analysis of visual field results in relation to NFL thickness, no significant correlation was seen between the sum of TD values in the unaffected quadrant and NFL thickness in the unaffected quadrant (Spearmann rank correlation test, p = 0.1889, r^2 = 0.328). Likewise, the sum of TD values in the affected quadrant and NFL thickness in that quadrant had no correlation (p = 0.3517,r^2 = 0.233). In contrast, correlation between the ratio of NFL thickness in the unaffected quadrant to that in the nasal quadrant and the sum of TD values in the unaffected quadrant was statistically significant (p = 0.0059; Figure 4A). There was no correlation between ratio of NFL thickness in the affected quadrant to that in the nasal quadrant and the sum of TD values in the affected quadrant (p = 0.3869; Figure 4B).

Figure 4a Correlation between the nerve fiber layer thickness ratio of unaffected to nasal quadrant and the unaffected quadrant total deviation. U-NFLT/N = 1.38 + 0.002 x U-TD;n=17; Spearmann rank correlation = 0.689, p=0.0059.

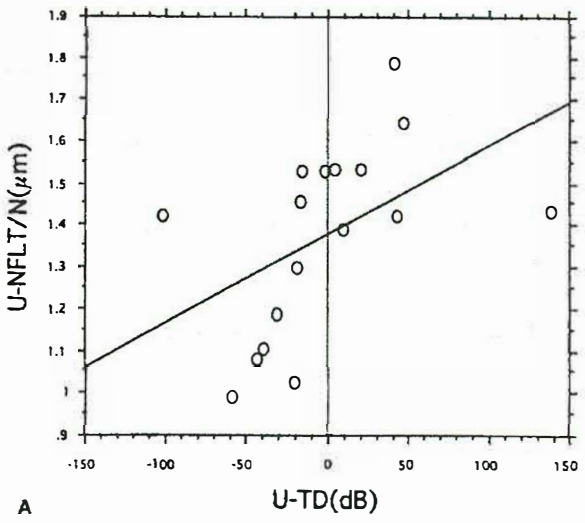
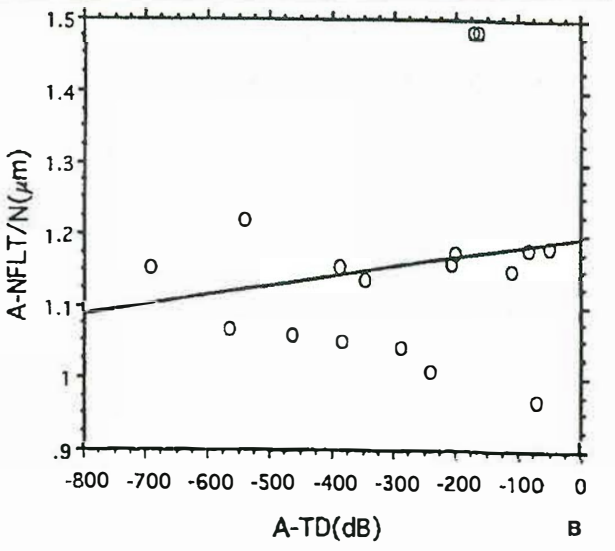


Figure 4b Correlation between the nerve fiber layer thickness ratio of affected to nasal quadrant and the affected quadrant total deviation. A-NFLT/N = 1.198 + 1.377E-4 x A-TD; n=17; Spearmannrank correlation = 0.216, p=0.3869. U-NFLT/N, unaffected to nasal quadrant nerve fiber layer thickness ratio; U-TD, unaffected quadrant total deviation;A-NFLT/N, affected to nasal quadrant nerve fiber layer thickness ratio; A-T, affected quadrant total deviation.

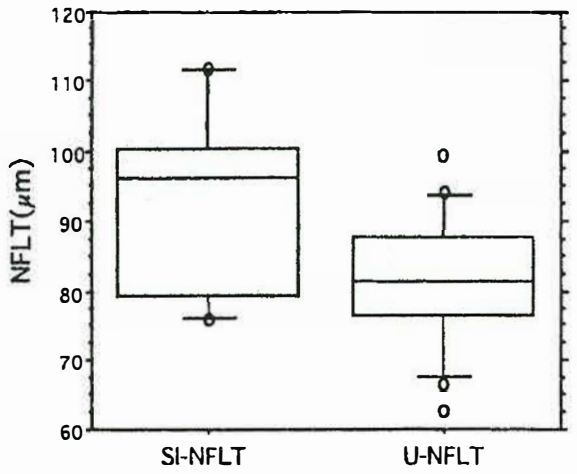


Normal Eyes

In the normal eyes, mean NFL thickness in the superior quadrant was 95-56 ± 15.78um , with a range of 69.60 to 118.70 um. Mean NFL thickness in the inferior quadrant was 91.27 ± 12.50 um, with a range of 72.90 to 109.10 um. No significant difference was seen between these two quadrants (Wilcoxon signed rank test, p = 0.0926). The average NFL thickness in the superior and inferior quadrants was 93.45 ± 13.47 um with a range of 75.90 to 111.70 um. This average NFL thickness measurement was used to evaluate relative difference in NFL thickness in the unaffected quadrants in eyes with NTG.

The average NFL thickness in the superior and inferior quadrants in normal eyes was greater than NFL thickness in the unaffected quadrants of eyes with NTG. This difference was statistically significant (Mann-Whitney U test, p = 0.0446; figure 5).

Figure 5 Box plot of nerve fiber layer thickness measurements of the average nerve fiber layer thickness of the superior and inferior quadrants of normal eyes, and nerve fiber layer thickness of the superior and inferior quadrants of normal eyes, and nerve fiber layer thickness of the unaffected quadrant of the eyes with normal tension glaucoma (Mann-Whitney U test, p=0.0446). In the box plot, the bottom and top bars represents the tenth and ninetieth percentiles, respectively. The box represents the twenty-fifth, fiftieth, and seventy-fifth percentiles. U-NFLT, unaffected quadrant nerve fiber layer thickness; SI-NFLT, average nerve fiber layer thickness of the superior and inferior quadrant of the normal eyes



Discussion

In this study we used scanning laser polarimetry to quantitatively evaluate NFL thickness in eyes with NTG with visual field defect confined to one hemifield. We compared these findings with NFL thickness measurements in normal eyes. Our examination of eyes with NTG with hemifield defect showed the disparity in NFL thickness between unaffected and affected quadrants. The NFL in the affected quadrant was significantly thinner than in the unaffected quadrant, consistent with the presence of a hemifield defect. This study also revealed that the NFL is significantly thinner even in the unaffected area of eyes with glaucoma than in the superior and inferior quadrants of normal eyes. These findings suggested that NFL changes are already present in the unaffected visual field of patients with NTG with hemifield-dominant visual field defects, although it is also possible that patients with NTG have congenitally thinner NFL than healthy subjects, and that this may predispose them to NTG.

Airaksinen and Drance[4] have discovered that there is a substantial amount of generalized loss of nerve fibers without measurable effect on the differential light threshold, but that after a certain level of diffuse structural changes has been reached, further loss in retinal NFL is associated with an increasingly steep reduction in retinal sensitivity. It thus seems that preperimetry changes in the NFL are already present but have not yet reached the critical point to elicit change in retinal sensitivity. We may also infer that when perimetry changes set in, the apparently unscathed areas of the visual field may already have subtle and diffuse NFL changes. In addition, it has been found that visual field sensitivity in automated testing begins to decline soon after initial loss of ganglion cells. Areas with 20% cell loss were seen in locations with 5 dB loss of sensitivity, and 40% cell loss of corresponded to a 10-dB decrease. [16] In this study, the difference in NFL thickness between the unaffected quadrant in

eyes with NTG and normal eyes was approximately 13% (81.55 um versus 93.45 um). Therefore, our findings seem to be consistent with the results of previous studies.

The NFL thickness measurements and visual field results revealed significant correlation only in the unaffected hemifield of the NTG group. The absence of significant correlation in the affected hemifield is in contrast to results of other investigations,[17,18]. We must consider, however, that glaucomatous damage is insidious due to the significant difference between rates of anatomical change and functional change. Perimetry assesses visual function, whereas image analysis examines anatomic structures. These two entities are not identical.[13] It may be said that as NFL thickness decreases, it reaches its end point much earlier than retinal sensitivity, which continues to diminish.

Our study revealed that NFL changes may already be present in areas with no apparent visual field damage in eyes with NTG, and that the NFA II may be used to quantitatively detect these changes. This has potential as an ancillary procedure in the evaluation of suspected glaucoma, and its ability to detect differences in NFL thickness may also enable us to monitor NFL changes in eyes with early stage NTG. However, our results were obtained from a relatively small number of patients due to the strict definition of hemifield defect in our study protocol. Therefore, further studies with larger numbers of patients are needed to confirm our conclusions.

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Management of Community-Acquired Pneumonia Among In-Patients in a Teaching Hospital: Adherence to the American Thoracic Society Guidelines†

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Abstract

This cohort was undertaken to determine the impact of the American Thoracic society (ATS) guidelines in the management scheme of community-acquired pneumonia at UERMMMC. One hundred eighty five patients were included, of which only 84 (44.41%) were found to be eligible for hospitalization based on the ATS guidelines. Only 8 of these patients (9.52%) were admitted in the Intensive Care Unit (ICU). Thirty-eight of the 76 patients (50%) admitted in the general ward had the indications for admission to the ICU if the criteria set by the ATS guidelines were followed. All the patients were divided into 2 groups based on compliance with the treatment recommendations of the ATS guidelines. Comparison of the two groups showed a significant correlation with positive outcome measures for patients who received therapy consistent with the ATS guidelines. The outcome measures include improvement of clinical symptoms, length of hospital stay, and survival. When the patients were subdivided into the different categories of pneumonia, patients belonging to Category 3 who received therapy consistent with the ATS guidelines had an earlier clinical response. Underutilization of bacteriologic studies was also observed, as only 58% and 21% of the patients were ordered sputum culture and blood culture, respectively. Moreover, 24% of those with sputum cultures and 47% of those with blood cultures were discharged prior to the release of culture report. Our study shows that the majority of physicians in UERMMMC do not conform to the guidelines set by the ATS in the initial management of community-acquired pneumonia.

Key words: *Community-acquired pneumonia, clinical practice guidelines, compliance*

Introduction

COMMUNITY-ACQUIRED PNEUMONIA continues to be a common and serious illness both in developed and developing countries in spite of the advent of new and sophisticated diagnostic techniques, potent antimicrobials and effective vaccines. It remains an important cause of morbidity and mortality for both non-hospitalized and hospitalized adults. It ranks as the sixth leading cause of death in the United States with the mortality rates generally reported at 20 to 40%.[1] In the Philippines, it is the fourth leading cause of morbidity and the second leading cause of death.[2]

The physicians' management of community-acquired pneumonia has been known to be varied.[3-10] Although many studies and recommendations have been made, several factors influence one's decision regarding its management. Such factors include cost-effectiveness of the therapy, anecdotal experiences, drug factors (like the influence of pharmaceutical companies), host factors, and social and moral issues.

One important aspect in the management of community-acquired pneumonia is the decision

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to hospitalize a patient. It is perhaps the single most important decision during the entire course of the illness. However, in-patient care does not only entail extra cost, but also, it theoretically increases the risk of iatrogenic complications associated with hospitalization. Previous studies have documented substantial variability in the hospital admission rates for adult community-acquired pneumonia.[11,12] This variation suggests that physicians do not use consistent criteria for hospitalization. Worse, it may reflect uncertainty among physicians in assessing the severity of the illness and the perceived benefits of hospital care.

Published reports have reiterated the necessity of initial empiric therapy in the management of pneumonia because of the nonspecificity of clinical and radiographic findings, and the limitations of diagnostic testing for identifying the etiologic pathogen.[1,8,13,15,16] This approach must be rationally based on an assessment of the likelihood that a given pathogen is causing disease in a patient.

In July 1993, the American Thoracic Society issued a consensus statement on the initial management of Community-acquired pneumonia (CAP) emphasizing the need to assess the severity of the illness because of its relevance to decisions about hospitalization.[13] Numerous host and disease factors were cited based on published data to guide physicians with regard to the possible etiologic organism involved, the prognosis and necessity of admission to the ICU and the initial therapy to be given. Presently, limited data are available regarding the impact of the ATS guidelines in the management of CAP, especially on patient outcomes. Gleason, et al[4] showed the cost effectiveness of the ATS recommendation in the management of community-acquired pneumonia among outpatients. A recent report showed that a majority of institutions in the United States follow the ATS guidelines in terms of the initial antibiotics for CAP.[14] It also showed that regimens not consistent with the guidelines were associated with a prolongation of hospital stay.

This study was undertaken to determine the impact of the ATS guidelines on the management scheme of community-acquired pneumonia at the UERMMMC. Specifically, this study aimed to determine the percentage of admitted patients who satisfied the criteria for admission set by the ATS guidelines and compare it with the percentage of admitted patients not fulfilling the conditions set by the ATS. It intended to determine the percentage of patients admitted in the ward and with its subgroup of patients with indications for ICU admission. Finally, it aimed to compare the medical outcomes (measures include survival, length of hospital stay, and improvement of clinical symptoms) for patients whose antimicrobial therapy was either consistent or inconsistent with the ATS guidelines.

Materials and Methods

This is a cohort study. All patients aged 18 years and above, admitted at UERMMMC by the Medicine service from January 1, 1994 to October 31, 1997 with an admitting diagnosis of community-acquired pneumonia were included . Each patient was followed up until discharge. Pertinent information, including demographic data, diagnostic work-ups, initial therapeutic intervention, co-morbid factors and presenting manifestations, and patient outcomes such as survival, improvement of clinical symptoms and duration of hospital stay, were recorded in a clinical data form. Excluded were patients who were immunocompromised, patients with concomitant infections (e.g. sinusitis, urinary tract infections, active PTB), patients who were admitted primarily because of another medical condition (and not the pneumonia), patients who had cardiopulmonary arrest on admission, patients who were discharged against medical advice, and patients who were allergic to antimicrobials specified as initial therapy by the ATS guidelines (e.g. sulfonamides, betalactams).

Definition of Terms

1. American Thoracic Society Guidelines on the Initial Management of Adults with Community-Acquired Pneumonia (CAP).[13]

   Four Major categories of CAP as defined by the ATS:
   a. Category 1 - CAP occurring in patients 60 years of age or younger who have no evidence of co-morbidity and who can be treated in an outpatient setting.
   b. Category 2 - CAP occurring in patients with evidence of co-morbidity and/or who are 60 years of age or older who can be treated in an outpatient setting
   c. Category 3 - CAP requiring hospitalization but not admission to an intensive care unit
   d. Category 4 - generally requiring ICU care
2. Specific risk factors for mortality or a complicated course of pneumonia (as enumerated by the ATS):
   a. Age over 65 years
   b. Presence of coexisting illnesses or other findings
      1. COPD, including chronic structural disease of the lung (bronchiectasis, cystic fibrosis)
      2. Diabetes mellitus
      3. Chronic renal failure
      4. Congestive heart failure
      5. Chronic liver disease of any etiology
      6. Previous hospitalization within 1 year of the onset of CAP
      7. Suspicion of aspiration (gastric or oropharyngeal secretions)
      8. Altered mental status
      9. Postsplenectomy state
      10. Chronic alcohol abuse or malnutrition
   c. Certain physical findings also predict mortality, increased morbidity, or a complicated course
      1. Respiratory rate in excess of 30 breaths/min
      2. Diastolic blood pressure ≤ 60 mm Hg or a systolic blood pressure ≤ 90 mm Hg
      3. Temperature > 38.3 °C
      4. Evidence of extrapulmonary sites of disease - presence of septic arthritis, meningitis, etc.
      5. Confusion and/or decreased level of consciousness
   d. Laboratory findings that also predict increased morbidity or mortality
      1. WBC < 4,000 or > 30,000 or an absolute neutrophil count below 1,000
      2. PaO_2 < 60 mm Hg or $PaCO_2$ > 50 mm Hg while breathing room air
      3. Need for mechanical ventilation
      4. Evidence of abnormal renal function, as manifested by serum creatinine of > 1.2 mg/dl or a blood urea nitrogen > 20 mg/dl
      5. Presence of certain unfavorable chest radiographic findings, e.g., more than 1 lobe involvement, presence of a cavity, rapid radiographic spreading and the presence of a pleural effusion
      6. Hematocrit of < 30% or hemoglobin < 9 g/dl
      7. Other evidence of sepsis or organ dysfunction as manifested by a metabolic acidosis, an increased prothrombin time, an increase partial thromboplastin time, decreased platelets, or the presence of fibrin split products > 1:40
3. Conditions identified by the ATS which necessitate admission to the ICU:
   a. Respiratory frequency > 30 breaths per min at admission
   b. Severe respiratory failure defined by PaO_2/FiO_2 ratio < 250

c. Requirement for mechanical ventilation
d. Chest radiograph showing bilateral involvement or involvement of multiple lobes. In addition, an increase in the size of the opacity by 50% or greater within 48 hours of admission
e. Shock (systolic blood pressure below 90 mm Hg or diastolic blood pressure below 60 mm Hg)
f. Requirement for vasopressors for more than 4 hours
g. Urine output lower than 20 ml/hr or total urine output lower than 80 ml in 4 hours unless another explanation is available or acute renal failure requiring dialysis.

Analysis of Data

Gathered data were grouped into two broad categories—a group of admitted patients not complying with the ATS guidelines, and a group of admitted patients fulfilling the conditions set by the ATS for admission. Each group was divided into 2 subcategories in such a way that the 4 subcategories would coincide with the 4 categories of the ATS guidelines. Each of the subcategories was further divided into 2 small groups based on the initial therapy given -either based on the ATS statement or not. The proportion of patients admitted and treated consistently and inconsistently with the ATS guidelines were computed. Final outcome measures including improvement of clinical symptoms, duration of hospital stay and survival for each group were determined and compared using the Chi-square test or Fischer's Exact Test.

Results

A total of 244 patients were initially studied but only 185 remained evaluable. Of the 185 patients included in the study, 101 did not satisfy the ATS criteria for admission (Group I) and only 84 admitted patients (45.4%) were found to be eligible for hospitalization based on the ATS guidelines (Group II). Under this second group, only 8 of the 84 patients (9.52%) were admitted in the Intensive Care Unit (ICU). This subgroup fulfills the requirements for ICU admission. Thirty-eight of the 76 patients (50%) who were admitted in the general ward had the indications for admission to the ICU if criteria set by the ATS guidelines were followed (Figure 1).

