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Full Length Research Article

Safety, Efficacy and Tolerability of Meprasil[m] in the Treatment of Dyspepsia among Nigerians.

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ABSTRACT

A clinical trial was carried out to establish the tolerability, safety and efficacy of Meprasil brand of omeprazole among Nigerians with acid peptic disease using 20mg daily or 20mg bid of Meprasil. Forty patients were enrolled for the study and were asked to rate their abdominal pains pre-commencement of therapy using a scale of mild, moderate or severe. Serum alanine transaminase (ALT), urinalysis, electrolytes, creatinine and urea were carried out before and after treatment. Patients were then evaluated on days 0, 1, 3, 7, 14, and 28, thereafter monthly for 4 months for relief of symptoms and adverse drugs effect. Only 32 patients completed the study, 17 (Group I) and 15 (Group II). Symptoms included abdominal pain (100%), vomiting 9.4%, haematemesis 3.1%, anorexia 25.0% and diarrhea 15.6%. Pain was rated as moderate in most patients (46.4%), mild in 21.4% and severe in 32.1%. Alanine transaminase (ALT) 27.8± 11.7 IU/L, Sodium 137± 4.3 mmol/L, Potassium 3.8±0.46mmol/L, Chloride 103.1±4.0mmol/L, Bicarbonate 22.4±1.8mmol/L, Urea 21.9±5.1mg/dl, creatinine 1.1±0.23mg/dl. No patient had glycosuria prior to enrolment while 2 out of 31 (6.5%) had a mild proteinuria. Ranked adverse drug reaction included diarrhea (21.9%), headache (21.9%), flatulence (15.6%), nausea (12.5%), constipation (9.4%), pruritus (9.4%), skin rashes (6.3%), dizziness (3.1%) and abdominal pain (3.1%). Intensity of pain and adverse events reported during follow up between the two doses of Meprasil showed no significant difference. The biochemical parameters before and after treatment among both treatment groups were similar. In conclusion, this study has shown that Meprasil taken as 20mg or 20mg twice daily, is safe, efficacious and well tolerated in amelioration of pain of acid peptic disorder among Nigerian patients.
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Key words: - *Meprasil, efficacy, tolerability, Dyspepsia, Nigerians*

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INTRODUCTION

Acid peptic disorder (APD) is a group of gastrointestinal disorders in which acid and pepsin play a major role. Thus, APD encompasses conditions such as peptic oesophagitis usually as gastroeosophageal reflux disease (GORD), gastritis, duodenitis or gastroduodenitis in addition to peptic ulcer disease, which may be gastric or duodenal. Peptic ulcer disease (PUD) is usually restricted to organic gastrointestinal disease defined as a breach in the continuity of the epithelial lining of the gastrointestinal tract (GIT) where there is excessive acid-pepsin activity relative to the degree of local resistance. Dyspepsia, the classic symptom of peptic ulcer disease, is defined by American Gastroenterological Association (1995) as pain centered in the upper abdomen or discomfort characterized by fullness, bloating, distention, or nausea. Dyspepsia is also grouped into ulcer and non-ulcer dyspepsia. Peptic ulcer disease (PUD) has a lifetime prevalence of 5%-10% world-wide Kurata *et al* (1984), Rosenstock *et al* (1995) and a lifetime prevalence of 10%-20% in *H. pylori* positive individuals. Kuipers *et al* (1995). In Nigeria, autopsy studies at the University College Hospital, Ibadan, on PUD, revealed a prevalence of 5%.Olubuyide (1989).With a population of about 126 million (WHO 2005), this would suggest that about 6.3 million Nigerians die with PUD. Another study of dyspeptics by Holcombe *et al* . (1991) in Northern Nigeria, an area well known for low incidence of PUD revealed a prevalence of 12% among hospital patients suggesting a community prevalence of 18/1000. Proton pump inhibitors (PPI) are well known to be potent inhibitors of parietal cell acid secretion and have been found to be effective in the control of acid-related gastrointestinal disorders including dyspepsia. The efficacy and safety of omeprazole, the prototype PPI has been well documented in the Caucasian population Labenz *et al* . (2003). They were found to be well tolerated, with notable side-effects being mild and mainly drowsiness, dizziness, headache, diarrhoea, flatulence and itching. Although omeprazole has been in use in Nigeria in the last few years, no particular study in Nigeria has evaluated its efficacy, safety and tolerability. Racial differences in pharmacogenetics, pharmcodynamics and pharmacokinetics are well known in drug metabolism. The objective of this study, therefore was to establish the tolerability, safety and efficacy of Meprasil brand of omeprazole in a Nigerian population.

