

Research article

PHARMACO-ECONOMIC ANALYSIS OF SOME BRANDS OF ANTACID FORMULATIONS AVAILABLE IN SOUTHERN NIGERIA, USING TITRIMETRIC METHOD.

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ABSTRACT

This study aims to evaluate the efficacy of some antacid brands as it relates to their cost effectiveness. Nineteen (19) commercially available brands of antacid formulations sold in some cities in South Nigerian Pharmacies were evaluated using the back titration technique. The antacids were mostly white with a few colored pink and yellow. Peppermint flavor was the most predominant. The efficacy of the brands was evaluated based on the Acid neutralizing capacity (ANC) while the cost effectiveness was done by calculating the cost per unit dose of the antacids. The results obtained showed that the cost of the antacid suspension varies between ₦50 and ₦5 per 5ml while that of tablet formulation is between ₦15 and ₦1 per tablet. ANC of an antacid is the dominant factor in the choice of antacids for the relief of symptoms of peptic ulcer disease (PUD) and not just the cost. The study shows that though brands AA and BA had the highest ANCs values for suspension and tablet but brands AJ and BF manufactured locally by the same company (JUHEL) were the most cost effective antacid suspension and tablet brands respectively available in Nigeria pharmaceutical market. It is recommended that the ANC values be included in the leaflets of the antacid products and also in hospital formularies to enhance proper prescribing practices.

Key words: Antacids, back-titration, ANC, cost effectiveness, end-point, pharmaceutical formulations and Thymol blue.

INTRODUCTION

Peptic ulcer disease refers to a group of disorders characterized by circumscribed lesions of the mucosa of the upper gastrointestinal (GI) tract.¹ It is a condition arising from a discontinuity in the entire thickness of the gastric or duodenal mucosa that persists as a result of acid and pepsin in the gastric juice. Antacids are available in two dosage forms (tablets and suspensions) commonly prescribed world over as Over-the-Counter (OTC) or prescription medications, administered orally for the primary therapy of peptic ulcers, gastritis, gastro-oesophageal reflux disease (GERD) and functional dyspepsia.² They are alkaline bases used to neutralize the excess gastric acidity resulting in an increase in the pH of the stomach and duodenum. They may cause milk-alkali syndrome, osteomalacia, hypophosphatemia, constipation, diarrhea, Aluminium-intoxication and dose dependent rebound hyperacidity. The analysis of antacid formulations is important for obtaining optimum therapeutic concentrations for the different constituents of antacids and also to determine the most cost effective of the various brands available to help enhance therapeutic interventions.

The constituents of antacid preparations are listed in the British Pharmacopoeia³ which describes a titrimetric method for their assay. In order to determine the safety, efficacy and other economic considerations of antacids in dosage forms⁴, several *In-vitro* studies have been reported by investigators to study the ANC, Sodium content and cost aspects of different marketed antacid formulation in several countries. However, the only study that has been carried out in the Nigerian market was done by Adepoju et al⁵ in Lagos. Therefore, this present investigation was aimed to study and compare the organoleptic properties, sodium content, cost effectiveness and ANC of Nineteen commercially available antacid formulations in Southern Nigeria using a simple, accurate and time saving back-titrimetric method.

MATERIALS AND METHOD

Nineteen marketed formulations of various dosage forms were purchased from pharmacies in Port Harcourt, Nigeria. Details are summarized in Tables 1 & 2. Universal indicator paper (Shanghai SSS reagent CO. Ltd), Filter paper (Whatman® 125mm Ø, Cat No: 1001-125), 2.5L Concentrated Hydrochloric Acid (Sigma Aldrich), Sodium hydroxide (Sigma Aldrich), Potassium Hydrogen Phthalate (Qualikems), Absolute ethanol, Deionized water, Phenolphthalein solution (BDH, England(1% by mass in ethanol) and Thymol blue solution (0.1% by mass in ethanol) of analytical grade were obtained.

The standard was prepared and standardized as per the procedures of United States Pharmacopoeia⁶.

Weight uniformity

A total of 20 tablets from each brand was randomly selected and weighed individually. The mean, standard deviation, coefficient of variance, percentage deviation and standard error of mean was calculated.

Sodium content (mg/dose) determination

The sodium content was determined for each of the formulations under study using the following formula;

$$\text{Sodium content(mg/dose)} = \frac{23}{84} \times \text{number of grams of NaHCO}_3 \text{ present in the formulation.}$$

Where; 23 is the molecular weight of sodium

84 is the molecular weight of NaHCO₃

Sodium content per defined daily dose of 280mEq of antacid was calculated using the formula;

$$\text{Sodium content in mg} = \frac{280 \times a}{b}$$

Where; 280mEq/day is the defined Acid Neutralizing Capacity (ANC) of antacid required per day

'a' is the quantity of sodium in mg present per dose of the antacid

'b' is the ANC calculated per dose in mEq.

Measurement of pH

The pH meter was calibrated using buffer solutions 4 and 9. The tablets were dissolved in water, and the pH of each tablet brand was read from the monitor of the pH meter. The same procedure was repeated for the antacid suspensions.

Titration (Suspensions)

Samples of the antacid suspension (5ml) were pipette into a 250ml Erlenmeyer flask. 10ml of 0.1M HCl was added to the flask and swirled. The pH was checked with continuous addition of the acid until a pH range of 2 was reached. The amount of excess acid added was recorded. The solution was boiled for 2mins, cooled and the pH was rechecked. An additional amount of acid was added to attain excess acidity (the volume was noted). After which 10 drops of Thymol blue was added and titrated against 0.1M NaOH to a blue end point. The titration was repeated twice.