Figure 1. Admitted patients at the UERMMMC with community-acquired pneumonia from January 1, 1994 to October 31, 1997

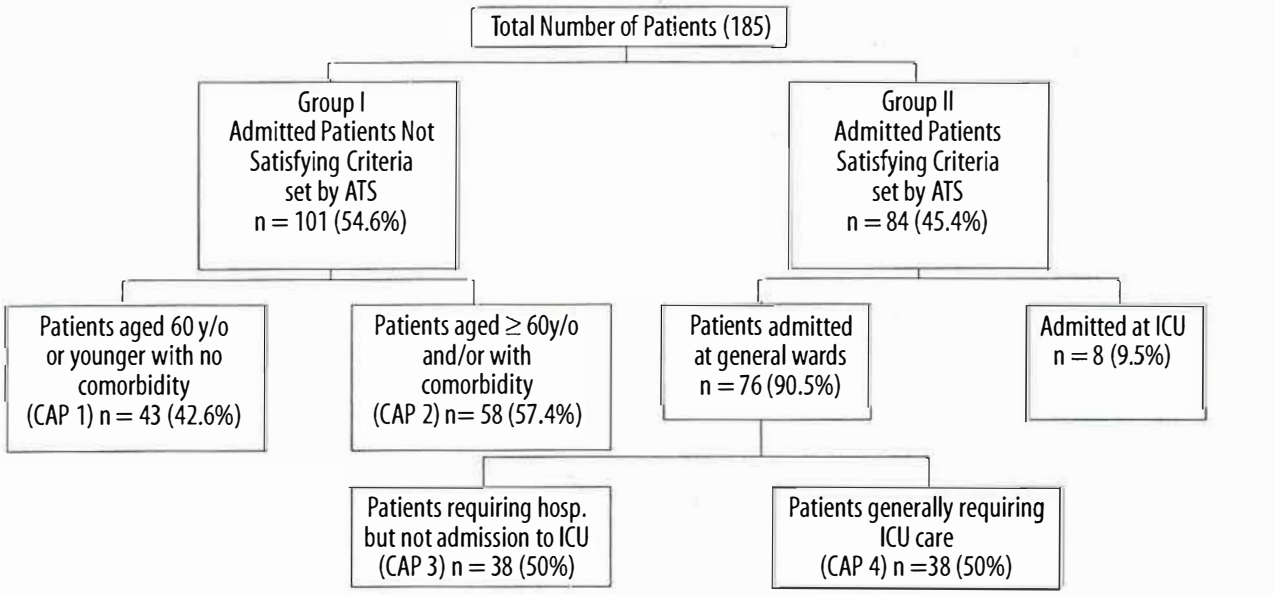

Table 1 shows the clinical characteristics of patients admitted even without fulfilling the criteria or conditions for admission set in the ATS guidelines. Majority of patients (57.43%) were more than 60 years old, with a female to male preponderance ratio (61% vs 39%). Seventy-one of the 101 patients (71.3%) had no comorbid factors. Diabetes mellitus was the most common comorbid factor, which was present in almost 14% of cases. Fever was present in 64% of patients while an abnormal WBC count was present in 81% of cases. The patients were assessed to have only mild infections.

Table 1. Clinical Characteristics of Patients Whose Admissions are Inconsistent with the ATS Guidelines

	Admitted without Fulfillment of ATS Guidelines (n=101)
Age	
≤ 60 y/o	43 (42.5%)
> 60 y/o	58 (57.5%)
Sex	
Male	39 (38.6%)
Female	62 (61.4%)
With Comorbid Factors	30 (29.7%)
DM	14 (13.9%)
COPD	11 (10.9%)
Congestive Heart Failure	2 (2.0%)
Chronic Renal Failure	2 (2.0%)
Chronic Liver Disease	1 (1.0%)
No Comorbid Factors	71 (71.3%)
With Fever	65 (64.4%)
Without Fever	36 (35.6%)
WBC > 10,000	
or WBC < 5,0000	82 (81.2%)
Normal WBC	19 (18.8%)

Table 2 shows the clinical characteristics of patients who satisfied the conditions set by ATS for admission. Again, majority of patients (67%) were more than 60 years old, with the proportion of males slightly higher than the females (52% vs 48%). Almost 74% of patients had at least one comorbid factor. Multiple risk factors presented on admission were seen in 42.9% of cases, with tachypnea as the most common physical finding (45.2%). Azotemia was the most common laboratory abnormality encountered in this group of patients (17.9%).

Table 3 shows the percentage of bacteriologic studies requested during the study period. Overall, only 108 of the 185 patients (58%) had bacteriologic studies, sputum gram stain and sputum culture. Twenty four percent (24%) of these patients were discharged prior to the release of the culture result. Only 38 of the 185 patients (21%) had blood cultures and 47% of these patients were discharged prior to the release of the culture result.

Table 2. Clinical Characteristics of Patients Whose Admissions are Consistent with the ATS Guidelines

	Patients satisfying the criteria for admission set by the ATS guidelines (n=84)
Age	
≤ 60 y/o	28 (33.3%)
> 60 y/o	56 (66.7%)
Sex	
Male	43 (51.2%)
Female	41 (48.8%)
With Comorbid Factors	62 (73.8%)
Single	39 (46.4%)
Multiple	23 (27.4%)
No Comorbid Factors	22 (26.2%)
Presence of S/Sx Specified as Risk Factors	
RR > 30	38 (45.2%)
T>38.3	31 (36.9%)
Hypotension	11 (13.1%)
Decreased sensorium	10 (11.9%)
Multiple risk factors	36 (42.9%)
Laboratory Predictors	
Unfavorable x-ray	12 (14.3%)
WBC <4,000 and >30,000	10 (11.9%)
Azotemia	15 (17.9%)
pO_2<60; pCO_2>50	8 (9.5%)
Anemia	5 (5.9%)
Metablic Acidosis	14 (16.7%)

Table 3. Bacteriologic Studies Requested during Confinement for Pneumonia

	Cat 1 n=43 (%)	Cat 2 n=58 (%)	Cat 3 n=38 (%)	Cat 4 n=46 (%)	Total n=185 (%)	Discharged Prior to Release of Culture Report %
Sputum GS	19 (44)	36 (62)	24(63)	29(63)	108(58)	
Sputum CS	18 (42)	36(62)	24(63)	29(63)	107(58)	26(24)
Blood CS	8 (19)	10(17)	9(16)	11(24)	38(21)	18(47)

Table 4. Comparison of Outcome of Patients who Received Treatments either Consistent or Inconsistent with the ATS Recommendations

	ATS	Not ATS	p value
Cat 1 (n=43)			
Improvement of Symptoms			
≤72 hours	12	25	NS
>72 hours	2	4	
Hospital Stay			
≤5 days	11	21	NS
>5 days	3	8	
Adherence to ATS (%)	14 (32.6%)	29 (67.4%)	
Cat 2 (n=58)			
Improvement of Symptoms			
≤72 hours	35	12	NS
>72 hours	6	5	
Hospital Stay			
≤5 days	34	12	NS
>5 days	7	5	
Adherence to ATS (%)	41 (70.7%)	17 (29.3%)	
Cat 3 (n=38)			
Improvement of Symptoms			
≤72 hours	21	3	<0.05
>72 hours	5	6	
Hospital Stay			
≤5 days	17	3	NS
>5 days	9	6	
Survival			
Yes	26	9	NS
No	2	1	
Adherence to ATS (%)	28 (73.7%)	10 (26.3%)	
Cat 4 (n=46)			
Improvement of Symptoms			
≤72 hours	5	10	NS
>72 hours	2	17	
Hospital Stay			
≤5 days	5	9	NS
>5 days	2	18	
Survival			
Yes	7	27	NS
No	1	11	
Adherence to ATS (%)	8 (17.4%)	38 (82.6%)	
Overall (n=185)			
Improvement of Symptoms			
≤72 hours	72	50	<0.05
>72 hours	15	32	
Hospital Stay			
≤5 days	67	45	<0.05
>5 days	21	37	
Survival			
Yes	88	82	<0.05
No	3	12	
Adherence to ATS (%)	91 (49.2%)	94 (50.8%)	

Table 5. Initial Antimicrobial Choices for the Treatment of Community-acquired Pneumonia

	Number	%
Cat 1 (n=43)		
Beta-lactam/Beta-lactamase inhibitor	18	41.86%
Macrolide	14	32.56%
Cefuroxime	6	13.95%
Others	5	8.63%
Cat 2 (n=58)		
Beta-lactam/Beta-lactamase inhibitor	25	43.1%
Macrolide	6	10.34%
Cefuroxime	11	18.97%
Cefuroxime + Macrolide	4	6.9%
Penicillin	4	6.9%
Cotrimoxazole	2	3.45%
Others		
Cat 3 (n=38)		
Beta-lactam/Beta-lactamase inhibitor	17	44.76%
Cefuroxime	6	15.79%
Ciprofloxacin	3	7.89%
Ceftriaxone	3	7.89%
Cefuroxime + Macrolide	2	5.26%
Cotrimoxazle	2	5.26%
Penicillin	2	5.26%
Others	3	7.89%
Cat 4 (n=46)		
Cefuroxime	15	32.6%
Beta-lactam/Beta-lactamase inhibitor	13	28.26%
Ciprofloxacin	6	13.04%
Ceftazidime	3	6.52%
Ceftazidime + Macrolide	2	4.34%
Penicilline + Aminogylycoside	1	4.34%
Ampicillin + Aminoglycoside	1	2.17%
Cephalexin + Aminoglycoside	1	2.17%
Cefuroxime + Aminoglycoside	1	2.17%
Others	2	4.35%

Table 4 shows the outcome of patients who received treatment for community-acquired pneumonia that was either consistent or inconsistent with the ATS guidelines. Overall, there was a statistically significant difference between the treatment following the ATS guidelines and the treatment that was inconsistent with the ATS in terms of all the outcomes measured. By category, however, there was only a statistically significant difference between the treatment following the ATS guidelines and the treatments that were inconsistent with the ATS guidelines

in terms of all the outcomes measured. By category, however, there was only a statistically significant difference between the two treatment groups in Category 3, in terms of the time of improvement of clinical symptoms. This table also shows the low percentage of treatment regimens adhering to the ATS guidelines over-all (49.21%), and in categories 1 (49.2%) and 4 (17.4%).

Table 6 shows the clinical characteristics of patients who died due to pneumonia. Eleven of the 15 patients (73%) were more than 60 years old, with 60% of the cases having multiple comorbid factors. Tachypnea (RR>30) was seen in 80% of cases, while metabolic acidosis was seen in 53% of cases. More than half were admitted at the ICU on admission.

Table 6. Clinical Characteristics of Patients Who Died Secondary to Pneumonia

	Number	%
Age		
≤ 60 y/o	4	26.67%
> 60 y/o	11	73.33%
Sex		
Male	7	46.67%
Female	8	53.33%
Comorbid Factors		
Single	6	40.00%
Multiple	9	60.00%
Presence of S/Sx Specified as Risk Factors		
RR > 30	12	80.00%
T>38.3	10	66.67%
Hypotension	5	33.33%
Decreased sensorium	4	26.67%
Laboratory Predictors		
Unfavorable x-ray	5	33.33%
WBC <4,000 ; >30,000	5	33.33%
pO_2<60; pCO_2>50	7	46.60%
Azotemia	4	26.67%
Anemia	3	20.00%
Metabolic Acidosis	8	53.33%
Others		
Need for MV		
Oliguria/Anuria		
Need for vasopressors		
Admission in ICU	8	53.33%

Discussion

Despite the several published reports and recommendations[1,13,15-18] on the management of community-acquired pneumonia, diagnostic and therapeutic interventions by the physicians have remained varied. Clearly, our study shows that the majority of the attending physicians at UERMMMC have different approaches to this common but serious problem. Majority do not adhere to the recommendations given by the American Thoracic Society. This finding is consistent with the finding of Wennberg[11] and Fine.[12] There were no absolute criteria or guidelines being followed in this important task in the initial management of CAP. As observed in the past, physicians often rely on their subjective impressions of a patient's clinical appearance in making that initial decision regarding the type of care.[12] Physicians tend to overestimate the risk of death in patients with pneumonia, and these overestimates are associated with the decision to hospitalize patients at low risk.[19,20] Our study has shown that adherence to the ATS guidelines should lower the rate of hospital admission, and subsequently lower costs of therapy. In addition, the choice of parenteral betalactam/beta-lactamase inhibitors as first line agent in our study proved the overestimation made by the attending physicians for patients that can be categorized as low risk (Category 1), and compound the problem of cost effectiveness of the therapeutic intervention.

Non-adherence to the ATS guidelines may also impose danger to our admitted patients. In our study, half of the admitted patients in the general ward, who, satisfied the criteria for admission, should have been categorized as high risk . The initial decision to admit patients to the ICU should make us aware that these patients should be watched closely and managed accordingly. As shown in previous studies, the mortality rates for severe community-acquired pneumonia may go as high as 47 to 76%.[21,22] Although we have seen treatment success with

the use of drugs not recommended by the said guidelines,[15] we have clearly showed that compliance to the guidelines have significant correlation with positive outcome measures.

Another serious problem uncovered by our study, is the limited influence of bacteriologic studies in the management of CAP. Previous studies have reported this perennial problem of underutilization of bacterial cultures,[23,24] and many physicians seemed to be unaware of the value of such diagnostic work-up. Even though thorough investigations for the responsible etiologic organism would still yield negative results,[13] the ATS guidelines, as well as other reports, emphasize the need for such work-up to provide our patients optimal and cost effective care.[1,13]

Conclusions

In this prospective study, non-conformity with the guidelines set by the American Thoracic Society in the initial management of community-acquired pneumonia was shown to occur frequently. An information campaign is hereby recommended, so that guideline can be utilized in the cost-effective management of community-acquired pneumonia.

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A Comparison Of Indices Of Gastric Erosion In Rats Given Aspirin, Aspirin + Misoprostol, Meloxicam And Placebo

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Abstract

Twenty four adult female Sprague-Dawley rats were weighed and randomly allocated into four groups. Group one received a placebo in the form of 0.5 cc distilled water twice daily. Group 2 received aspirin at 54 mg/kg body weight/day divided into two daily doses. Group 3 received aspirin at 54 mg/kg body weight /day and misoprostol at 36 mcg / kg body weight / day divided into 2 daily doses. Group 4 received meloxicam at 0.675 mg / kg body weight in a once daily morning dose and 0.5 cc of distilled water administered in the afternoon. All medications were dissolved in 0.5 cc of distilled water and were administered using a gavage tube for 7 days. On the eighth day, all rats were sacrificed using chloroform overdose. The stomach and duodenum were excised and opened along the greater curvature, gently cleaned with saline and placed in formalin. Specimens were grossly and microscopically reviewed by a pathologist blinded to the study medications and were scored according to a predetermined gastric erosion index. Group mean erosion indices were computed and were tested for variance. A significant difference between at least two of the group mean erosion indices was detected (f=4.0, α=0.05). Duncan's multile range test showed that both the aspirin and the meloxicam groups had significantly greater mean erosion indices compared to the placebo group (α= 0.01). The mean erosion index of the group which received aspirin + misoprostol was significantly lower compared to the group which received aspirin alone and the group which received meloxicam (α= 0.01). Based on these results, it appears that the prototype combination of aspirin + misoprostol provides better gastric mucosal protection in the rat compared to meloxicam.

Introduction

NON-STEROIDAL ANTI- INFLAMATORY DRUGS (NSAIDs) are commonly sold over the counter for the relief of various aches and pains. Each year, physicians write approximately 60 million NSAID prescriptions[1]. Because of the magnitude of patient exposure, gastrointestinal and other side effects of NSAIDs are a significant clinical concern.

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Regular use of NSAIDs is associated with the development of gastric erosions, ulcers and even gastrointestinal hemorrhage. Users of NSAIDs have approximately three times greater relative risk for developing serious adverse gastrointestinal events than non-users. Additional risk factors include age greater than 60 years, previous history of gastrointestinal events and concomitant corticosteroid use. The risk for serious gastrointestinal events appears to be equal among men and women[2]. These complications significantly increase the overall cost of chronic treatment with NSAIDs.

Many medications are often concomitantly prescribed with NSAIDs in an attempt to offer a

degree of protection to the gastric and duodenal mucosa. H_2 receptor antagonists and proton pump inhibitors are commonly prescribed over sucralfate and antacids because of the common belief that the latter two decrease the absorption of the NSAID, a belief that has been largely disproven[3]. However, numerous studies have proven the efficacy and superiority of misoprostol, a prostaglandin E1 analogue, over antacids, H_2 receptor antagonists and proton pump inhibitors in the prevention of both gastric and duodenal ulcers[4,5,6,7,8,9,10,11].

However, co-administration with misoprostol significantly increases the cost of treatment (PhP13.35/200 mcg tablet) since it must be administered during the entire treatment at a minimum dose of 200 mcg BID. When combined with aspirin at a dose of 600 mg/day, the daily cost of treatment and prophylaxis amounts to PhP29.70. When NSAIDs such as naproxen, diclofenac and piroxicam are used in conjunction with misoprostol, daily treatment cost with minimum recommended dose increases to PhP43.50, PhP43.80 and PhP47.70 respectively[12]. Meloxicam, an NSAID belonging to the enolic acid group, was recently introduced into the market. It differs from other NSAIDs in its preferential inhibition of cyclooxygenase-2 (COX-2) over cyclooxygenase-1 (COX-1)[13] with efficacy in analgesia and anti-inflamatory activity comparable with other NSAIDs[14] but with fewer adverse gastrointestinal events[15,16,17,18,19,20,21,22]. Like other NSAIDs, its absorption is not affected by concomitant use of H_2 receptor antagonists and antacids[23,24] and its long half-life (20 hours) makes once daily dosing possible, ensuring better compliance with treatment. At a cost of PhP16.00 per 7.5 mg tablet, this new NSAID may offer a more economical alternative to the previously mentioned treatment regimens which combine the NSAID with misoprostol. With the relative difficulty of procuring misoprostol which came about because of steps taken to decrease its illegal use as an abortifacient, physicians often have to make do with concomitant administration of H_2 receptor antagonists or proton pump inhibitors as prophylaxis against adverse gastrointestinal events - therapy which has been shown to be ineffective prophylaxis against gastric ulcer formation[4,5,6,7]. The availability of an NSAID that possesses "mucosal sparing" comparable with combination therapy using NSAIDs and misoprostol offers the advantages of a single drug, once-daily regimen which is also cheaper and easier to procure. Whether meloxicam is this NSAID is the question which this study seeks to answer.

Objectives

General Objective

To compare the degree of gastric mucosal injury (gastric erosion index) of a group of rats given Meloxicam for one week with that of other group of rats given Aspirin + misoprostol for the same duration.

Specific Objectives

1. To determine the individual and mean gastric erosion index in a group of 6 Sprague-Dawley rats given 0.5 cc af distilled water daily (10 hours apart) as placebo for a period of one week.
2. To determine the individual and mean gastric erosion index in a group of 6 Sprague-Dawley rats given Aspirin at 54 mg/kg body weight divided into 2 doses (10 hours apart) with each dose dissolved in 0.5 cc of distilled water for a period of one week.
3. To determine the individual and mean gastric erosion index in a group of 6 Sprague-Dawley rats given Aspirin at 54 mg/kg body weight with misoprostol at 36 mcg/kg body weight divided into 2 doses (10 hours apart) with each dose dissolved in 0.5 cc of distilled water for a period of one week.
4. To determine the individual and mean gastric erosion index in a group of 6

Sprague-Dawley rats given Meloxicam at 0.675 mg/kg body weight dissolved in 0.5 cc of distilled water given once daily with 2 cc of distilled water given 10 hours apart for a period of one week.

Methods

Twenty-four adult female Sprague-dawley rats were obtained for the study and were randomly allocated into 4 groups as follows:

Group 1 : Placebo
Group 2 : Aspirin
Group 3 : Aspirin + Misoprostol
Group 4 : Meloxicam

The rats were designated A,B,C,D,E, and F within each group and were housed in identical containers in the same room. All rats had access to food in the form of pigeon pellets and water ad libitum. Each rat was weighed at the start of the study. Upon initiation of the study, the following regimens were administered to the groups of rats for a period of 7 days:

1. Group 1 received 0.5 cc of distilled water using a gavage tube with rats recieving their doses in alphabetical order starting at 7:00 A.M. each day. A second dose of 0.5 cc distilled water was administered using the same gavage tube at 5:00 P.M. with the rats receiving the dose in the same order as at 7:00 A.M.
2. Group 2 received Aspirin at 54 mg/kg body weight divided into 2 daily doses with each dose dissolved in 0.5 cc of distilled water. The first dose was administered to the rats in alphabetical order via gavage tube immediately following the completion of the administered doses in Group 1. The second dose was administered in the afternoon also in alphabetrical order immediately following the completion of the administered doses on Group 1.
3. Group 3 received Aspirin at 54 mg/kg body weight and misoprostol at 36 mcg/kg body weight divided into 2 daily doses with each dose dissolved in 0.5 cc of distilled water. The first dose was administered to the rats in alphabetical order via gavage tube immediately following the completion of the administered doses in Group 2. The second dose was administered in the afternoon also in alphabetical order immediately following the completion of the administered doses in Group 2.
4. Group 4 received Meloxicam at 0.675 mg/kg body weight in a once daily doses dissolved in 0.5 cc of distilled water administered to the rats in alphabetical order via gavage tube immediately following the completion of the administered doses in Group 3. 0.5 cc of distilled water was then administered in the afternoon in alphabetical order immediately following the completion of the administered doses in Group 3.