PATIENTS AND METHODS

The study was carried out at the University College Hospital, Ibadan, Nigeria. It was to compare the safety, efficacy and tolerability profile of 20mg daily and 20mg bid of Meprasil brand of omeprazole among patients with dyspepsia. It was not meant to be a clinical trial of omeprazole.

Forty patients (20 each in Groups I and II) with dyspepsia attending the Medical outpatient Department of the University College Hospital, Ibadan, Nigeria were enrolled for the study. Diagnosis of dyspepsia was made based on persistent symptom of upper abdominal pains with nocturnal exacerbation, aggravated by fasting and relieved by meals and/or antacids. Patients were asked to rate their abdominal pains pre-commencement of Meprasil therapy. On a scale of mild, moderate or severe. Included in the study were consenting patients with features of dyspepsia, with or without endoscopic confirmation, who had ability to comply with study protocol. Excluded from the study were patients on or requiring NSAID therapy, pregnant or lactating mothers, known allergy to the test drug or patients treatment with antacids or anti-ulcer drugs in the last 4 weeks preceding the study. Ethical approval was sought and obtained from the University of Ibadan/University College Hospital, Joint Ethical Committee. Verbal informed consent was obtained from all the patients.

Serum alanine transaminase (ALT), urinalysis, electrolytes, creatinine and urea were carried out on all the recruited patients before and after treatment with Meprasil. Meprasil was given at a dose of 20mg twice daily to seventeen patients in one arm (Group I) and 20mg daily to fifteen

patients in the second arm (Group II) for a total period of 4 weeks. To ensure compliance, each patient was issued drug stock that would last for a week and were only issued their next stock by bringing the foil of the previous one, which were collected. They were also informed to avoid taking any other drug apart from the study drug except when essential and such should be reported during the next appointment.

The investigations carried out before commencement of therapy were repeated within 48 hours of completion of therapy. Samples for ALT, creatinine and urea were run on Hitachi 912 automated system (Roche diagnostics) while sodium and potassium were estimated using corning 410 flame photometer with appropriate standards. Urinalysis was done with multistix (Bayer Diagnostics Europe). Patients were seen and evaluated for review of symptoms of acid peptic disease on days 0, 1, 3, 7, 14 and 28, thereafter monthly for 4 months. Withdrawal from the study was based on withdrawn consent, violation of study protocol or development of complication of the disease. Safety and efficacy were measured by review of physical examination, adverse events record, serum biochemistry and symptoms. Each patient was asked to note any symptom during the course of the drug therapy and report immediately to the investigators or during their next appointment if judged mild and tolerable.

Statistical analysis

Data generated were analysed using SPSS statistical software for frequency, proportions, means and tests of significance.

RESULTS

Out of the 40 patients enrolled, 8 dropped out due to inability to follow study protocol and loss to follow-up. Of the 32 patients that completed the study, 17 were in Group I while 15 belonged to Group II. The age range among all the subjects was 12-63 years with a mean of 37.6±12.5 (SEM 2.2), median of 35.5. There were 10 males (31.2%) and 22 females (68.8 %), with a male to female ratio of 1:2.2. One patient (3.1%) had a history of alcohol use, while 2(6.2%) had history of cigarette use, of 31 patients who had such history taken. (It was noticed at the time of analysis that the response was mistakenly omitted).