Each group had separate syringes, gavage tubes and bottles of distilled water. On the eighth day, all rats were sacrificed using chloroform overdose. The stomach and duodenum of each rat were excised and opened along the greater curvature and gently cleaned with NSS. Specimens were placed in identical containers with 10 % formalin and assigned a specimen number for identification which was recorded in the corresponding rat's data sheet. Each specimen was examined grossly by a pathologist who was blinded to the groupings. Findings were entered in a different specimen data sheet (no group identification data). Specimens were sectioned and examined microscopically by the same pathologist. Findings on microscopy were then entered in the same data sheet. The total score of each specimen comprised its erosion index (Table 1). The erosion indices were then copied from pathologist's data sheets to the rat's data sheets corresponding to theirs pecimen numbers. The data was then collated and tabulated.

Definition of Terms

The gastric erosion index as utilized by Andal, et al.[28] was also utilized in this study. Erosion scoring was performed in accordance with the definitions and standard terms set by the World Congress of Gastroenterology[25] in 1990 (Sydney classification of Gastritis) where appropriate:

Normal Mucosa Gastric lining is an even pink color with a uniform smoothness and luster.

Erosion A break in mucosal continuity which may be grossly visible (macroscopic) or apparent only on microscopy (microscopic). These may be flat or raised.

Opacity Mucosal vessels are grossly not visible.

Translucency Mucosal vessels are grossly visible.

Hemorrhage May range from punctate ecchymoses on the mucosa to the presence of blood clots within the stomach lumen.

Results

The weights of the study rats ranged from 149g to 197g with a mean weight of 171.1g. The mean weight of each study group was computed and compared with the others. Analysis of variance (Appendix B) did not detect any significant difference between the mean weights of the 4 study groups ($f=0.018$, $\alpha=0.05$). All rats tolerated the administration of study medications well and survived up to the conclusion of the experiment. Erosion indices were obtained and group mean

Table 1. A Comparison of Indices of Gastric Erosion in Rats Given Aspirin, Aspirin + Misoprostol, Meloxicam and Placebo: Drug Dose, Erosion Index and Group Means

Group	Rat	Weight (grams)	Drug Administered (per day) Aspirin	Misoprostol	Meloxicam	Erosion Index	Group Mean
I	A	168	-	-	-	0	0.83
	B	158	-	-	-	1	
	C	179	-	-	-	1	
	D	158	-	-	-	1	
	E	166	-	-	-	1	
	F	183	-	-	-	1	
II	A	194	10.5mg	-	-	2	2.0
	B	185	10.0 mg	-	-	3	
	C	163	8.8 mg	-	-	1	
	D	151	8.2 mg	-	-	2	
	E	180	9.7 mg	-	-	2	
	F	160	8.6 mg	-	-	2	
III	A	167	9.0 mg	6.0 mcg	-	1	0.83
	B	162	8.7 mg	5.8 mcg	-	0	
	C	197	10.6 mg	7.1 mcg	-	2	
	D	165	8.9 mg	5.9 mcg	-	1	
	E	167	9.0 mg	6.0 mcg	-	0	
	F	168	9.1 mg	6.0 mcg	-	1	
IV	A	149	-	-	0.10 mg	2	2.0
	B	160	-	-	0.11 mg	3	
	C	183	-	-	0.12 mg	3	
	D	182	-	-	0.12 mg	3	
	E	166	-	-	0.11 mg	0	
	F	186	-	-	0.13 mg	1	

erosion indices and standard deviations were computed and tabulated (Table II). It was noted that grossly visible erosions, ulcerations, evidence of hemorrhage or necrosis were not seen in any of the study groups. Findings consisted mainly of microscopic erosions, translucency, decrease in mucosal thickness and mild inflammation. Mean erosion indices were noted to be lower in the placebo and aspirin + misoprostol groups compared to the aspirin and meloxicam groups. The mean erosion index of the placebo group was identical to that of the aspirin + misoprostol group while the mean erosion index of the aspirin group was identical to that of the meloxicam group. A greater variability in index results was also noted in the meloxicam group ($s = 1.26$). Analysis of variance for the erosion indices (Appendix C) detected a significant difference in at least 2 of the group means ($f = 4.0$, $\alpha = 0.05$). On post-hoc comparison, Duncan's multiple range test (Appendix D) showed that both the aspirin and meloxicam groups had significantly greater mean erosion indices compared to the placebo group ($\alpha = 0.01$). The mean erosion index of the group which received Aspirin and misoprostol was significantly lower compared to the group which received aspirin alone and the group which received meloxicam ($\alpha = 0.01$). All other group pairs showed no significant difference between their mean erosion indices.

Discussion

In designing this study, efforts were made to ensure the uniformity and comparability of the study groups. The study animals were housed in identical cages in the same room, fed the same kind of food and had access to food and water ad libitum. All groups received study-related manipulation (gavage tube insertion) twice a day. With regard to aspirin and meloxicam, the respective minimum anti-inflammatory adult human dose was obtained and the equivalent dose in the rat was computed.[26] For misoprostol, the adult human anti-ulcer prophylactic dose of 200 mcg BID was utilized and the equivalent dose in the rate computed. Since maximal acute mucosal injury with aspirin occurs within one week. 25 of daily aspirin intake in rats, the duration of drug administration for the study was limited to 7 days.

The results of the study pertaining to the addition of misoprostol as prophylaxis for aspirin administration were consistent with previously established data in both rat and human studies. Gastric mucosal injury as evidenced by microscopic erosions, thinning of the mucosa and translucency was documented in the rats which received aspirin alone, resulting in a mean erosion index which was significantly greater that than of the placebo group. In contrast, the rats which received the combination of aspirin and misoprostol appeared to have benefited from the addition of the prostaglandin analogue, producing a mean erosion index which was significantly less than that of the rats which received aspirin alone. These results demonstrated the protective effect of misoprostol in NSAID related gastric mucosal injury in the rat, providing the study with its benchmark for comparison.

The group which received meloxicam produced a mean erosion index which was higher than the groups which received placebo and aspirin + misoprostol and was equal to that of the group which received aspirin alone. On statistical testing, the meloxicam group did not produce a significantly lower mean erosion index compared to the aspirin group, in contrast to the aspirin + misoprostol group which was able to produce a mean erosion index which was significantly lower compared to the aspirin group. The meloxicam group's mean erosion index was also signficantly greater compared to the aspirin + misoprostol group. This result is indicative of the superiority of gastric mucosal protection in the rat provided by co-administration of misoprostol with NSAIDs over the selective COX-2 inhibition of meloxicam.

These results, although disappointing, are not contradictory to previous data in both rat

and human studies involving meloxicam. It must be remembered that all previous studies compared meloxicam with other NSAIDs such as piroxicam, diclofenac and naproxen with the former comparing favorably in terms of adverse gastrointestinal events (symptoms and documented injury). Although meloxicam was consistently superior to the other NSAIDs in this aspect, no previous comparisons were made with an NSAID/ misoprostol combination.

Conclusion

Based on these results, it is concluded that althought meloxicam may provided a greater degree of gastric mucosal sparing compared to other NSAIDs as proven by previous studies in rats and humans, it's gastric mucosal sparing in rats does not approximately nor favorably compare with the gastric mucosal protection provided by the prototype combination of aspirin + misoprostol. Whether the results of this rat study are predictive of the results in man remains to be assessed by a future study in humans. Although the results of this study do not favor meloxicam, its role as the first of a new generation of selective COX-2 inhibitors has already earned it a niche in the armamentarium of NSAIDs. And although the world may still be a long way from finding the non-dyspeptic, non-ulcerogenic NSAID, the introduction of meloxicam has perhaps shortened the time to the realization of that goal.

Limitations of the Study

The foremost limitations of this study is its applicability to humans. Although results in animal studies are often similar to the results in humans, these results cannot be accepted as predictive of results in human trials without the benefit a proper study in humans. In the context of studies in rats, the evaluation of gastric mucosal injury was limited to that of acute mucosal injury (within one week) and may not necessarily predict the outcome of longer studies dealing with chronic intake of these same medications. Lastly, only the equivalent minimum anti-flammatory dose of aspirin and meloxicam in rats was evaluated in this study. As documented in previous studies, gastric mucosal injury is dose-related in so far as NSAID use is concerned. The results of a comparison between equally efficacious higher doses of these drugs and their combination with misoprostol may not necessarily be in agreement with the results of this study.

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An In-Vivo Study on the Effect on Psychosis of the Crude Seed Extract of Swietenia macrophylla King (mahogany) on Mus musculus (Albino mice)

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Abstract

For the acute toxicity study, the extract from swietenia macrophylla King seeds were administered to 30 two-month old Albino mice, five males and five females per dose level) by gavaging at constant volume after 12 hours of non per orem and prepared in three dosages: 10, 20, 40 grams of seed extract per kilogram body weight of the mouse. Using the logarithmic probit graph method of Miller and Tainter, the LD50 was computed to be 50 grams of seeds extract per kg body weight of the mouse. Using One-way ANOVA at 95 % confidence level, significant differences across treatment groups were seen in the following observed parameters: motor activity depression and fine body tremors.

Twenty two-month old male Albino mice were randomly grouped to monitor any antipsychotic effects of mahogany. They were grouped accordingly into random blocks of placebo, 20 g/ kg, 40 g/kg and chlorpromazine. Drug-induced alterations in behavior were monitored though changes in escape response and avoidance response time. A general suppression of the avoidance response was evident after the administration of the mahogany extract and chlorpromazine. Analysis of variance show that mahogany approximates the action chlorpromazine. The suppression of Swietenia macrophylla of the avoidance response is a strong indication of its antipsychotic properties.

Introduction

Psychosis

The first anti-psychotic drug that relieved signs and symptoms of psychosis by suppression of spontaneous movement and complex behavior rather than merely producing sedation was chlorpromazine, a phenothiazine derivative. From then on, more anti-psychotic drugs that have increased or decreased potential for causing extrapyramidal effects have been discovered.

Herbal medicine as an alternative to the more expensive drugs which are currently available in the market has been one of the foci of medical research in the Philippines today. This research would provide valuable information that may be used in medical practice especially in treating psychosis-related psychiatric disorders.

Swietenia macrophylla seed extracts have not been studied or verified to date with regards to its CNS depressant effects, particularly its antipsychotic effects. This study will scientifically demonstrate the potential of mahogany seeds as an antipsychotic agent. If the results of this study prove to be positive, it would provide a more affordable and readily available drug for use as an antipsychotic agent.

Swietenia macrophylla

The seeds of *swietenia macrophylla* are used for the treatment of hypertension, diabetes, and malaria as a folk medicine in Indonesia (Kadota

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et. al., 1990). In Malaysia, natives and common folks chew and swallow the seeds in "curing" high blood pressure (Chan et. al.,1976)

In UERMMMC, a study conducted by Castro et. al. (1995) showed significant hypotensive effect of ethanolic extract of the seeds of *Swietenia mahogany* on normotensive Spague-Dawley rats (SDR).

Oral acute toxicity study of the crude seeds extract of *Swietenia macrophylla* King (mahogany) on *Mus musculus* showed significant loss of righting reflex, ataxia, changes in respiratory rate, hindleg paralysis, foreleg and hindleg screen grip loss. The decrease in spontaneous motor activity, analgesia, abdominal gripping, and ataxia, all point to an effectiveness of the substance on the central nervous system (Geronimo, et. al. 1996).

These findings suggest the need exploring the central nervous system (CNS) depressant affect of the mahogany, particularly its effect on psychosis on *Mus musculus.* It is then the goal of this experiment to determine the effect on psychosis on the crude seed extract of *Swietenia macrophylla* (mahogany) on *Mus musculus* (Albino rats). Specifically, the Approximate Lethal Dose (ALD) and Median Lethal Dose (LD_{50}) of *S. macrophylla* were determined through Probit Analysis by Fischer and Yates Method and adverse effects using F. Sandberg's Multidimensional Screening method. The effects on psychosis of varying concentrations of *S. macrophylla* though the Pole Climbing Test as compared to Chlorpromazine were also determined.

Methodology

Preparation of S. macrophylla seeds

The mahogany seeds were obtained from the Manila Seedling Bank. The seeds were chosen according to the following requirements: normal appearance for the plant species; whole, i.e. no part of the seed is eradicated or damaged: free from invasion of internal and external diseases; practically clean and free from foreign smell or taste.

A total amount of 1.08 kg of the seeds of *Swietenia macrophylla* was coarsely ground. The ground plant material was covered with distilled water in a glass vessel and boiled for thirty minutes, cooled to room temperature and filtered. Filtrate was filtered using cheesecloth. The mark after filtration of the first extract was then boiled again with approximately the same quantity of distilled water, this time the boiling was continued for one to two hours and then filtered through cheesecloth. The combined extract was let to stand overnight. On the next day, the liquid part was decanted, and passed through filter paper. The total volume reached 1.6 liters. The solvent in the filtered extract from the preceding step was removed by rotavap. The total amount of the final extract is 104 ml.

ALD_{50} Determination

Ten adult Albino mice, fasted for 8 hours, were randomly allocated into five groups of two (1M/1F). An arbitrary dose was designated as the initial dose of the extract from S. macrophylla and was given by oral gavage to four groups. The fifth group received 5% polyvinylpyrolidone by oral gavage and served as control.

The dose level was increased logarithmically using a 0.6 log interval and was administered to the assigned groups until two consecutive doses were obtained in which the lower dose did not produce any toxic effects, whereas the higher dose produce death in the group. The LD_{50} was presumed to be within this range of values, corresponding to ALD.

Twelve hours after drug administration, food and H_2O were made available to the mice. The mice were observed every 2 hours for the first 8 hours after drug administration for changes in behavior, vital signs and the number of deaths. Observations were then done once daily for seven days at convenient time intervals.

LD_{50} Determination

Forty adult *Albino* mice were randomly allocated into four groups of ten (5M/5F). Three groups

received different dosage of mahogany extract by oral gavage and the fourth group served as a control and was given 5% PVP by oral gavage. Dosing was based on the LD_{50} as determined in the exploratory phase. One group was given the low dose by oral gavage, another the medium dose and the third group the high dose. LD_{50} was determined by the Method of Probits using the Fischer and Yates table.

Observation Phase

Observations were made every 2 hours for the first 8 hours after drug administration, then once daily for 7 days at convenient time intervals. Behavioral changes were observed using parameters from the F. Sandberg's Multidimensional Screening Method.

Determination of Antipsychotic affect

This method was devised by Dr. Horacio Estrada (1966). Twenty mice (all males) were randomly selected, weighed, and divided into four treatment groups. The tails were coded for proper identification with indelible markers. Each mouse was placed in a conditioning cage with an electrified grid floor. A platform was positioned in the cage such that the mouse maybe trained to avoid electric shock by jumping onto the platform. The mouse was placed in the conditioning cage for one minute. A bell was rung for 2 seconds. After 3 seconds, the mouse was electrified for 5 seconds. The current was turned off as soon as the mouse jumped onto the platform. The jumping of the mouse onto the platform upon electric shock is an unconditioned response or an escape behavior. The jumping of the mouse onto the platform upon hearing the bell is a conditioned behavior or an avoidance behavior. This procedure was repeated three times within one session. The procedure was repeated in subsequent sessions until the conditioned response of jumping onto the platform after the ringing of the bell was established.

After the mice were conditioned, the recording of data began. The mouse was placed in the conditioning cage for one minute. A bell was rung 2 seconds. The time it took for the mouse to jump to the platform after the bell was rung was recorded. This procedure was repeated ten times for each mouse.

Each mouse received an oral gavage corresponding to its treatment group. Each group received one of the following, reconstituted to equal volumes of 0.5 ml: 5% PVP, chlorpromazine, and 20 g per kg body weight mahogany extract, and 40 g per kg body weight mahogany extract. Thirty minutes after administration, behavioral studies were performed again. The time of response before and after treatment was compared.

The experiment proper involved the analysis of the effect of the test drug on psychosis as compared to that of the positive control drug (chlorpromazine) and a control (5% PVP). Analysis was done via the One-way Analysis of Variance.

Results

Based on the determination of the approximate Median Lethal Dose, at 20 g of seed extract/kg body weight of mouse, a 20% mortality was obtained.

Using One-Way ANOVA, significant differences between groups were noted in the following parameters (Table 1):

Table 1. Tabulation of Significant Findings (F. Sandberg's Test)

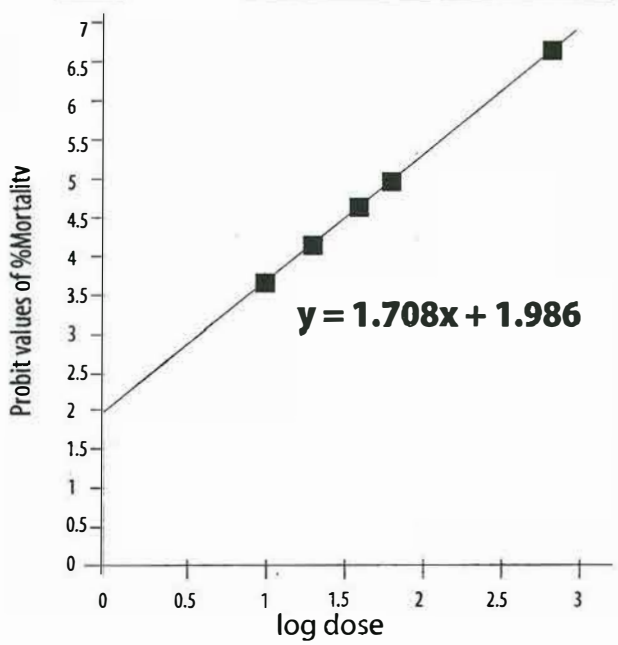
	Control vs. Low	Control vs. Middle	Control vs. High
Loss of righting reflex			
Ataxia			
Analgesia			
Respiratory rate			
Loss of corneal reflex			
Coarse body tremors			
Fine body tremors			X
Paralysis: hind leg			
Screen grip: hind leg			
Screen drip: front leg			
Motor activity depression		X	X
Startle response			
Convulsion			
Exophthalmos			
Hyperemia			
Salivation			
Pilomotor erection			
Robichaud test			
Abdominal gripping			
Diarrhea			
Excess curiosity			

For motor activity depression, a significant difference was noted between the control and the medium dose, F(1,20)=5.3333, Mse=0.0052, Fprob=4.4940.

For fine body tremors, a significant difference was noted between the control and the high dose, F(1,20)=4.9526, Mse=0.1868, Fprob=4.5431.

The LD_{50} (Figure 1) was determined to be 50 g of seed extract per kg body weight of the mouse. From this, the toxic dose, which would cause death in 95% of the population was extrapolated to be 95 g of seed extract/kg body weight of mouse.

Figure 1. Extrapolation of Median Lethal Dose



The mortality rate due to treatment was 40% for the high dose, 20% for the middle dose, 10% for the low dose, and 0% for the control (Table 2).

Table 2. Percent Mortality Per Dose Mahogany, LD50 Determination

Treatment	Dose (g seed extract per kg body weight of mouse)	% Mortality
5% PVP	0	0
Mahogany	10	10
Mahogany	20	20
Mahogany	40	40
Mahogany	50*	50*
Mahogany	95*	95*

**extrapolated values are based on Fischer and Yates Probit Logarithmic Graph (see Figure 1).*

Results revealed that chlorpromazine, 20g and 40g of mahogany seed extract per kg body weight of mouse suppressed avoidance response. Administration of 5% PVP had no effect on the avoidance response (Tables 3,4, and 5).

Table 3. General Findings with Respect to Avoidance Response

Treatment	Before Treatment	After Treatment
5% PVP	3.385	3.278
Chlorpromazine	3.032	suppression
Mahogany, 20 g	3.67	suppression
Mahogany, 20 g	2.322	suppression

Table 4. General Findings with Respect to Escape Response

Treatment	Before Treatment	After Treatment
5% PVP	0	0
Chlorpromazine	0	2.02*
Mahogany, 20 g	0	0
Mahogany, 20 g	0	7.584*

**based on statistical analysis, no marked difference*

Table 5. General Findings with Respect to Avoidance and Escape Response

Treatment	Avoidance Response	Escape Response
5% PVP	no difference	no difference
Chlorpromazine	suppression	suppression
Mahogany, 20 g	suppression	no difference
Mahogany, 40 g	suppression	suppression

Findings revealed that chlorpromazine and 40g/kg body weight of mahogany suppressed escape response. This dosage of mahogany approximates the action of chlorpromazine on the escape response. Administration of 5% PVP and 20g/kg body weight of mahogany had no effect on the escape response (Tables 3, 4, and 5).

Discussion

To obtain comprehensive and physically pertinent data regarding the effects of the mahogany extract on the whole body, the following parameters using the F. Sandberg's Multidimensional Screening method were determined and the results between the control and the mahogany extract were tested for statistical significance by ANOVA. Presence is determined by the F-value and the F-critical.

If the F-value is greater than the F-critical, then there is a significant difference between the causation of the outcome by the control and the mahogany extract and a relationship can be established between the outcome and the mahogany extract. If the F-value is less than the F-critical then a relationship between the outcome and the mahogany extract cannot be established. Significant differences between treatment groups in the motor activity depression and fine body tremors strongly indicate the antipsychotic potential of mahogany.

Central nervous functions on which an antipsychotic drug may take effects comprise of two parameters: spontaneous motor functions and behavior alterations. Significant depression of these two aspects without the induction of toxic syndromes suggests the antipsychotic potential of a drug.

To assess behavior activities, demonstrations were made exhibiting a differential sensitivity in suppressing the avoidance behavior and the escape behavior. Mahogany extract clearly suppresses the avoidance behavior more readily than the escape behavior therefore supporting the antipsychotic characteristic of the extract. Mahogany extract also approximates the effects of chlorpromazine as shown by the data (refer to Tables 3, 4, 5).

Conclusion

The computed Median Lethal Dose of *Swietenia macrophylla* was 50 g of seed extract/kg body weight. The demonstration that *Switenia macrophylla* can more readily suppress avoidance behavior (bell) than escape behavior (electric shock) is a strong indication of its antipsychotic property. Mahogany, at 40 g/kg body weight approximates the antipsychotic property of chlorpromazine.

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Use of Computed Tomography in the Pre-treatment Assessment of Gallstone Type†

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Abstract

The chemical composition of gallstone is of major importance in selecting for nonsurgical therapy. The densities of forty gallstone were evaluated by computed tomography (CT) and subsequently subjected to chemical analysis for stone composition. In general, cholesterol stones had negative attenuation values while pigment stones had positive attenuation numbers. The mean CT number (Hounsfield Unit) was significantly different for cholesterol and pigment stones (-88.4117 vs 104.3304 HU). The accuracy of CT in predicting predominant cholesterol composition if gallstones was 88.2 percent and in predicting pigment stones was 82.6 percent. These findings suggest that gallstone imaging using CT scan can predict gallstone composition and could play a role in selecting patients for nonsurgical theraphy.

Key words: *computed tomography, gallstone.*

STUDIES ON THE NATURAL history of gallstone diseases indicate that from 40-60 percent of all persons with gallstone are asymptomatic.[1] Aside from surgery, other treatment options for these patients are observation, dissolution, fragmentation and a combination of fragmentation and dissolution. These alternative treatment approaches are primarily tailored for patients in Western countries where 75 percent of all gallstone are formed completely or predominantly of cholesterol.[2] Observation has been an accepted form of management since only 10-30 percent of these patients subsequently develop symptoms.[3] However, nonsurgical forms of therapy such as chemolitholysis and lithotripsy are only effective for cholesterol stones.

In contrast, 28-70 percent of gallstone in the Orient are pigment stones.[4] Such stones are usually found in association with infected bile with bacteria that have B- glucoronidase activity. Sometimes, eggs or fragments of cuticles of ascaris lumbricoides, act as nuclei for precipitation of calcium bilirubinate. Because of the predominance of pigment stones and its etiologic association with infection, nonsurgical therapy of gallstones has not gained wide acceptance among Orientals.

Recent studies however, have found that the incidence of pigment stones among Orientals had been decreasing and that there had been an increasing number of individuals who have cholesterol stones.[5] With this apparent shift in the prevalence of stone types, nonsurgical forms of therapy should begin to play a role in the management of gallstone in the Oriental population. Although it is not proposed as the principal mode of management, nonsurgical therapy would probably have its greatest application for patients not suitable for surgery.

Previous attempts at non-invasive differentation of cholesterol from pigmant stones using flat plate abdominal radiography, oral cholecystography and ultrasound have met with limited success. Since computed tomogra-

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phy (CT) is capable of detecting subtle differences in density, the authors embarked on this study to determine if it would be possible to predict gallstone composition with confidence.

Methods

Forty gallstones were obtained and stored in normal saline solution. The stones ranged in size from 4 mm to 30 mm. CT scans of the stones were obtained with a Hitachi W450 (1990) at settings of 1200 KV and 100 ma. Sections of 10 mm thickness were made.

In vitro CT examination was performed in a glass containing water. Water, which has an attenuation value of 10 - 15 Hounsfield units (HU) was chosen as a suspension agent to standardize the background density seen on the CT images. This is within the reported range of CT attenuation values for bile (5 - 25 HU).[6]

A region of interest was chosen by use of the cursor. After magnification of the scan by a factor of 10, the scanner's cursor was used to determine the representative CT attenuation of each stone as expressed in Hounsfield units (HU). Separate density readings were obtained from within the stone to encompass all parts of the stone and an average density was obtained.

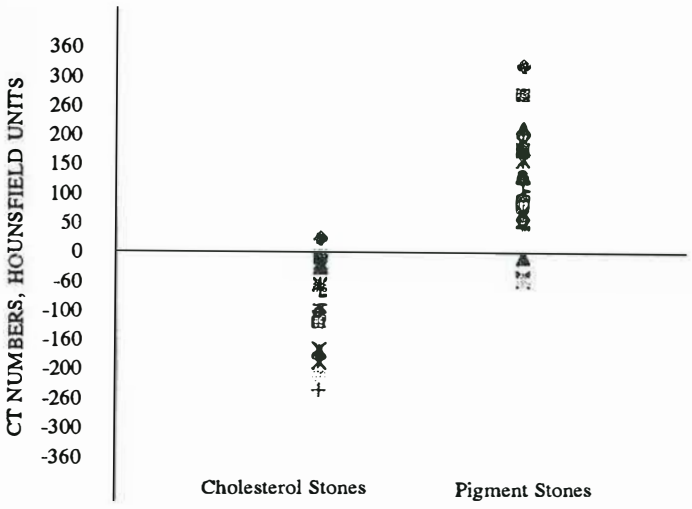
After imaging, the gallstones were analyzed en bloc by qualitative stone analysis. Stone samples were pulverized and desiccated to constant weight. Dried gallstone powder was then extracted with ether and chloroform. The presense of cholesterol was indicated by the appearance of a dark green color in the De Liebermann-Burchard reaction with addition of acetic anhydride and sulfuric acid. The presence of bilirubin was indicated by a pink to purple color after treatment with diazo reagent. Stones were then categorized as pigment or cholesterol. The chemical analysis of the gallstone composition served as the standard of reference.

Relationships between CT numbers and chemical composition were then analyzed using student's T-test at .05 level of significance.

Results

Figure 1 shows the distribution of the different types of gallstones with the CT number for each type.

Figure 1. Computed tomographic (CT) values (Hounsfield units) for cholesterol and pigment gallstones.



Mean values are significantly different ($p<0.05$)

Of the forty stones analyzed, seventeen (17) were classified as cholesterol stones. The range of CT numbers was from -234 HU to +44 HU. The average CT attenuation value for this group was -88.41 HU. Twenty-three (23) stones were of the pigment type. The range of CT numbers was from -49.1 HU to +319 HU. The mean CT number for the group was 104.33 HU ($p = < 0.05$).

Samples classified as cholesterol stones by chemical composition were noted to have CT numbers less than 44 HU and pigment stones were found to have CT numbers greater than -49 HU. There existed a range (+44 to -49 HU) within which one may not be able to accurately predict the predominant stone component based on CT attenuation value.

Table 1 shows that using the CT scan, with chemical analysis of the gallstone as gold standard,

the positive predictive value was 82.6 percent and the negative predictive value was 88.2 percent.

Table 1. Sensitivity, Specificity and Predictive Values of Computed Tomography in Determining Gallstone Composition

		Stone Analysis		
		Pigment	Non-Pigment	Total
Computed Tomography	Pigment	19	4	23
	Non-Pigment	2	15	17
	Total	21	19	40

Sensitivity: 19/21 = 90.5%

Spexcificity: 15/19 = 78.9%

Positive Predictive Value: 19/23 = 82.6%

Negative Predictive Value: 15/17 = 88.2%

Discussion

The success of nonsurgical treatment of gallstones is high dependent on patient selection and one of the major selection criteria is the chemical composition of the stones. Stones rich in cholesterol dissolve most readily whereas pigment stones that contains small quantities of cholesterol but substantial amounts of calcium bilirubinate are highly insoluble.

Several imaging techniques had been used to select patients for stone dissolution. Flat plate abdominal roentgenography identified calcified stones but in vitro studies suggested that least 50 percent of calcified stones evaluated in this way remain undetected.[7] In a study by Trotman et al., the criterion of stone lucency alone allowed inclusion of a number of subjects (14%) with luscent pigment stones, which could have accounted for about one-half of the 33 percent incidence of treatment failures with chenodeoxycholic acid[8]. Conversely, among patients with opaque stones, one third will have cholesterol stones and would be excluded from chenodeoxycholic acid treatment.

Floating or buoyant gallstones can be distinguished by oral cholecystography. The presence of such floating low density stones is a specific sign for high cholesterol content unless the bile shows an increased density following dye ingestion[9]. This finding, however, is relatively insensitive and is not evident in the majority of patients with cholelithiasis[10].

Nuclear magnetic resonance appears to be of no value since a majority of gallstones produce no measurable signal.[11]

In our study, the CT attenuation af gallstone was found to be closely related to the predominant chemical component. In general, stones composed primarily of cholesterol were associated with negative CT attenuation values while pigment stones were found to have positive CT numbers. However, there existed a range of CT attenuation values (-49 to +44HU) within which one may not be able to discriminate gallstone composition by means of CT. This may be due to the degree of non-homogeneity in chemical composition and structure of these stones. Stones with these CT numbers may be mixed cholesterol and pigment stones which have significant quantities of calcium salts, proteins, and other inorganic insoluble material which may be variably distributed within the stone. This composition heterogeneity might affect the action of litholytic agents and thus allow only partial dissolution of the stone.[12]

With the promising results of this in vitro study, an in vivo study may now be done.

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The Additive Effect of Cyclopentolate to Unoprostone Eyedrops in Lowering Intraocular Pressure†

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Abstract

Unoprostone isopropylate (Rescula) is a modified PGF2 alpha analogue belonging to a new class of drugs currently being used in the treatment of open angle glaucoma and ocular hypertension. Its mechanism of action has been attributed to its ability to increase the uveoscleral outflow of aqueous humor. Cyclopentolate hydrochloride is an anticholinergic drug which induces ciliary muscle relaxation and thereby increases the potential space between the ciliary muscle bundles. Theoretically, this event will enhance uveoscleral outflow. This study was undertaken to determine if Cyclopentolate exerts an additive effect to the pressure-lowering properties of Unoprostone. Thirty subjects were enrolled in this randomized double-blind study. Group A (N1=15) received one drop of Unoprostone and one drop of placebo (balanced salt solution) to the right eye. Group B(N2=15) received one drop of Unoprostone plus one drop of 2% Cyclopentolate to the right eye. The left eyes of both groups received two doses of placebo eyedrops. Intraocular pressures of both eyes of both groups were taken at one, two and three hours after instillation of the second test drug. Using one-tailed t-test, the difference in the means of the intraocular pressure readings were compared. Results showed a statistically significant difference between the two groups at one and two hours post-instillation, therefore, cyclopentolate has a potential role in enhancing the pressure-lowering effects of Unoprostone in a select group of patients.

Key words: *Cyclopentolate, Unoprostone Intraocular Pressure, Additive Effect*

Introduction

THE INTRODUCTION OF PROSTAGLANDIN analogues in recent years as an additional armamentarium in the management of open angle glaucoma and ocular hypertension has received much attention in the global ophthalmologic community. Numerous studies have been undertaken to investigate whether these drugs work best alone or whether they exert better pressure-lowering effects in combination with other classes of pressure-lowering medications. To date, the additive effects of prostaglandin analogues to Beta-adrenergic antagonists, carbonic anyhydrase inhibitors, cholinergic and adrenergic agonists have already been documented. However, there is limited data elucidating the relationship between the prostaglandin analogues and the anticholinergic drug Cyclopentolate hydrochloride.

One of the currently available prostaglandin analogues is the modified PGF2-alpha metabolite Unoprostone (Rescula: Ciba Vision). Unoprostone, as with the other prostaglandin analogues, exerts its pressure lowering effect by increasing the uveoscleral outflow of aqueous humor. The uveoscleral or unconventional path-

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way of aqueous accounts for 4-27% of the total outflow of aquenos humor. In this pathway, aqueous humor percolates through the ciliary muscle into the supraciliary and suprachoroidal spaces and leaves the eye through the sclera. Theoretically, Cyclopentolate HCI (Cyclogyl: Alcon) induces relaxation of the ciliary muscles which then increases the space between the muscle bundles. This will also result in an increase in uveoscleral outflow.

This study was undertaken to see if Cyclopentolate HCI exerts an additive pressure-lowering effect to Unoprostone isopropylate via the previously discussed mechanism of action. The results of the study may shed light on future treatment regimens utilizing prostaglandin analogues together with topical cycloplegics.

Materials and Methods

Thirty normal individuals aged 20-30 years old, of either sex, were recruited for the study. The research followed the tenets of the "Declaration of Helsinki" and informed consent was obtained after the nature and possible consequences of the study were explained.

Volunteers not falling within the prescribed age group (20-30 years old) were excluded from the study. Other exclusion criteria include a positive family history of glaucoma, a history of hypersensitivity to any of the test drugs and any female who is pregnant or presumed to be such. Patients with a narrow or occludable iridocorneal angle as determined by gonioscopy, and those with suspicious cup:disc ratios on fundus examination were also excluded from the study.

All volunteers were interviewed and screened by the author. All preliminary examinations like visual acuity testing, refraction, funduscopy, biomicroscopy and gonioscopy were also performed by the author. Baseline intraocular pressure determination by applanation tonometry was performed by an impartial observer. The volunteers were subjected to a double-masked trail and randomly assigned to either of two groups. Group A subjects received one drop of Unoprostone to the right eye. This was followed by a drop of balanced salt solution (BSS: Alcon) after five minutes. The left eye acted as a control and received two doses of BSS five minutes apart. Group B subjects on the other hand received one drop of Unoprostone on the right eye followed by a drop of 2% Cyclopentolate hydrochloride after five minutes. The left eye also acted as a control and received 2 doses of BSS five minutes apart.

The intraocular pressures of both eyes for both groups were then taken by an impartial observer by applanation tonometry. The readings were taken one, two and three hours after the instillation of the second test medication. All values were recorded and tabulated and the mean values per group were subjected to statistical analysis.

Results

The difference in the means of the intraocular pressures compared to the baseline intraocular pressures at one, two and three hours post-instillation of eye medications for groups A and B were subjected to one-tailed t-tests with a level of significance (alpha value) of 0.01. For the first hour post-instillation of test drugs, the t-statistic was computed to be 2.99. This value lies above the critical region of $t>2.492$. Hence, subjects in Group B experienced a larger drop in intraocular pressures compared to Group A.

The same results are seen two hours post-instillation of the test drugs. The t-value was computed to be 2.997 which also lies above the critical region of $t>2.473$. Therefore, Group B again experienced a greater drop in intraocular pressures compared to Group A two hours after instillation of the test drugs. However, for the third hour post-instillation, the t-value was noted to be 2.296. This value lies below the critical region of $t>2.467$. Therefore, at the third hour post-instillation, there is no longer any statistical difference between the values noted in Groups A and B.

Table 1. Intraocular Pressures for Group A in mm Hg (Unoprostone + BSS Placebo)

	Right Eye				Left Eye (Control)			
Subject	Baseline	1 hr	2 hrs	3 hrs	Baseline	1 hr	2 hrs	3 hrs
A	15	14	16	17	14	15	14	14
B	18	17	13	13	14	10	8	13
C	12	12	12	12	10	9	8	10
D	15	15	15	15	14	16	15	15
E	18	16	17	16	20	18	14	15
F	10	7	8	10	8	10	8	8
G	12	16	10	10	11	10	10	10
H	14	14	12	8	10	10	12	12
I	12	12	12	14	13	12	12	12
J	10	12	10	10	10	12	12	12
K	10	9	9	9	10	12	12	10
L	10	10	8	8	8	8	6	6
M	13	12	12	12	15	14	14	14
N	9	10	10	10	11	10	10	10
O	13	13	14	13	12	12	10	12
Mean Values	12.7	12.6	11.9	11.8	12.0	11.0	11.0	11.5
Difference from Baseline		0.1	0.8	0.9		1.0	1.0	0.5

Table 2. Intraocular Pressures in mm Hg for Group B in mm Hg (Unoprostone + Cyclopentolate)

	Right Eye				Left Eye (Control)			
Subject	Baseline	1 hr	2 hrs	3 hrs	Baseline	1 hr	2 hrs	3 hrs
A	13	10	10	11	11	10	10	10
B	14	10	10	10	13	14	14	14
C	17	11	11	12	13	10	10	12
D	14	16	15	15	12	15	15	15
E	14	10	10	10	14	10	8	10
F	18	10	12	10	18	16	10	10
G	15	12	12	10	16	13	10	10
H	9	10	9	9	10	10	9	9
I	13	12	12	12	12	12	12	12
J	17	17	15	15	18	17	17	17
K	16	14	13	13	14	14	15	14
L	15	13	13	13	15	15	15	15
M	12	10	10	10	12	11	11	12
N	14	12	10	11	15	15	14	15
O	13	10	10	11	13	14	14	14
Mean Values	14.3	11.8	11.5	11.5	13.7	13.1	12.3	12.6
Difference from Baseline		2.5	2.8	2.8		0.6	1.4	1.1

Discussion

As reflected in the statistical analysis of data, it appears that topical cyclopentolate exerts an additive effect on the intraocular pressure lowering capabilities of Unoprostone up to the second hour post-instillation. This could be attributed to the fact that cyclopentolate achieves its maximum level in aqueous humor at 55-125 minutes after instillation. Unoprostone on the other hand begins to exert its effect 15-20 minutes after instillation, therefore it is plausible to infer that based on the pharmacokinetic properties of the two drugs, the additive effect of Cyclopentolate to Unoprostone will be experienced within the first 60 to 120 minutes after instillation of both drugs. Interestingly, the left eyes of both study groups which were used as controls also exhibited some degree of intraocular pressure reduction. This could be explained by possible systemic absorption of the test drugs. It was also noted, especially in Group B, that some of the volunteers complained of headache and lightheadedness which persisted for several hours after giving the test drugs. This strengthens our contention that there is some degree of systemic absorption. A few subjects in Group B also compalined of transient blurring of near vision in the right eye. This can be readily explained by the mydriatic and cycloplegic effects of cyclopentolate.