Clinical Parameters at enrolment were weight 70.86±14.89 (SEM 2.77) kg, height 1.61± (0.10) (SEM) m, Systolic blood pressure 118.7±12.5 (SEM 2.4) mmHg, diastolic blood pressure 75.96±10.1 (SEM 1.95) mmHg. Symptoms at enrolment were abdominal pain 32(100%), vomiting 3(9.3%), haematemesis 1(3.1%), anorexia 8(24.8%), and diarrhea 5(15.6%). Others were constipation, weight loss, nausea and early satiety. Location of the abdominal pain was epigastrium 28(87.5%), hypochondrium 2(6.2%) and paraumbilical 2(6.2%). Pain was rated as mild in 7(21.7%) moderate in most patients 15(46.5%), and severe in 10(31.2%). There was no significant difference of pain rating with gender (p=0.327). In pain severity rating, 1(3.1% male and 6(18.6%)females rated pain as mild, 7(21.7%) males and 8(24.8%) females reported moderate pain while 2(6.2%), males and 8(24.8%) females rated their pains as severe. Location of pain was not significantly associated with the severity (p=0.725).

Table 1: Some features of patient distribution between the doses of Meprasil

	Meprasil BD	Meprasil Dly	P value
Age	38.65±13.05	36.33±12.12	0.609*
Male	6	4	0.599**
Time of relief of abdominal pain	28±14.8	20.6±15.9	0.115*
Abdominal Pain duration prior to treatment (Days)	26.37±48.98	120.71±136.62	0.015*
Endoscopy done	11	2	0.003**

*Student t- test; ** Chi-square

Table 2:
Comparative efficacy of Meprasil BD and Daily dose using abdominal pain

	Score	Meprasil BD	Meprasil Dly	P (chi- square)	Fisher's Test
Day 1	No Pain	5	5	0.818	
	Mild pain	10	9		
	Moderate pain	1	1		
	Severe Pain	1	0		
Day 3	No Pain	9	6	0.622	
	Mild pain	6	8		
	Moderate pain	1	1		
	Severe Pain	1	0		
Day 7	No Pain	12	14	0.242	
	Mild pain	4	1		
	Moderate pain	1	0		
	Severe Pain	0	0		
Week 2	No Pain	11	14	0.256	
	Mild pain	4	1		
	Moderate pain	1	-		
	Severe Pain	1	-		
Week3	No Pain	15	15	0.170	0.486
	Mild pain	2	0		
	Moderate pain	0	0		
	Severe Pain	0	0		
Week 4	No Pain	16	14	0.927	1.0
	Mild pain	1	1		
	Moderate pain	0	0		
	Severe Pain	0	0		
Week 8	No Pain	17	15		
	Mild pain	0	0		
	Moderate pain	0	0		
	Severe Pain	0	0		

Table 3:
Adverse effects reported by patients on twice a day and daily doses of Meprasil

Adverse effects	Meprasil BD N=17	Meprasil Daily N=15	Total N=32	P value X^2	Fisher's Exact test
Headache	3	4	7	0.538	0.678
Diarrhea	5	2	7	0.272	0.402
Flatulence	3	2	5	0.737	1.000
Nausea	2	2	4	0.893	1.000
Constipation	3	0	3	0.087	0.229
Pruritus	2	1	3	0.621	1.000
Skin rash	1	1	2	0.927	1.000
Dizziness	1	0	1	0.34	1.000
Abdominal pain	0	1	1	0.279	0.469

Alcohol and cigarette use were not related to severity of pain. Family history of dyspepsia was positive in 12 (37.5%), and this was in mothers in 24(74.4%) of the patients. Previous drug use were antacids 8(24.8%, H-2 receptor blockers 8(24.8%), proton pump inhibitors 3(9.3%), NSAIDs and others 5(15.3%), while 8(24.8%) had not used any drugs in the past. Four patients (12.4%) had history suggestive of some complications like abdominal pain penetrating to the back and bleeding episodes. Baseline biochemical parameters were as follows: Alanine transaminase (ALT) 27.8 ±11.7 (SEM 2.1) IU/L, Sodium 137±4.3 (SEM 0.76) mmol/L, Potassium 3.8±0.46 (SEM 0.08) mmol/L, Chloride 103.1±4.0 (SEM 0.71) mmol/L, Bicarbonate 22.4±1.8 (SEM 0.32) mmol/L, Urea 21.9±5.1 (SEM 0.90) mg/dl, creatinine 1.1±0.23 (SEM 0.04) mg/dl. No patient had glycosuria prior to enrolment while 2 out of 31 (6.5%) had a mild proteinuria. Upper gastrointestinal endoscopy was done in 13 (40.3%) patients due to the high cost of the procedure. There was a significant difference in the number of patients on BD dose of Meprasil that had upper gastrointestinal endoscopy (p=0.003, Table 1). Patients on BD dose of Meprasil also had a shorter duration of pain before commencement of therapy (p=0.015, Table 1).