None of the subjects in Group A complained of any blurring of vision while all subjects in Group B had normal vision the day after the test drugs were instilled. Although the initial results show that cyclopentolate indeed exerts an additive effect to Unoprostone, future attempts at replicating the study should minimize the systemic effects of cyclopentolate. This could be achieved by punctal occlusion for several minutes after instillation. Also, Cyclopentolate 2% was used throughout the study so the possibility of giving a less potent concentration)0.5%or 1%) could be used in the future to minimize side effects. Cyclopentolate may also be given at bedtime in order to minimize the visual side-effects. Future applications of the study could include patients with open angle glaucoma and normotensive glaucoma provided that the patients are properly screened and evaluated beforehand.

Finally, given the encouraging initial results of this study, Cyclopentolate HCL may indeed play a future role in augmenting the therapeutic effects of the prostaglandin analogues in a select group of glaucoma patients.

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The Efficacy of Intramuscular Ketoprofen as Postoperative Analgesic in Abdominal Operations

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Introduction

ADEQUATE CONTROL AND MANAGEMENT of postoperative pain remains one of the most important and pressing issues in the field of surgery and anesthesia with significant impact on the delivery of health care. Narcotic analgesics remain to be the most commonly used and indeed the standard method of treating postoperative pain.[2] The central nervous systems and cardiovascular complications of narcotics has spurred a search for an analgesic with lesser side effects. The nonsteroidal anti-inflammatory drug (NSAID) Ketolorac, has been utilized as an alternative analgesic but had to be administered every four to six hours.[3] A longer-acting NSAID like Ketoprofen which has both central and peripheral actions secondary to prostaglandin release inhibition, may be equally, if not more effective. It has a distinct advantage of being administered every twelve hours.[1]

This study compares the efficacy of 100 mgs intramuscular Ketoprofen given every twelve hours against an accepted standard of 50 mgs Meperidine given every four hours, as postoperative analgesic in lower abdominal operations.

Materials and Methods

This single blind study involved 40 consecutive patients confined at our institution for lower abdominal surgeries, i.e. general surgical, urologic, gynecologic and obstetric, with ASA risk I and II, 18 to 55 years of age with an informed consent. The patients were randomized into two groups with Group I being given Meperidine (Demerol) 50 mgs IM immediately after the end of surgery with additional doses given every 4 hours for a total of 8 doses. Group II patients were given Ketoprofen (Orudis) 100 mgs deep IM immediately after the end of surgery with additional doses given every 12 hours for a total of 4 doses. In case of breakthrough pain, patients will be given Nalbuphine 10 mgs IM every 4 hours on a prn basis.

Excluded in this study were patients who received NSAID and/or narcotics intraoperatively, known allergy to Ketoprofen, history of hypersensitivity to aspirin, patients with chronic peptic ulcer disease and patients with chronic life-threatening diseases like cardiac, renal or hepatic diseases.

A visual Analogue Scale (VAS) was used to quantity pain relief where 0 represented no pain and 100 represented severe pain. Prior to evaluation, all patients in the study were instructed on how to quantify pain relief on the VAS. An independent pre-trained observer was asked to evaluate pain relief scores using the VAS every 4 hours for the first 24 hours and every 12 hours for the next 24 hours for a total observation time of 48 hours. Likewise, the following data were also observed: respiratory rate, blood pressure, presence or absence of nausea, presence or absence of vomiting, and the level of sedation.

The level of sedation was graded according to the following scale:

1- fully awake
2- sleepy but responds to verbal commands
3- sleeping, responds only to painful stimulation
4- no response to either verbal or painful stimulation

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All pertinent data were analyzed using the Microstat or Epistat packages where applicable. The Chi Square Test, Fischer's Exact Probability Test and The T-test were utilized at 95% level of confidence.

Results

Of the forty patients in this study, 31 were females and 9 were males resulting in a male: female ratio of 1:3.6. Four males and 16 females were in Group I while 5 males and 15 females were in Group II. The two groups were comparable in size with no significant statistical difference between them (Table 1). The sample population mean age was 32.5 years with the youngest being 18 and the oldest at 47 years old (Table 2). Both groups were comparable as to age distribution.

Table 1. Sex Distribution

Sex	Group I	Group II	Total
Male	4	5	9
Female	16	15	31
Total	20	20	40

Table 2. Age Distribution

Age in Years	Group I	Group II	Total
18-22	7	3	10
23-27	4	4	8
28-32	6	5	11
33-37	3	4	7
38-42	0	3	3
43-47	0	1	1
Total	20	20	40

p=0.2447

The most common type of surgical procedure was low transverse cervical cesarean section (Table 3). Spinal anesthesia was the most common type of anesthesia used (Table 4). There were no significant differences between the two groups as far as type of surgical procedure and type of anesthesia were concerned.

Table 3. Distribution as to Type of Surgery

Surgery	Group I	Group II	Total
Varicocoelectomy	0	2	2
Appendectomy	4	4	8
LTCCS	13	11	24
TAH-BSO	1	1	2
Salpingectomy	2	0	2
Total	20	20	40

Table 4. Distribution as to Type of Anesthesia

Type of Anesthesia	Group I	Group II	Total
Spinal Anesthesia	18	20	38
General Anesthesia	2	0	2
Total	20	20	40

p=0.2435

The preoperative and postoperative blood pressures, and respiratory rates in both groups showed no statistically significant differences. However, comparing the change in the level of sedation of both groups, using the T-test, Group II had better postoperative level than Group I (Table 5). The incidence of postoperative nausea or vomiting directly related to ketoprofen administration was not significant (Table 6).

Table 5. Mean Pre- and Postoperative Parameters

Parameters	Group I	Group II	p value
Blood Pressure (mm Hg)			
Pre-op	123.5/72	123/76.5	
Post-op	115.5/72	117/76.5	0.934
Respiratory Rate/min			
Pre-op	18.8	20.3	
Post-op	19.9	19.4	0.685
Level of Sedation			
Pre-op	1.1	1.1	
Post-op	2.0	1.2	<0.05

Table 6. Drug-Related Nausea and Vomiting

Symptom	Group I	Group II	p value
Nausea			
Pre-op	2	4	
Post-op	0	3	0.4167
Vomiting			
Pre-op	1	1	
Post-op	0	1	0.6667

The comparative mean VAS scores in only 3 types of surgery were available for computation since some samples were absent in both groups. Using an independent T-Test, the mean VAS scores of the groups did not have statistically significant differences (Table 7). The comparative mean VAS scores with regard to sex showed no statistical differences (Table 8). The comparative mean VAS scores with regard to age likewise showed no statistical differences between the two groups (Table 9). The comparative mean VAS scores during the period of observation (48 hours), showed no significant differences between the two groups after the 4th hour (Table 10. Graph 1). No patient in both experimental and control groups required a dose of Nalbuphine from the 4th to the 48th hour.

Table 7. VAS Score as to Type of Surgery

Type of Surgery	Group I	Group II
Varicocoelectomy	0	3.1
Appendectomy	2.9	3.2
LTCCS	3.7	3.4
TAH-BSO	3.2	2.7
Salphingectomy	0	2.9

p>0.05

Table 8. VAS Score as to Sex

Sex	Group I	Group II
Male	2.9	3.3
Female	3.6	2.9

p=0.521

Table 9. VAS Score as to Age

Age in Years	Group I	Group II
18-22	3.9	3.6
23-27	2.3	3.2
28-32	3.9	4.0
33-37	3.7	3.5
38-42	-	3.3
43-47	-	2.7

p>0.2246

Table 10. VAS Score as to Time of Observation

Hours	Group I	Group II
4	4.8	5.4
8	4.5	4.6
12	4.3	4.5
16	3.7	3.7
20	3.4	3.0
24	3.2	2.6
36	2.7	2.6
48	2.0	1.1
Mean	3.6	3.5

p=0.8455746

Discussion

New horizons in the management of pain have emphasized that the historical dogma of peripheral sensitization must be updated to include the emerging concept of central sensitization. Unlike other NSAIDs, Ketoprofen has been shown to exhibit this dual mode of action by increasing the 5 HT levels and decrease prostanoid levels.[3] Ketoprofen has been shown also to reduce the levels of substance P after the injection of 100 mgs of the drug. Because of the peripheral action of Ketoprofen due to the inhibition of prostaglandin release and because of the recent finding that Ketoprofen may have a unique secondary neurosensory effects centrally by diffusing through the blood brain barrier.[3,6] we compared the efficacy of the drug with Meperidine in postoperative pain relief.

In the first 4 hours postoperative, our results showed a significant difference in the mean VAS scores of the two groups. This can be due to the slower onset of clinical pain relief by Ketoprofen. Studies have shown that after an intramuscular injection of Ketoprofen will have a maximum plasma level in 20-30 minutes and a plasma half-life of 1.8 hours.[1] It has also been proven that Ketoprofen can diffuse through the blood-brain barrier as early as 15 minutes after a single intramuscular injection with the CSF levels of the drug in equilibrium with the plasma level from the 2nd to the 13th hour.[4] We believe

that this delay in attaining a CSF-Plasma equilibrium could partially explain the delay in attaining the comparable clinical postoperative pain relief. It could also be due to the fact that Ketoprofen has to undergo a secondary pathway in blocking pain messages at the level of NMDA receptors through an increase in the activity of tryptophan 2.3 dioxygenase (TDO) which has the prosperity of increasing kynurenic acid concentration in the CNS, blocking the ion channels by keeping magnesium ions in place.[5]

Our results have shown that Meperidine offered no advantage in terms of postoperative pain relief compared to ketoprofen from the 8th to the 48th hour after surgery (Graph 1). If the mean VAS scores of Group II were time-adjusted by minus 4 hours, there will be a significant difference between the two groups (Graph 2). From the 16th hour, the mean VAS scores of the experimental group was even lower than that of the control group.

It was likewise shown that Ketoprofen did not significantly alter the postoperative blood pressures and respiratory rates of our patients. The level of sedation, as expected was significantly better (lower grade) than the group receiving narcotics.

Conclusions

Ketoprofen is as effective as Meperidine in relief of acute postoperative pain. It has a significantly longer duration of action and is relatively well-tolerated. It can be a good alternative to a narcotic for the relief of postoperative pain without the side effect of sedation. Respiratory and cardiovascular alterations are not significant.

Recommendation

It is recommended that Ketoprofen, if used as the sole postoperative analgesic, should be given at least 4 hours prior to surgery to achieve maximum clinical efficacy.

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A Descriptive Study on the Therapeutic Response of Pediatric Patients with Nosocomial Infections to Piperacillin/Tazobactam

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Abstract

This descriptive study aims to describe the therapeutic response of patients with nosocomial infections to Piperacillin/Tazobactam. This was undertaken because of significant increase in antibiotic resistant gram-negative bacteria that cause nosocomial infections. Furthermore, this study is important as a documentation on the therapeutic response of pediatric patients to Piperacillin/Tazobactam. Medical records of patients admitted at UERMMMC Neonatal Intensive Care Unit (NICU) and Pediatric Intensive Care Unit (PICU) from April 1996 to November 1997 with nosocomial infection were reviewed. Patients who received Piperacillin/Tazobactam for a nosocomial infection were included. Fifteen patients met this study's criteria. Of the 15 patients, thirteen patients (87%) were considered cured and eventually discharged from the hospital. The therapeutic response rate of Piperacillin/Tazobactam is 87%. Clinical response of patients with nosocomial infections shows improvement within 3 to 5 days after initiation of treatment with Piperacillin/Tazobactam. Of the 15 patients, no adverse reactions were noted.

Introduction

NOSOCOMIAL INFECTIONS POSE A serious threat to survival, particularly in pediatric patients whose immune systems tend to be immature. They affect at least 6% of patients admitted to hospitals and represent one of the ten leading causes of hospitals deaths.[1] Factors that increase the incidence of nosocomial infections include: length of stay in an ICU; age less than 2 years; the use of diagnostic or therapeutic devices (e.g. catheters for parenteral nutrition); exposure to hospital staff, and the use of broad-spectrum antibiotics.[1,2,3,4,5,6]

The etiologic agents of nosocomial infection are different from one hospital to another. In a hospital surveillance (February, 1997) in the NICU at our institution, the following pathogens were cultured: Enterobacter sp., Acinetobacter, Staphylococcus epidermidis and Bacillus subtilis. In a study done by Bibera (1993), an outbreak of 9 cases of Enterobacter septicemia were identified during a 3 month period (June to August 1993) at the NICU of UERMMMC. Contributory factors such as overcrowding and a break in the aseptic technique were identified.[7]

There is a growing concern however, on the alarming increase of antibiotic resistance to nosocomial infections. Antibiotic resistant gram-negative bacteria (ARGNB) are frequently implicated. These include the enteric gram-negative rods Enterobacter, Klebsiella, Citrobacter and Serratia and non-enteric bacteria, such as, Pseudomonas and Acinetobacter.[8] Infants who are colonized or infected with ARGNB frequently have received prior antibiotic treatment.[9,10] Several reports have described epidemics due to organisms

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resistant to ampicillin, kanamycin or gentamycin.[8,11,12,13,14] The adoption of third generation cephalosporins and amikacin has also led to outbreaks with organisms resistant to these antibiotics.[8,15,16,17,18,19,20] Although most organism currently remain susceptible to Imipenem, resistance to this agent has also been described.[8,19]

In the Second Annual Convention of the Pediatric Infectious disease Society of the Philippine, Starke named some new drugs that may be used to treat resistant pathogens. For gram positive cocci, the following drugs may be used: Vancomycin/Teicoplanin; Rifampicin; Amoxicillin/Clavulanate; Ticarcillin/Clavulanate; Ampicillin/Sulbactam and Piperacillin/Tazobactam. For gram negative bacilli, the following may be recommended: Imipenem; Meropenem: Aztreonam; Flouroquinolones, Trimethroprim/Sulfamethoxazole and Piperacillin/Tazobactam.[21] Among these drugs, only Piperacillin/Tazobactam has a good activity against both gram positive cocci and gram negative bacilli.

Despite these recommendations, the antimicrobial of choice remains largely dependent on the results of culture and sensitivity testing. At the UERMMMC, 70% of nosocomial infections in pediatric patients were found to be sensitive to Piperacillin/Tazobactam. It is in this light that this study was done.

Objectives

The purpose, therefore, of this study is to describe the therapeutic response of patients with nosocomial infections to Piperacillin/Tazobactam. This study specifically aims to:

1. To describe the susceptible organisms to Piperacillin/Tazobactam;
2. To describe the response rate of patients with nosocomial infections to Piperacillin/Tazobactam;
3. To describe the average length of time before clinical improvement of patients based on given parameters can be seen; and
4. To describe the frequency of adverse effects of Piperacillin/Tazobactam in pediatric patients.

Significance

This descriptive study is undertaken because there is significant increase in antibiotic resistant gram-negative bacteria that cause nosocomial infections. The advent of new antimicrobials like Piperacillin/Tazobactam (a beta-lactam/beta-lactamase inhibitor) is timely because these organisms are susceptible to it. Furthermore, this study is important as a documentation on the therapeutic response of pediatric patients to Piperacillin/Tazobactam. So far, no studies of Piperacillin/Tazobactam have yet been published in pediatric patients.

Review of Literature

Piperacillin is a broad spectrum, semisynthetic penicillin active against many gram-positive and gram-negative aerobic and anaerobic bacteria. It exerts bactericidal activity by inhibition of both septum and cell wall synthesis.[22] Tazobactam is a penicillanic acid sulfone B-lactamase inhibitor with a structure similar to that of Sulbactam but with a potency similar to clavulanic acid. It is a potent inhibitor of many B-lactamases including the plasmid and chromosomally mediated enzymes that commonly cause resistance to penicillins and cephalosporins.[23] The presence of tazobactam in the piperacillin/tazobactam formulation enhances and extends the antibiotic spectrum of piperacillin to include many B-lactamase producing bacteria normally resistant to it.[24]

Piperacillin/Tazobactam is active against gram-negative bacteria like E.coli, Citrobacter sp. Klebsiella, Enterobacter, Proteus sp., Serratia, Salmonella, Pseudomonas, Neisseria, Acinetobacter, Campylobacter, Gardnerella vaginalis, Haemophilus sp. It is also active against gram-positive bacteria which are B-lactamase and non B-lactamase producing strains of Streptococci sp.,

Enterococci, Staphylococcus aureus, Corynebacteria, Nocardia sp., and Listeria monocytogenes. It is also effective in anaerobes such as Bacteroides sp., Clostridia and Actinomyces sp.[24, 25, 26, 27, 28, 29,30]

The efficacy and safety of Piperacillin/Tazobactam in the treatment of bacteremia, respiratory tract, intra-abdominal, urinary tract, skin, and soft tissue has been extensively studied producing highly favorable results in adults.[24, 25, 26, 27, 28, 29, 30] In one study,[30] the clinical response of Piperacillin/Tazobactam was favorable in 96% and bacterial eradication rate was 93% in respiratory tract infection. In another study,[29] the cure rate for bacteremia was 82%. For skin and soft tissue infections, 85% eradication of pathogens was obtained.[31] As of present, no published studies supporting the use of Piperacillin/Tazobactam in children have been written.

Adverse reactions are generally not severe and rarely interfere with continuation of therapy.[24, 25, 26, 27, 28, 29, 30,31] The adverse effects are as infrequent as with other penicillins.[31]

In study by Kuye and associates, 29 adverse reactions noted with Piperacillin/Tazobactam compromise mainly of allergic skin reactions and gastrointestinal disturbances, the most common of which is diarrhea. The most significant changes in laboratory values involve elevation of liver function test, which resolves after discontinuation of the drug.

Subjects and Methods

Definition of terms

1. **Nosocomial Infection** - is any positive growth on culture (blood, ETA, urine, CSF or surgical wound) after 72 hours of admission at the NICU and PICU in patients already broad-spectrum antibiotic coverage.
2. **Bacteriologically evaluable patients** - patients who have a positive growth on any culture.
3. **Cured** - eradication of organism on repeat culture after 7 days and clinical improvement of the patient based on the following parameters: good suck, good activity, weight gain, defervescence of fever, normalization of heart rate and respiratory rate and weaning from the mechanical ventilator.
4. **Failed** - persistence of the organism or emergence of a new organism on repeat culture and clinical deterioration of the patient.
5. **Response rate** - percentage of patients 'cured' and 'failed'

This is a descriptive study done in an academic tertiary hospital. Medical records of patients admitted at UERMMMC Neonatal Intensive Care Unit (NICU) and Pediatric Intensive Care Unit (PICU) from April 1996 to November 1997 with nosocomial infection were reviewed. All bacteriologically evaluable pediatric patients from 0 to 12 years old who received Piperacillin/Tazobactam as an antimicrobial for a period of 4 to 21 days for any nosocomial infection were included.

Patients included have a documented nosocomial infection with a positive culture on blood, endotracheal tube aspirate (ETA), urine, cerebrospinal fluid (CSF), or surgical wound discharge. Excluded in the study are patients who received Piperacillin/Tazobactam with another antimicrobial. Patients who have expired while using Piperacillin/Tazobactam of immediate causes other than infection (i.e. pneumothorax secondary to prolonged mechanical ventilation, hyaline membrane disease, bronchopulmonary dysplasia, congenital heart disease in congestive failure and others) were also excluded.

Data analysis was done using means, averages and percentages computed manually. The mean ages of the patients admitted at the NICU and PICU was taken and the number of male and female patients and the number of positive cultures from blood, ETA and wound

were computed to get the averages and equivalent percentages. These characteristics of patients (age, sex, positive bacteriological cultures) were tabulated. Etiologic agents susceptible to Piperacillin/Tazobactam according to incidence were given equivalent percentages and presented in a graph. Bacteriologically evaluable patients who met the study's criteria were assessed by the investigator as 'cured' or 'failed' and response rates were computed using percentages. The therapeutic response rate was computed from the total number of patients cured over the total number of patients. Clinical improvement of patients was determined by the following parameters: good suck and activity, weight gain, normalization of heart rate and respiratory rate, defervescence of fever (if with fever), and weaning from mechanical ventilation. The number of days when these clinical parameters were noted in the fifteen patients were averaged and tabulated. Adverse effects noted were also reviewed.

Results

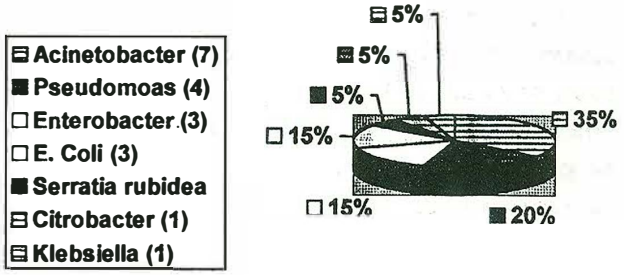
A total of 115 charts from April 1996 to November 1997 were reviewed. Out of these, 20 bacteriologically evaluable patients used Piperacillin/Tazobactam as an antimicrobial for nosocomial infection. There were 11 patients (55%) admitted at the NICU and 9 patients (45%) at the PICU. There were a total number of 12 males (60%) and 8 females (40%). The age of the NICU patients ranged from 31 weeks to 37 weeks with a mean age of 33 weeks and the PICU patients ranged from 0 to 8 months with a mean of 4 months. There was a total of 12 patients (60%) who had isolates from blood; 7 patients (35%) with isolates from endotracheal tube; and only 1 patient (5%) from a surgical wound culture secondary to repair of an omphalocoele. [Table I]

Table 1. Characteristics of Bacteriologically Evaluable Patients

Characteristics	NICU	PICU	Total	%
No. of Patients	11 (55%)	9 (45%)	20	
Mean Age	33 weeks	4 months		
Range	31-37 wks	0-8 mos		
Sex				
Male	7	5	12	60
Female	4	4	8	40
Positive cultures				
Blood	7	5	12	60
ETA	4	3	7	35
Wound	0	1	1	5

The etiology agents that were susceptible to Piperacillin/Tazobactam in this study according to incidence are the following: Acinetobacter (35%); Pseudomonas (20%); Enterobacter (15%); E. Coli (15%); Serratia rubidea (5%); Citrobacter (5%); and Klebsiella (5%) [Figure I].

Figure 1 Frequency of Susceptible Organism to Piperacillin/Tazobactam



Fifteen patients met this study's criteria. Five patients were excluded. Three, because an aminoglycoside was used in combination with Piperacillin/Tazobactam and the other two because they expired secondary to pneumothorax. Of the 15 patients, thirteen patients (87%) were considered cured and eventually discharged from the hospital. Two patients (13%) were failures and subsequently expired. [Table 2] The two failures showed persistence of the following

organisms: E. coli and Klebsiella. The response rate to Piperacillin/Tazobactam is 87%.

Table 2. Response Rate of Patients with Nosocomial Infections to Piperacillin/Taxobactam

Response	Frequency n=15	%
Cured	13	87
Failed	2	13

Clinical response of patients with nosocomial infections show improvement within 3 to 5 days after initiation of treatment with Piperacillin/Tazobactam. Table 3 shows the clinical parameters of patients that determine clinical improvement.

Table 3. Average Days of Clinical Improvement in Patients to Piperacillin/TAzobactam

Characteristics	Average Days of Improvement withPiperacillin/Tazobactam	
	NICU	PICU
Good Suck	5	4
Good activity	4	4
Weight gain	4	4
Defervescence of fever	2	3
Normalization of HR	4	4
Normalization of RR	4	4
Weaning from Mechanical Ventilator	4	5

In the 15 patients in this study, no adverse reactions necessitating drug discontinuation was noted. The only adverse reaction noted was phlebitis secondary to the administration of drug in 6 patients.

Discussion

Success in the treatment of nosocomial infections largely depends on appropriate therapy. Antibiotic resistance, however, plays a crucial role in the outcome of the patient. The antibiotics given like aminoglycosides and third-generation cephalosporins for nosocomial infections in pediatric patients have developed resistance. In a study by Moellering, up to 50% resistance to Amikacin was documented.[32] Outbreaks of Amikacin-resistant enterobacteriaciae in the NICU has also been reported by Cook.[15] In a study of Meyer, Klebsiella and Acinetobacter have become resistant to third generation cephalosporins like Ceftazidime resulting in a crude mortality rate of 53%.[18] Meyer mentioned that these pathogens have minimal resistance to Piperacillin/Tazobactam, a beta-lactam/beta-lactamase inhibitor, of up to 100% susceptibility by disk diffusion.[18]

Antibiotic-resistant gram-negative bacteria which are commonly implicated like Enterobacter, Klebsiella, Citrobacter, Serratia, Pseudomonas and Acinetobacter are the organisms susceptible to Piperacillin/Tazobactam in this study. Different studies done by Sorgie,[24] Grenim,[25] File,[26] Nord,[27] Kuye,[28] Wise,[29] Mouton,[30] in adult patients show these same organisms' susceptibility to Piperacillin/Tazobactam. In this study, the most susceptible organism was Acinetobacter. In a study by Wise,[29] E., coli was the most common susceptible organism. Tassler,[30] identifies Piperacillin/Tazobactam as active against beta-lactamase producing strains of S. Aureus and S. epidermidis in up to 23%.

In this study, the therapeutic response rate is 87%. This correlates well with other clinical trials in adult patients. In a study by Wise of bacteremic patients, the cure rate was 82% and mortality rate was 3%.[29] The study by Tassler reports,[38] the clinical response at 96% with bacterial eradication rate of 93% for respiratory infections. In patients with skin and soft tissue infections, the cure rate is 93% as documented by File.[26] Vestweber reports 87%

cured and improved in patients with intra-abdominal infections.[33]

In this study, the dose of Piperacillin/Tazobactam was 100 mg/kg/day based on Piperacillin. It was given for 21 days in patients with isolates from blood; and 14 days for patients with isolates from endotracheal tube and surgical wound discharge. This is based on recommendations for treatment of sepsis, which is 21 days, and for pneumonia and skin & soft tissue infections which is at least 14 days.[34,35]

Clinical parameters like good suck; good activity; weight gain; normalization of heart rate and respiratory rate; defervescence of fever; and weaning from mechanical ventilator, which are observable signs of improvement, are monitored by a pediatrician to gauge the clinical response to an antimicrobial. The average length of time of clinical improvement in patients noted in this study is from 3-5 days which is favorable.

Piperacillin/Tazobactam was found to be safe and well tolerated in phase I and III clinical trials by Kuye.[28] The adverse effect reported was 13%, comprising of gastrointestinal disturbances, the most common of which is diarrhea and allergic skin reactions.[28] These adverse effects were not noted in the patients in this study. Phlebitis after administration of the drug was noted in 6 patients in this study which maybe secondary to the smaller veins in infants that are friable. There were no documented adverse effects in the hepatorenal, gastrointestinal, skin or other systems noted in the patients in this study.

Conclusion and Recommendation

The overall therapeutic response rate of Piperacillin/Tazobactam in this preliminary study is 87%. The susceptible organisms are: Acinetobacter, Pseudomonas, Enterobacter, E. coli, Serratia rubidea, Citrobacter and Klebsiella. Clinical improvement occurs 3 to 5 days after initiation of Piperacillin/Tazobactam. Phlebitis was noted in 6 patients.

No general conclusion however can be made in this study due to the limited number of subjects. Further studies of Piperacillin/Tazobactam on nosocomial infections in children are recommended. An analytical study with statistically evaluable patients must be undertaken to further determine the efficacy and safety of this drug.

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Conservative Approach in the Management of Vulvar Cancer: A Case Report

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Introduction

Vulvar Cancer present a challenge to any oncologist who is presented with such a case. Cancers of this kind are rare, and therefore the opportunities to manage these cases do not come very often. To add to this, the classic management of Radical Vulvectomy with bilateral lymphadenectomy can be a rather formidable procedure. Many studies have been done to try to establish a definitive etiology to this disease, but due to its multifactorial nature the cause is still speculated at this time.. The wide range of research on the role of Human Papillomavirus as a precursor of the cancer has shed new light on pathogenesis. The literature presented will also try to showcase the new innovations of management, in an effort to avoid the high morbidity of the traditional management.

Case Protocol

P.C. a 67 year old G10P6 (6046), hypertensive, non-diabetic, was admitted at the Gynecology wards on October 1, 1997 for the first time. She was referred for management of a previously diagnosed Vulvar carcinoma.

The present condition started as chronic vulvar pruritus 13 years ago. The patient consulted several physicians and was prescribed topical medications which included topical steroids. The medications afforded temporary relief and the patient continued to self-medicate. One year ago, she noted a small fleshy mass above her urethra. The mass tended to resolve and recur spontaneously, so no consultation was sought. Two months prior to admission, she felt a 2 cm right inguinal mass described as firm, nontender and reddish in color. Upon consultation, it was noted to be fixed and it was treated as a case of lymphadenitis using Bacampicillin capsules. The mass was noted to increase to "chicken egg" size and 3 weeks PTA, a thick yellow discharge was seen to ooze from it. A consultation with another physician was made and an I & D with biopsy was performed. She was sent home on Anti-Koch's meds. 9 days PTA, due to severe pain at the groin and the presence of a non-healing ulcer at the biopsy site, she was admitted at the Pasay City General. On work-up, anemia was noted and 2 units of fresh whole blood were transfused. The source of the anemia was observed to come from a gastro-intestinal bleed. A referral for colonoscopy revealed Diverticulosis of the ascending colon. The results of the biopsy of the inguinal mass showed Well-Differentiated Squamous Cell Carcinoma. A referral to Gynecology confirmed the presence of a primary vulvar lesion. The patient was transferred to our institution upon her request.

On admission, her vital signs were stable and she was noted to be in pain. She appeared pale and weak. A tender mass with a 8 cm x 6 cm open wound was noted over the right inguinal region, 2 cms deep, with necrotic tissue and a dark yellowish-green foul smelling discharge. The mass was movable. Palpable lymph nodes were noted over both inguinal areas with an average size of 3 cm, and all were movable. The vulva was noted to be hyperpigmented, with a swollen right labia majora, and a 3 cm x 2 cm mass was seen in the area of the clitoris. The mass was irregularly shaped, reddish, firm and non-bleeding. A biopsy was taken from the mass. The rest of the gynecology exam was unremarkable. A Pap smear was done with normal results. The diverticulosis was referred to our GIT service and colonoscopy with sclerotherapy was

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done which resolved the bleeding. The biopsy of the vulvar mass revealed Vulvar carcinoma, Squamous cell type, Well-Differentiated. After cardiopulmonary clearance, the patient underwent Radical vulvectomy on the 13th hospital day.

Intra-operatively, two incisions were made. The first was to excise the infected mass at the right inguinal area and with a deeper dissection to harvest the right femoral node. It was then extended to include the clitoral mass and part of the superior aspect of the vulva. A second smaller incision was made on the left inguinal region to harvest the left inguinal nodes. The large defect was closed with silk sutures and drains were left in place below both inguinal incisions.

The histopathological report revealed Squamous Cell Carcinoma, Well-differentiated, vulvar Mass, with margins of resection negative for tumor involvement. The specimens labelled as left and right superior inguinal lymph nodes were positive for Metastatic Carcinoma, while the specimen labelled as right femoral node was negative for metastatic carcinoma.

Post-operatively, the patient's legs were wrapped in elastic bandage to prevent lymphedema, the wounds were dressed and the drains were gradually mobilized.

On the 7th post-op day, the right inguinal area started to show signs of wound breakdown, eventually becoming necrotic and opening up. Debridement and cleansing with hydrogen peroxide was done and the use of honey dressings three times a day. The wound gradually began to heal and signs of infection were arrested. The patient is presently at the ward with good progress and with wound care ongoing.

Case discussion

Vulvar carcinoma is a relatively uncommon neoplasm and generally a disease of older women.[1] Our patient falls well within the age bracket as noted by Benitez which would be between 51-70 years of age, 75% of whom would be above 60 years old. Historically, cancer of the vulva has accounted for 3% -5% of all female genital malignancies.[2]

In the last review of this cancer at the Philippine General Hospital (PGH) from 1961 to 1990, a 30 year period, it accounted for 2.5% of all female genital tract cancer. This ranks vulvar cancer 4th among the different gynecology cancers.[3]

It has been reported recently however that there has been an increase in the incidence of vulvar cancers. Green attributes this to:

1. earlier detection of the malignancy;
2. continued rise in the life expectancy of the female population[3,2]

The rise has been most observed in the younger females, ranging between 31-40 years old and they would account for 8% of the cases[3].

The overwhelming majority of all vulvar cancer is squamous in origin. The vulva is covered with skin, and any malignancy that appears elsewhere on the skin can appear in this region[2]. Squamous carcinoma accounts for 80% - 85% of these malignancies[3]. Our patient has been diagnosed with the squamous cell type, well-differentiated vulvar carcinoma.

A review of the clinical profile of the patients would conform to our patient. Benitez has observed that the disease is one that is prevalent in the lower socio-economic class. The same observation was made by Mack and Casagrande in Los Angeles women. Our patient belongs to a lower income bracket. Hypertension, diabetes mellitus, and obesity have been associated with patients with vulvar cancer. Strongly implicated in the course and the prognosis of vulvar Ca is cigarette smoking. Although she claims to have stopped smoking 10 years ago our patient has had a prior 20 years history of consuming 1-2 packs a day.

Much of the etiology of vulvar cancer is still not established. It is a disease that afflicts a spectrum of women. Gravidity and parity apparently do not play a role.

The disease has been associated with granulomatous vulvar diseases, chronic inflammatory

disorders of the vulva and with the Human papillomaviruses. There are many views regarding the role of any of these conditions with regard to vulvar cancer.

Leibowitch et al. stated that several epithelial abnormalities in the vulva may have premalignant potential. He noted that majority of patients with vulvar cancer had Lichen sclerosus (LS) (61% of patients) and that the cancer occurred where the LS was most intense. He places the risk of acquiring vulvar cancer in those with Ls at 10%.[4]

It may be relevant to note since our patient had the primary lesion at the clitoris that this same study mentions squamous cell carcinoma in patients with LS occurred exclusively in the labia minora and clitoris. On the other hand, Benitez noted in a recent reassessment of vulvar dystrophies, that there is actually little data to support such progression to invasive cancer. It is believed that they are simply forms of ordinary dermatitis or dystrophies and are without prognostic value[3].

The involvement of Vulvar Intraepthelial Neoplasia (VIN) is also under investigation. Leibowith et al. observed VIN III in 31% of patients with vulvar cancer, and that in more than 50% of patients with Lichen Sclerosis, VIN III was also present. He then strongly argues in his study that there are two main precursors for invasive carcinoma of the vulva; namely, Lichen Sclerosus and VIN III (undifferentiated)[4]. It is the general contention, however, that VIN may not have the same malignant potential as CIN. It has been estimated that the progression from VIN to invasive vulvar cancer is only 6%.

Of the different venereal diseases studied that have been associated with Vulvar carcinoma, much emphasis has been given to the role of Human Papillomavirus.

Associations have been established between vulvar carcinoma, syphilis and chronic granulomatous disease; however, these may just be markers for sexual activity. Papillomaviruses provide the strongest direct connection between vulvar cancer and sexually transmitted diseases.[5]

HPV 16 appeared to be the most prevalent type in squamous cell carcinoma of the vulva. There are several explanations why HPV 16 was not as often detected in vulvar carcinomas as in cervical cancers.

1. HPV 16 might play a role in early stages of vulvar carcinogenesis, and the viral DNA sequences are lost at the later stages.
2. Some vulvar carcinomas may be associated with HPV types only distantly related to the known genital types, and thus may go undetected.
3. Finally, many vulvar carcinomas may develop in the absence of HPV infection, particularly in older women[1].

Recent studies have shown that the epidemiologic, histopathologic and prognostic features of HPV-associated vulvar cancers differ from those that are HPV-negative[6].

Existing data suggests the hypothesis that vulvar carcinoma comprises at least 2 subsets:

1. those to be related to sexual factors (HPV)
2. those whose pathogenesis remains largely undefined.

Those with HPV positive tumors were likely to be younger than the mean age (<70 years old) and tended to smoke. HPV DNA was found in 95% of the warty, basaloid, verrucous tumors, but only in 39% of the typical squamous tumors[6].

The absence of HPV DNA in most vulvar cancers found in older women suggests that the potential epidemiological heterogeneity of vulvar carcinomas needs to be reassessed[5]. Evidence gathered by Crum et al. suggests, at least in American women, that a substantial proportion of vulvar carcinomas may not be related to a transmitted agent.

It appears that among vulvar carcinomas, there may be 2 separate pathways of carcinoma development, with different prognoses[6]. It would be a disservice to older women to invoke the STD theory in discussing vulvar cancer with these patients [5].

As shown in our patient's history, the disease is one of a long duration. It may take months to several years for it to develop and to be recognized. Non recognition by either the patient or the physician is a cause of delay of diagnosis and treatment[3]. Fortunately, vulvar cancer is indolent, extends slowly, and metastasizes fairly late. Biopsy must be done on all suspicious lesions of the vulva, including lumps, ulcers, or pigmented areas even if the patient is not complaining of burning or itching[2].

Most patients complain initially of a palpable vulvar mass, followed by the presence of pruritus. Pain would be the fourth most common complaint. At the time of examination, all the physician might see is a thickening or a roughening or an erythema or a black discoloration of the skin of the vulva[3]. The patient might also present with an obvious mass that leads to biopsy.

The primary lesion may be found anywhere in the vulva, but the most common site involved are the labia, both majora and minora[2,3,7]. The clitoris is the second most affected part of the vulva. It is important to determine the extent of the lesion in so far as the areas involved, for this would also dictate the probable lymph node involvement.

The vulvar area is rich in lymphatics with numerous cross connections. Tumors located in the middle of either labium tend to drain initially to the ipsilateral femoral-inguinal nodes, whereas perineal tumors can spread to either the left or right side. Tumors in the clitoral or urethral areas can also spread to either side.