Following drug administration, pain was relieved in both groups in 24.6±15.6 (SEM 2.8) hours. On the first day post medication, 31.1% reported no pain while 59.4% only had a mild pain, by the 7th day 81.3% had no pain, while 15.6% only had a mild pain. By the 3rd week, 93.8% had no more pain. From the 8th week to the end of follow up in the 20th week there was no record of pain in all the patients. Ranked adverse drug reaction that were reported following drug use included diarrhea (21.9%), headache (21.9%), flatulence (15.6%), nausea (12.5%), constipation (9.4%), pruritus (9.4%), skin rashes (6.3%), dizziness (3.1%), abdominal pain (3.1%). Others were anorexia, internal heat, bitter taste in the mouth and weakness. Patients on daily dose of Meprasil had pain relief faster than patients on twice daily dose, 20.6±15.9 versus 28.1±14.8hours, but this was not statistically significant (p=0.115) Table 1. There was no difference between the intensity of pain and adverse events reported during follow up between the two doses of Meprasil (Tables 2 & 3). There was no significant difference in the biochemical parameters before and after treatment among both treatment groups.

DISCUSSION

Dyspepsia remains a major cause of morbidity and cause of loss of man-hours worldwide. Epigastric abdominal pains still remain the cardinal symptom. Other variable symptoms like anorexia, vomiting, and nausea are less frequent. A few may however present with hypochondrial or periumbilical pain as revealed in this study, among Nigerians. This mainly due to poor localization of visceral pain in contradistinction to parietal pain, which is usually well localized. Though a significant number had severe pain at presentation, it is evident that about half of the patients presented with moderate pain with no gender difference in pain rating. This contradicts the general but unsubstantiated belief that women are more able to tolerate pain than men. A significant number of the patients had had prior exposure to antiulcer drugs, especially antacids and H2-receptor blockers.

Patients usually present in hospital when these are ineffective. The supposed ineffectiveness is usually due to inappropriate use of these drugs as they are readily available over the counter in Nigeria. Alanine transaminase, the most specific enzyme denoting hepatic damage did not show any significant difference before and after the use of Meprasil, suggesting that the drug had no significant damaging effect on the hepatocytes. It should however be noted that omeprazole generally has the potential to interfere with the cytochrome 450 enzyme system and thus to induce or inhibit the metabolism of drugs such as diazepam, warfarin, caffeine and possibly phenytoin. Peterson (1995; 2003), however reported that these effects are minor and not reproducible in every patient. Similarly, following administration of Meprasil, there was no significant difference in the baseline and post

exposure biochemical parameters of renal function among the study population. This attests to the safety of Meprasil among Nigerians. Concerning pain relief, this study showed no significant difference between twice daily and once daily dosing of Meprasil (Tables 1&2). Indeed it appeared that onset of relief of pain is faster with the once daily dosing, in spite of the fact that the duration of abdominal pains before commencement of Meprasil was significantly longer in patients on daily dosing. This finding is difficult to explain based on the parameters studied. Reported adverse effects such as headache, diarrhea anorexia and constipation among others were quite similar to what has been reported by Martin *et al* . (2000) in Caucasian populations and are largely self-limiting. Some of the patients actually presented with these symptoms. In conclusion, this study has shown that Meprasil is safe, efficacious in amelioration of dyspeptic pain and well tolerated among Nigerian patients.

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