From the inguinal-femoral nodes, the lymphatic spread is cephalad to the deep pelvic and obturator nodes. Our patient's lymph node bilaterality can be further explained by a study done by Iverson and Aas using injected Te-colloid into different areas of the vulva. The clitoral and perineal injections developed a bilateral nodal distribution of radioactivity in all patients. Deep lymph node metastasis occurs only in those with positive superficial nodes[9].

Clinical staging of vulvar cancer has been left in favor of the 1988 FIGO system based on the TNM classification, which is a staging system using surgical pathologic evaluation. The new system does away with the discrepancies previously noted when clinical staging was compared with pathological findings. The parameters used include tumor size, nodal involvement, and presence of metastasis. Based on the TNM classification, we have

1. T2: tumor confined to the vulva/ perineum more than 2 cm in diameter;
2. NC: bilateral lymph node metastasis;
3. Mo: No clinical metastasis. Basing on the FIGO classification, a T2 N2 Mo with bilateral regional lymph node metastasis would qualify this as a Stage IVA tumor.

The traditional treatment of vulvar cancer was introduced by Way in 1954. Radical vulvectomy with bilateral lymphadenectomy is an en-bloc dissection of the whole vulva, together with the inguinal skin, the subcutaneous tissue and nodes in the groin and femoral triangles[3]. This procedure has been associated with a high cure rate and significant morbidity. This included wound breakdown and secondary infection, occurring in practically all patients. Overall mortality was reported as high as 5.7%[8]. Women who undergo this procedure often have sexual dysfunction and a significant decrease in self image[8].

The procedure done to our patient was a partial vulvectomy with bilateral lymphadenectomy using two separate incisions, a large incision in the right groin area extending to the vulva and a smaller left groin incision to dissect the left superficial inguinal nodes. We have seen this wound breakdown fairly early into her post-op course. This is mostly attributed to the rather wide incision at the right groin area, resulting to a repair with high tension at the edges.

We may also surmise that since majority of these women have the disease late in life, their ability to heal efficiently is also compromised. Therefore, there were several studies and efforts to delineate patients that can be managed with less radical

procedures without compromising survival.

A recent dissertation by Abad, M.D. outlined the different alternative to the classic Way procedure

1. Vulvar conservation for unifocal lesions and an otherwise normal vulva

For early vulvar cancer, the vulva is spared as much as possible for stage lesions with 5mm or less invasion. The treatment starts with dissection of the superficial inguinal nodes then sent for frozen section. If there is no metastatic disease, the groin incision is closed and wide local excision of the lesion is done. The findings of positive nodes mandates complete inguinal dissection.

2. Elimination of routine pelvic lymphadenectomy

Traditionally, pelvic nodes are dissected in the presence of positive groin nodes. The pelvic nodes are involved 25% of the time when groin nodes are positive. In a study by the Gynecology Oncology Group on patients who have positive groin nodes, results show significant benefits in those who received postoperative radiotherapy versus those who underwent only pelvic node dissection. Most authorities now recommend that patients with clinically evident nodes or two or more microscopically positive groin nodes receive bilateral groin and pelvic radiotherapy.

3. Omission of groin dissection for patients with stage 1 tumors and less than 1mm of invasion. In these tumors, groin dissection may be omitted because the incidence of node metastasis approaches 0%.
4. Omission of contralateral groin dissection in patients with lateral lesions and negative ipsilateral nodes. It is not necessary to perform bilateral groin dissection if the primary tumor is unilateral, because the risk of positive contralateral nodes without positive ipsilateral nodes is less than 1% for Stage 1 tumors.
5. Use of separate incisions for groin dissection. Tumor spread is by embolization and not by permeation. This is the justification of the three-in-one incision with no fear of recurrences between the skin bridges. A significant improvement over the 40% - 80% incidence of wound infection and breakdown was observed.
6. Use of preoperative radiation therapy to obviate the need for exenteration in patients with advanced disease. Pelvic exenteration with radical vulvectomy and bilateral groin dissection carries an operative mortality of 10%, with a high post operative morbidity. Preoperative radiation therapy has been used to shrink the primary tumor with radical vulvectomy carried out in 6 weeks.

It would be interesting to note our management of the post-op complication of would breakdown. On the advice of Dr. Abad, an area may be left open to granule and epithelialize. The wound breakdown is cleansed with hydrogen peroxide and honey dressings are applied three times daily[8]. We have used this method of dressing in our patient and we have noted good healing and an arrest in the deterioration of the wound.

The prognosis of a patient with vulvar carcinoma is related to the stage of the disease, lesion size, as well as the presence or absence of cancer in the regional nodes. The presence of carcinoma in regional lymph nodes correlates with the size of the primary lesion, the degree of tumor differentiation, and the extent of involvement of vascular spaces by tumor. The status of the regional lymph nodes is important prognostically. The Gynecologic Oncology Group indicate that tumor stage, location on the vulva, microscopic differentiation, vascular space involvement, and tumor thickness are all important prognostic factors. Based on the 20th Annual Report on the Results of Treatment of gynecology Cancer, the worldwide 5 years survival rate for Stage IV A cancer is 13%[7]. The 3 years survival rate as reported by the PGH, in a 30 years review is 40%[3].

Kirschmer et al. noted other contributing factors to a poor prognosis. As previously mentioned, the report adds a new factor, namely smoking, that invariably affects the survival rate. They observed significant findings related to survival were smoking, tumor size and node status. The estimated risk from dying was 6.3 times higher in smokers than in non-smokers, and 8.3 times higher in those with positive nodes than those with negative nodes. Also, for every 1 cm increase in size, there was a 46% increased risk death[10].

In another study, Sturgeon et al. found that patients with vulvar cancer also have an elevated risk for the development of subsequent smoking related tumors. These associations indicate that the follow-up care of women with vulvar cancers should involve to promote smoking cessation[11].

Recommendations

The patient will still require an extended hospital stay due to the care of her wound breakdown. Upon discharge, a close follow-up should be emphasized to the patient, paying careful attention to any signs and symptoms that may indicate recurrence. The exposure from this case should teach us not to take lightly any complaints of persistent vulvar pruritus or the presence of any vulvar lesion or suspicious discoloration, as subtle as it may seem. As previously mentioned, this is a slow disease entity, allowing us the opportunity to intervene early and to prevent the onset of advanced disease. The vulva is an easily accessible area requiring no special equipment to examine. Therefore, with careful attention, the incidence of vulvar cancer can be kept low. With regards to the increasing incidence in the younger population and it's association with HPV, a more aggressive education of our patients would bring about awareness in the prevention of the disease.

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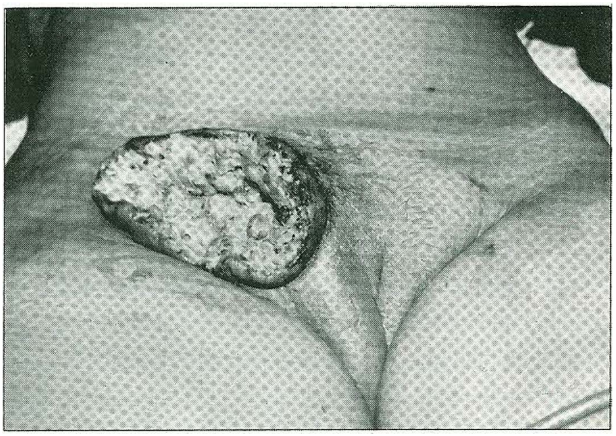
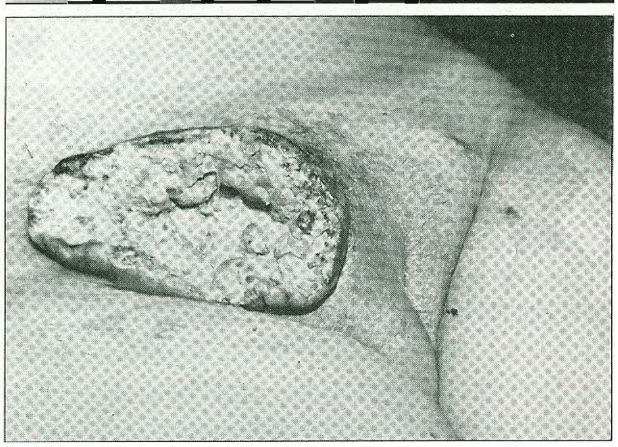
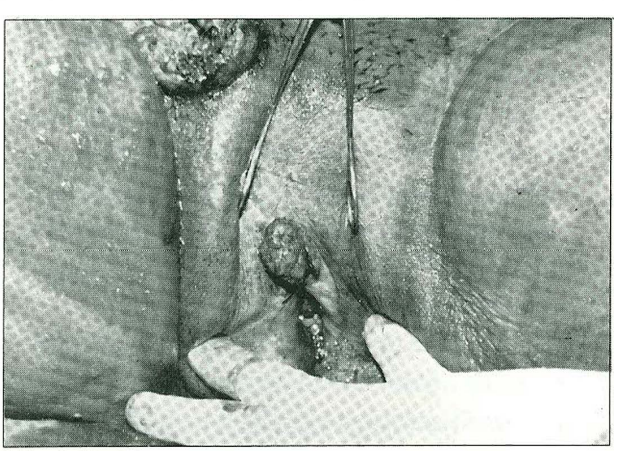
View of affected biopsy site, right inguinal region and the swollen right labia Majora



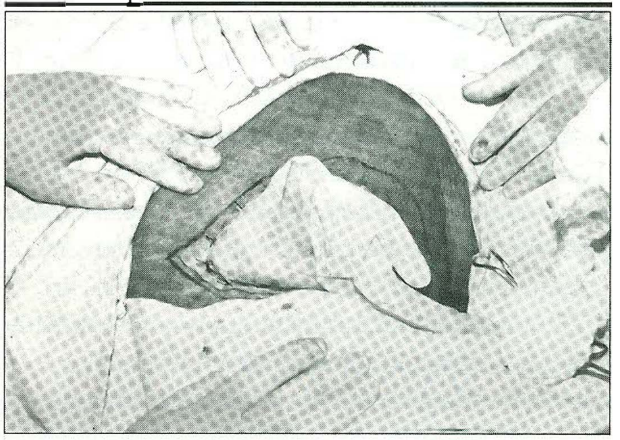
Closer inspection of right inguinal are pre-op



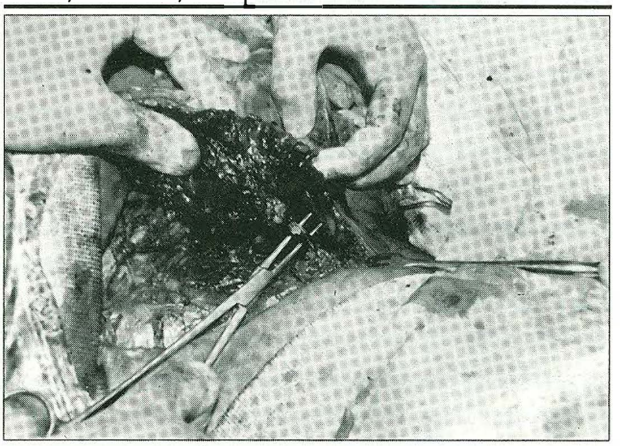
Squamous cell Vulvar Cancer with primary tumor located at the clitoris. Note location of infected biopsy site.



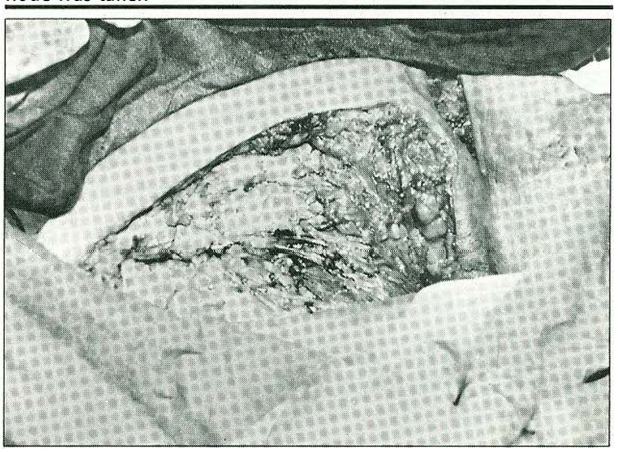
Area to be incised was prepared, drapedm and a rubber glove was sewn around the wound edges to prevent handling infected tissue intra-op.



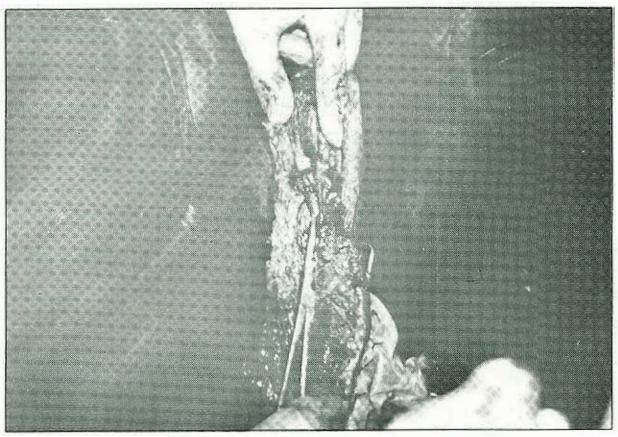
Excision of lesion with the right superficial inguinal lymph node. Note careful dissection, identification and ligation of blood vessels, in this case, the saphenous vein



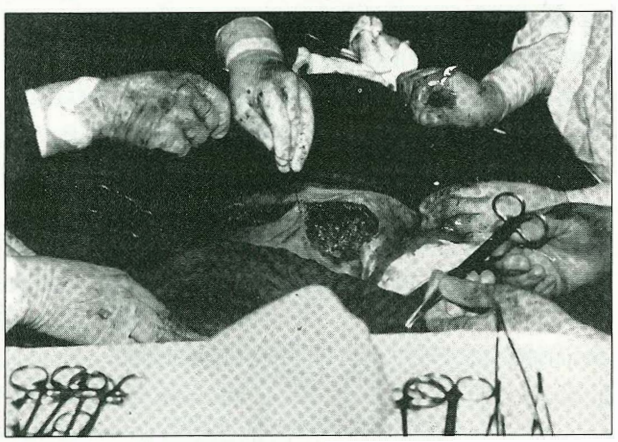
Large defect at the right groin, note separate and smaller incision at the left inguinal area where the left superficial inguinal lymph node was taken



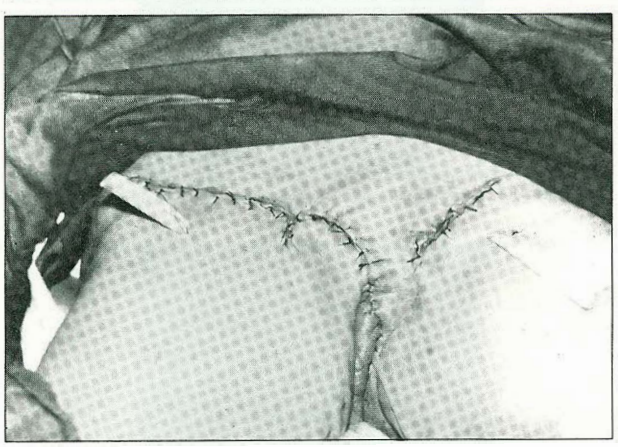
The incision on the right inguinal region was extended to include the sperior half of the vulva.



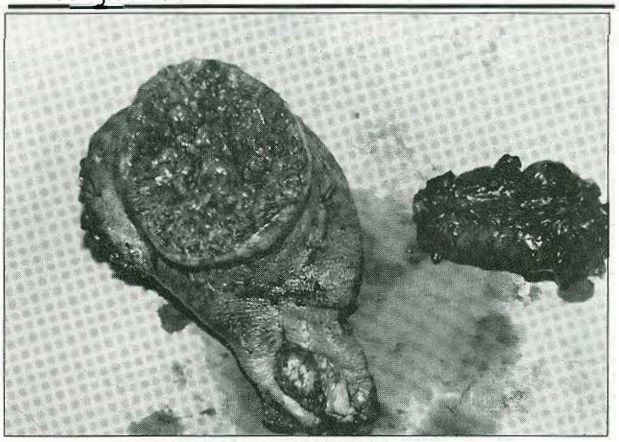
Closure of the large defect with silk sutures.



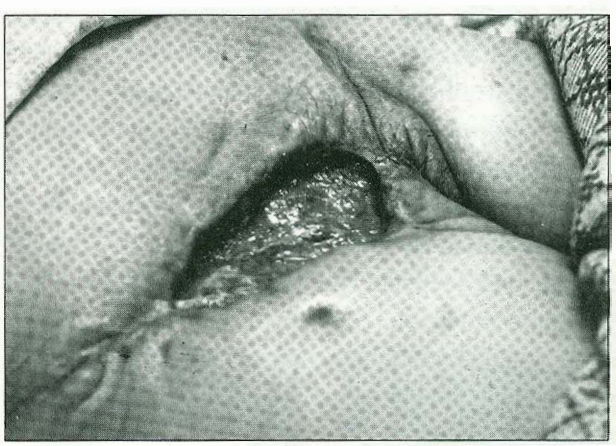
Finished surgery and drains in place.



Gross specimens. The left superficial lymph node is on the right. The right inguinal lymph node and the vulvar tumor were taken in this single incision.



Wound breakdown at the right inguinal repair post-op. Note however, the absence of infection and clean wound edges. Honey dressing is used here. The left incision has healed completely.



Imperforate Oral Cavity : A Case Report†

ALFONSO H. FAMARAN JR., M.D.* AND VIRGILIO R. DE GRACIA, M.D.**

Abstract

This paper reports a rare case of imperforate oral cavity in a 2 year old male. The paper also discusses the possible pathophysiology involved in this case, its consequences as well as proposed logical surgical intervention. Associated findings were a wide intercanthal distance, flattening of the nasal bridge, and splaying of the alae nasi, hypoplastic mandible, bowed legs, right pes planus and left pes plano-valgus. By performing a bilateral coronoidectomy, the patient was provided with a near normal conduit for food and an oral aperture.

***Keywords**: Imperforate Oral Cavity, Bilateral coronoidectomy*

Introduction

INTEREST IN STRUCTURAL ABNORMALITIES in the newborn dates to around 5000 B.C. when Babylonian priests made a list of 62 malformations recognizable at birth. However, widespread scientific interest and public concern did not develop until 1960 with the first report of teratogenicity associated with the sedative-hypnotic drug thalidomide. While this tragedy stimulated an enormous growth in basic and applied research in this field, there is still little knowledge about how drugs and chemicals cause congenital anomalies and even less about how genetic and environmental factors interact in individual unborn children. About 20% to 30% of reported defects is thought to result from spontaneous genetic aberration and 6% is clearly related to drugs and chemicals, leaving the cause unknown in nearly 70%.[6] These figures underestimate the magnitude of the problem, since there are unknown percentages of unrecognized and unreported cases, and instances of failure to associate a teratogen with an abnormality.

Case Report

This is the case of P.T., a 2 year male, born at Fabella Maternity Hospital to a 31 year old G4P4 (4-0-0-4) by normal spontaneous delivery, full term with a birth weight of 1900 grams, who presented with an imperforate oral cavity. Patient was placed in an incubator and nutrition was provided through a nasogastric tube. An attempt to document an existing oral cavity was done. This was confirmed by inserting a 10cc syringe with a 19 gauge needle, yielding air from the supposed oral cavity.

Figure A: Photograph showing external facial features
-wide intercanthal distance
-flat nasal bridge, splayed alae nasi
-rounded face, hypoplastic mandible

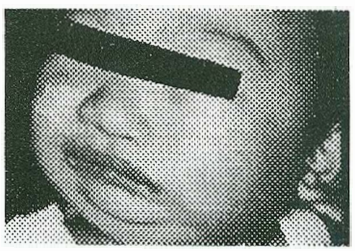
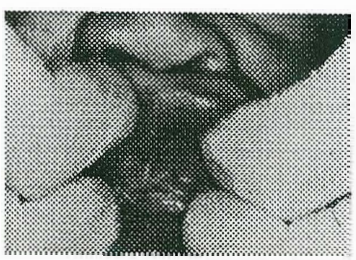


Figure B: Photograph showing gingivo-buccal sulcus, frenulum of upper lip and imperforate oral cavity



† *3rd Prize, Clinical Case Report Contest, PSO Mid-year Convention, Subic International Hotel*

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At 1 year and 7 months, the patient was referred to a private teaching hospital for further evaluation and management. On initial examination, the patient was mildly stunted, not wasted and was not in any respiratory distress. Vital signs were within normal limits. Eye examination revealed a wide intercanthal distance and unremarkable fundoscopic findings. Ear findings were normal. Nasal examination showed a flattened nasal bridge and splayed alae nasi. Oral cavity examination revealed a gingivobuccal sulcus without an oral aperture. A hypoplastic mandible was evident. Lower extremities presented with bowing of the legs with right pes planus and left planovalgus. All other organ systems were essentially normal. The patient underwent a battery of laboratory work-ups which include complete blood count revealing anemia which required blood transfusion. Cranial CT Scan showed normal maxillae, mandible, temporo-mandibular joints, and a porencephalic cyst at the basal ganglia. Bleeding parameters, chest x-rays and urinalysis were normal. The service contemplated releasing the intraoral adhesion under general anesthesia. Referrals to the pediatric, neurosurgery and orthopedic services were done. The patient was not cleared for surgery due to malnutrition. Weekly and monthly follow-ups were undertaken to monitor weight gain and general health.

Figure C: CT Scan of the Temporo-mandibular joint (axial cut)

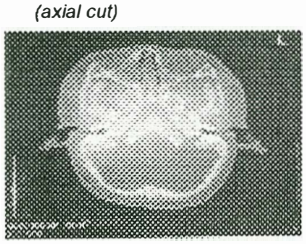
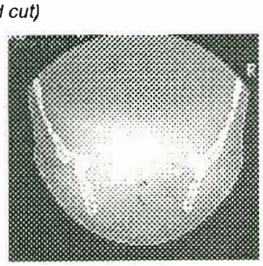


Figure D: CT Scan of the Temporo-mandibular joint (coronaal enhanced cut)



At 1 year and 9 months, the patient was admitted for the contemplated procedure. Repeat CT scan on the mandible still revealed a normal temporomandibular joint, without any evidence of ankylosis or sclerosis; however, it also showed that the lateral borders of the coronoid processes were in contact with the inner surface of the zygomatic arches. Again, overall condition and nutrition were monitored weekly and monthly follow-ups. A chromosomal study revealed no abberations.

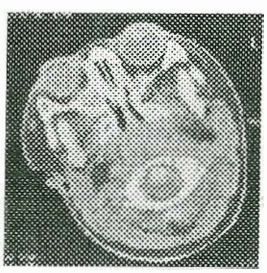


Figure E: CT Scan of the Mandible (repeat axial cut)

At 2 years and 4 months, the patient underwent bilateral coronoidectomy with release of intraoral adhesions via the submandibular approach. Airway was provided through fiberoptic-guided insertion of a nasotracheal tube. Intraoperatively, the soft and hard palate were noted to be absent, tooth buds present and the tongue hypoplastic. Manual manipulation of the mandible showed mobility permitting a maximum opening of 2 cms.

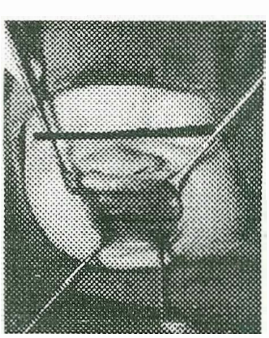


Figure F: Release of intra-oral intra- adhesions (first operation)

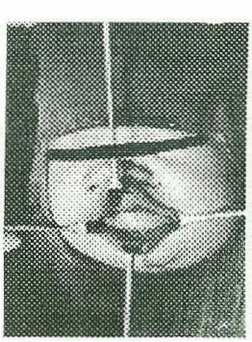


Figure G: Installation of oral device (first operation)

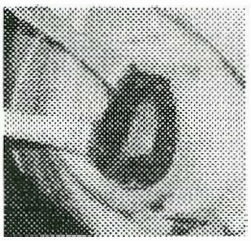


Figure H: Coronoidectomy, left (second operation)

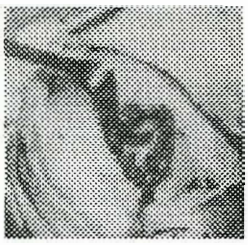


Figure I: Coronoidectomy, right (second operation)

Post-operatively, a Denhard mouth gag was installed to maintain the patency and to prevent synecchiae. A dental obturator was fitted at the third post-operative day for less traumatic maintenance of an oral cavity.

Discussion

Because of the high rate of cellular differentiation, function development and growth taking place over a relatively brief period of time, the fetus is susceptible to chemical insults which may result in congenital anomalies. The kind of anomalies caused by these insults depend critically upon the development stage at the time of exposure.

Figure J: Tabulation of syndromes with oral manifestations

Syndrome	Cause/ Inheritance	Major systematic manifestations	Oral manifestation
Aarskog-Scott syndrome	X-linked	Growth retardation	Hypoplastic narrow maxilla,relative mandibular prognathism
Achondroplasia	80% sporadic 20% autosomal dominant	Dwarfism with large head	Malocclusion, anterior crowding of teeth, anterior overjet, various crossbites
Acrodynia	Etiologic agent: mercury	Neurologic signs: bruxism, causing chewing of buccal mucosa and tongue	Stomatitis with ulceration, spongy red gingiva with periodontal abscesses and shedding of teeth
Acrodysostosis	Sporadic	Growth retardation, short stubby fingers	Maxillary hypoplasia, prominent upper aveolar process, open bite, relative mandibular prognathism
Arachnodactyly (Marfan's syndrome)	Autosomal dominant	Tall thin, ocular lens, subluxation, aortic wall defects	High palatal vault, cleft palate, bifid uvula, dental malocclusion, long narrow teeth, mandibular prognathism
Ascher's syndrome	Possible autosomal dominant	Blepharochalasis, non-toxic thyroid enlargement	Duplication of upper lip
Ataxia telangiectasia (Louis-Bar syndrome)	Autosomal recessive	Ataxia, mental deficiency	Telangiectasia of hard and soft palate, drooling diminished or absent orophryngeal lymphatic tissue
Beckwith-Wiedemann syndrome	Sporadic	Omphalocele	Macroglossia, class III malocclusion, anterior open bite, retroclined mandibular incisors
Chediak-Steinbrinck-Higashi syndrome	Autosomal recessive	Defective pigmentation, abnormal granulation of leukocytes, increased susceptibility to infection	Aphthae and/or gingivitis, rapid breakdown of periodontium
Cleidocranial dystostosis	Autosomal dominant	Clavicular aplasia or hypoplasia, delayed ossification of fontanels, large cranium	High-arched palate, submucous or overt cleft palate, non-union of mandibular symphysis, failure of eruption of deciduous and permanent teeth; poor premaxillary development with relative prognathism
Cockayne's syndrome	Autosomal recessive	Dwarfism	Congenital absence of teeth, increase in dental caries, atrophy of alveolar process, and condylar hypoplasia
Craniocarpotarsal dysplasia (whistling face syndrome)	Autosomal dominant	Growth retardation, flexion contracture of fingers	Microstomia, small mandible and tongue, high-arched palate, lips held as in whistling, fibrous band from chin to the middle of lower lip
Familial dysautonomia (Riley-Day syndrome)	Autosomal recessive	Nervous system, cutaneous and eye manifestation	Mouth transversely elongatedinto a horizontal slit; absence of fungiform and most circumvallate papillae with decreased sensitivity to sweet and bitter; excessive crooling, swallowing disturbance, dental-arch crowding, periodontal disease
Hyperkeratosis palmaroplantaris and periodontoclasia in childhood (Papillon-Lefevre syndrome)	Autosomal recessive	Palmar and plantar hyperkeratosis	Gingival swelling with loss of primary and secondary teeth after alveolar process is destroyed
Hypospadias/dysphagia (G syndrome)	Autosomal dominant	Genitourinary	Ankyloglossia, bifid uvula, neuromuscular dysfunction of swallowing mechanism, large laryngopharygeal cavity causing aspiration
Inability ti open mouth fullly and pseudocampodactyly	Autosomal dominant	Reduced stature, abnormalities of extremities	Enlarged coronoid process limiting the aperture between upper and lower incisions to 1,0 to 1.8 cm

de Lange syndrome	Sporadic	Musculoskeletal, cutaneous, genitourinary manifestations	Micrognathia, prominent mental spur, thin lips with corners of mouth downturned, long philtrum with delayed tooth eruption, cleft palate, oral self-mutation
McCune-Albright syndrome	Sporadic	Endocrine, cuteneous manifestations, bone problems	Large expanded distorted jaws, dense maxillary mass protruding into the oral cavity, oral pigmentation on lips and mucosa
Multiple endocrine	Autosomal dominant	Pheochromacytoma, medullary thyroid carcinoma	Mucosal neuromas on lips and tongue, enlarged and nodular lips; tongue lesions are pink, pedunculated, and limited to anterior dorsal surface
Oral-facial digital syndromes I and II	I-Dominant X-linked II-Autosomal recessive	Skeletal cutaneous, and neurologic manifestations	Cleft lip and palate, cleft tongue, abnormally developed frenula with intraoral synechia
Peutz-Jeghers syndrome	Autosomal dominant	GI polposis	Brown-bluish maculae periorally, perinasally and periorbitally; 98% have lip pigmentation, 88% have buccal mucosa pigmentation

An imperforate oral cavity occurs in much the same way as the more common imperforate hymen, which is secondary to failure of disruption of the formation of the connection between the vaginal canal an the vestibule at 6 to 12 weeks AOG. At 6 to 12 weeks AOG, once the mesoderm has completed its migration and reinforcement of the entire primary plate, the early facial structures are refined by a process of ectodermal sculpting wherein cells proliferate, move into areas, carve furrows, dig cavities and hollow tunnels. This sculpting is accomplished through a sequence of cell colonization, followed by differentiation of those cells close enough to the basement membrane to be nourished by transudate, and cell death of those farthest from the source of nourishment. This sculpting separates the dental lamina within the developing alveolus from the lip, thereby creating the alveolar-labial sulcus. It is also responsible for the deepening of the nasal pit and the lateral rupture of the bucco-pharyngeal membrane. Insults during the sculpting stage results in failure of the bucco-pharyngeal membrane to rupture resulting in imperforate oral cavity.

Between 4 to 12 weeks AOG, the cartilaginous bars and the branchial arches differentiate into the initial cartilages of head and neck. The ventral portion of the first bar, also known as Meckel's cartilage, is destined to form the mandible by intramunhaous ossification. Failure to do so results in hypoplastic mandible. At the same time, porencephalic cysts, a defect in the development of the cerebral mantle with the replacement of the temporo-parietal areas by fluid filled spaces develops secondary to insult to the cerebrum. While skeletal structure at the leg region are being formed, insult at this time would result in femoral tibial and feet abnormalities.

The striking feature of the newborn skull is the small size of the facial portion in comparison with that of the cranium. At birth, the relative proportions are about 1:8; by age 5, they are 1:4 and in adult, they are 1:2.5. The infant's face is proportionately wide, short, thus appearing flat with a pug nose beneath a bulging forehead. The small face is almost entirely due to immaturity of the maxilla and mandible. Vertical growth of the face, which is absent in this patient, occurs in spurts related to respiratory needs and tooth eruption and takes place during the first six months after birth and then during the third and fourth years until 19 years old. This continuity between the maxilla and the mandible due to intraoral adhesion prevents continuous expansion of facial soft tissue.[2] This will hinder posterior elongation of the maxillary arch through bony deposition on the posterior surface of the maxillary tuberosity providing no space for future molar teeth. Absence of resorption of the inner face of the tuberosity will not enlarge the maxillary sinus. Non-displacement of the maxilla anteroinferiorly will not lead to sutural growth which further enlarges the bone. Furthermore, anterior

displacement of the mandible accompanies that of the maxilla, providing for the balanced growth of these bones so that the relationship of the teeth remains reasonably constant throughout life. Growth of the mandible will not occur since there is no growth of the ramus and condyle in a backward and upward direction.[4] Absence of bony deposition posteriorly is equaled by absence of resorption of the anterior surface of the ramus. With this pathology, the patient retains the regional proportions among the various facial regions apparent in neonatal life.

Conclusion

Based on the above development scheme, it can be inferred that an insult was introduced between 4 to 12 weeks AOG. Many cases of unknown causation probably resulted either from unrecognized exposure to drugs and chemicals or from a complex interaction between drug effect, genetics and environmental factors. From statistics, it was found out that the average woman takes 10 prescription or non-prescription drugs during pregnancy, most of them without the physician's supervision.[5] Needless to say, many women of childbearing age are exposed frequently to potential chemical teratogens in their jobs, and presumably all women are exposed, to some extent, to an enormous array of environmental chemicals. The conglomeration of congenital defects in this patient do not conform with non-cleft disorders as listed by Cummings. It will be a geneticist's concern and interest to establish a new name for this syndrome and its precipitating insult. This being the first case of an imperforate oral cavity reported in the Philippines, there is understandably a lack of literature both local and foreign. It is, therefore, proposed that physicians regardless of their specialties, report congenital defects with possible associated prenatal insults. This will create a wealth of study material for establishment of a more definitive means of diagnosis and management.

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Instructions to Contributors

Aim and Scope

The UERMMMC Journal of Health Sciences will publish papers, reviews, and editorials written by members of the medical staff, the allied medical staff, and the students of the UERM Memorial Medical Center whether such are original or previously published articles.

Style of Papers

All contributions should be written in English. Papers should be written so as to be intelligible to the professional reader who is not a specialist in the field. The editor and his staff reserves the right to modify manuscript to eliminate ambiguity and repetitions, and improve communication between author and reader. If extensive alterations are required, the manuscripts will be returned to the author for revision. Therefore, to minimize delay in publication, manuscripts should be submitted in accordance with the instructions detailed herein. The editor will not be held responsible for views expressed in this journal.

Submission of Manuscript

A single copy of the manuscript, including tables and figures should be submitted to the editor. To facilitate revision of the manuscript, the editor requires submission of a 1.44 megabyte floppy disk containing a recorded copy of the manuscript using a standard word processor program. All pages of the typed manuscript should be numbered including those containing acknowledgments, references, tables, and figures. The manuscript should be arranged as follows: a) title, b) abstract, c) key words, d) introduction, e) materials and methods, f) result, g) discussion, h) acknowledgment, i) references, j) tables, k) figure legends, and l) figures.

Title

The title should be as concise and informative as possible and should contain all key words to facilitate indexing and information retrieval. If the title consists of more than forty (40) characters (including spaces), a short running title of less than forty (40) characters should be provided. This should be followed by the list of authors' names to be written as follows: first name, middle initial, family name. The department or institution of each of the authors should also be provided.

Abstract

This should be a concise summary of no more than 250 words of the purpose, basic procedures, main findings and principal conclusions of the investigation. New and important information should be emphasized.

Key Words

Three to ten keys words or phrases should be provided which will assist in cross-indexing the article.

Introduction

This should contain a summary of the rationale of the study and provide an outline of pertinent background material. It should not contain either results or conclusions.

Materials and Methods

This should contain the procedures undertaken in the study in sufficient detail as to leave no doubt to the reader how the results were arrived at.

Results

This should be presented in logical sequence in the text, tables, and figures avoiding repetitive presentation of the same data. This section should not include material appropriately belonging to the discussion. Results must be statistically analyzed when appropriate.

Discussion

Data mentioned in the results in relation to any hypothesis advanced in the introduction. This

may also nclude an evaluation of the methodology and the relationship of new information to previously gathered data. Conclusions should be incorporated in the final paragraph and should be commensurate with and completely supported by data gathered in the study.

Acknowledgments

Only persons who have made genuine contributions and who endorse the data and conclusions should be acknowledged. Authors are responsible for obtaining written pemission to utilize any copyrighted text and/or illustrations.

References

References cited in the text shall be written as Arabic numerals in superscript in the order in which they appear in the text. Titles of journals should be abbreviated in the reference list according to the style used in Index Medicus. Unpublished observations and personal communications may not be used as references. Examples of the correct manner of listing references are illustrated below:

Standard journal article (list all authors when six or less; when seven or more, list only the first three then add et. al.)

1. Francis D. P. , Hadler S.C., et. al. The Prevention of Hepatitis B with Vaccine. Ann. Intern. Med., 1982; 97;362-366.

2. Krugman, S., lacy L.R., et al. Viral Hepatitis Type B. N. Engl. J. Med. 1979; 300:101-106

Books and other monographs

Personal authors

3. Adams R.D., Victor M. Principles of Neurology. McGraw-Hill, New York. 1981.

Chapter in a book

4. Selwyn A.P., Braunwald E. Ischemic Heart Disease. In: Braunwald E., Isselbacher K.J., Petersdorf R.G., eds., Harrison's Principles of Internal Medicine. McGraw Hill, New York. 1987; 975-982.

Tables

These should be typed on a separate sheet, numbered with Arabic numerals and accompanied by a title and an explanatory caption at the top. Each table must be referred to in the text and an indication of the preferred position in the text should be given. Other explanatory materials should be placed in footnotes below the tables. All non-standard abbrevations should be explained in the footnotes. Vertical and horizontal rules between entries should be omitted.

Figure legends

All illustrations require legends, typed on a separate sheet. When symbols, arrows, numbers, and letters are used to identify parts of illustratios, each one should be identified and explained in the legend.

Figures

Illustrations should be sharp, glossy, black and white prints. Letters, numbers and symbols must be clear and of sufficient size to retainn legibility when reduced. Titles and detailed explanations should be confined to figure legends and not included in illustrations. Each figure should be identified clearly on the back with its number and author. Photographs of persons must be retouched to make the subject unidentifiable or be accompanied by written permission from the subject to use the photograph. Figures should be numbered in Arabic numberals.

The Editorial Board of the UERMMMC Journal of Health Sciences (UERMMMC-JOHS)

congratulates

the authors of the paper

"An *In Vitro* Assay and an Electron Microscopic Analysis on the Schizonticidal Effect of *A. Scholaris* (Dita) Bark Extract on the Intra-Erythrocytic *P. Chabaudi* using Mice Red Blood Cells"

first published in the maiden issue of the UERMMMC-JOHS (July–December 1998, pp. 41-48), for garnering **FIRST PRIZE in the GRUPPO MEDICA AWARD**, *an award which gives recognition to relevant and innovative research work on herbal medicine undertaken by undergraduate students. The winning authors are:*

Ida Cristina E. Zarraga; Ma. Elena T. Viterbo; Xanthe Yvonne A. Zafra; Ma. Vanessa N. Villarosa; Reynaldo B. Torres; Emmare Jane O. Tuazon; Milagros D.C. Uy; Primo B. Valenzuela; Richard John Valenzuela; Janis Natherlene L. Veroy; Ravi S. Victoria; Jaydee D.C. Vila; Myra P. Villamonte; Richard F.E. Villegas; Tony S. Villena; Antonio V. Viray III; Poh-lim Wie; Victor Joseph T. Yamat; and Alfaretta Luisa Reyes, m.d.,

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