Titration (Tablets)

The tablets were pulverized using a mortar and pestle. An amount equivalent to the weight of one tablet was weighed and transferred into a 250ml Erlenmeyer flask. 10ml of 0.1M HCl was pipette into the flask and swirled. The pH of the solution was checked with continuous addition of the acid until a pH of 2 was obtained. The total volume of the 0.1M HCl added was recorded. 10 drops of thymol- blue indicator was added and titrated against 0.1M NaOH to a blue end point. The titration was carried out in triplicate.

STATISTICAL ANALYSIS

The standard deviation and coefficient of variation was calculated for each brand of tablet antacid. The level of significance considered was 5%. Analysis of variance (ANOVA) was performed. Software program SPSS version 19 was used for statistical calculation. Data generated from the batch of tablets were analyzed for brand to brand comparison of commercially available samples using ANOVA. For this comparison, readings for all three batches of a product were posted to obtain a mean value.

RESULT AND DICUSSION

TABLE 1: PHYSICO-CHEMICAL PARAMETERS OF ELEVEN BRANDS OF ANTACID SUSPENSIONS

BRAND CODE	AA	AB	AC	AD	AE	AF	AG	AH	AI	AJ	AK
SHELF LIFE (YEARS)	2	2	1	3	1.5	4	3	3	3	3	2
NAFDAC REG. NO	-	A4-7058	A4-0799	04-0480	A4-1299	04-6991	04-6546	04-2233	04-1508	04-1973	-
COLOUR	CREAM	CREAM	YELLOW	PINK	PINK	CREAM	CREAM	PINK	PINK	OFF WHITE	OFF WHITE
FLAVOUR	-	PINEAPPLE	PINEAPPLE	-	COOLMINT	-	-	-	-	-	CITROUS LEMON
pH	7.96	7.26	6.70	6.95	7.49	6.73	6.87	7.18	6.91	7.41	6.83
CONTENT	Mg(OH) ₂	NaHCO ₃ CaCO ₃	Al(OH) ₃ Mg(OH) ₂ MgSiO ₃	Al(OH) ₃ Mg(OH) ₂ SMT	Al(OH) ₃ Mg(OH) ₂ SMT	Al(OH) ₃ Mg(OH) ₂ SMT	SMT MGD	Al(OH) ₃ Mg(OH) ₂	Al(OH) ₃ Mg(OH) ₂	NaHCO ₃ MgSiO ₃ MgCO ₃	Al(OH) ₃ Mg(OH) ₂

			DMPS					Al_2O_3 AMP	MgSiO_3 DMPS		
SODIUM CONTENT	NA	73.11	NA	NA	NA	NA	NA	NA	NA	68.45	NA
SPECIFIC GRAVITY	1.043	1.056	1.069	1.119	1.105	1.106	1.155	1.157	1.205	1.065	1.021
UNIT COST/5mL (₹)	40.00	25.00	11.25	11.30	8.75	16.67	15.00	9.50	10.00	5.00	50.00
COST EFFECTIVENESS	0.2952	0.8392	0.4557	0.5396	0.1735	0.9641	0.2738	0.3212	0.4034	0.0966	0.5258
VOL. OF HCl CONSUMED/5mL	135.52	29.79	24.69	20.94	50.42	17.29	54.79	29.58	24.79	51.77	95.10
ANC (mEq/5mL)	13.55	2.98	2.47	2.09	5.04	1.73	5.48	2.96	2.48	5.18	9.51

TABLE 4: PHYSICO-CHEMICAL PARAMETERS OF EIGHT DIFFERENT ANTACID TABLETS

BRAND CODE	BA	BB	BC	BD	BE	BF	BG	BH
SHELF LIFE (YEAR)	4	3	4	2	3	5	4	3
NAFDAC REG. NO	A4-1902	A4-7553	O4-1068	O4-2185	A4-5660	O4-1001	O4-1554	O4-0172
COLOUR	PINK	YELLOW	WHITE	WHITE	WHITE	WHITE	WHITE	WHITE
FLAVOUR	PEPPERMINT	MINT	PEPPERMINT	-	PEPPERMINT	PEPPERMINT	-	-
pH	8.48	7.92	7.06	8.05	7.27	7.72	7.58	7.60
CONTENT	$\text{Al}(\text{OH})_3$ $\text{Mg}(\text{OH})_2$ SMT	$\text{Al}(\text{OH})_3$ $\text{Mg}(\text{OH})_2$ MgSiO_3 SMT	$\text{Al}(\text{OH})_3$ MgSiO_3	$\text{Al}(\text{OH})_3$ $\text{Mg}(\text{OH})_2$ MgSiO_3 SMT	$\text{Al}(\text{OH})_3$ MgSiO_3	NaHCO_3	$\text{Al}(\text{OH})_3$ MgSiO_3	$\text{Al}(\text{OH})_3$ MgSiO_3
SODIUM CONTENT	NA	NA	NA	NA	NA	82.14	NA	NA
AV. WEIGHT/ TABLET (g)	1.407	1.027	1.161	1.150	0.957	0.345	1.023	1.198
WEIGHT EFFECTIVENESS ($\text{mol/g} \times 10^{-3}$)	2.16	1.46	1.10	0.92	1.29	6.25	1.39	1.15
UNIT COST/ TABLETS (₹)	5	2	3	5	15	1	2	12.5
COST EFFECTIVENESS	0.158	0.128	0.163	0.454	1.171	0.047	0.135	0.869

VOL. OF HCl CONSUMED/ TABLET (mL)	31.67	15.63	18.44	11.04	12.81	21.35	14.79	14.38
ANC (mEq/tablet)	3.17	1.56	1.84	1.10	1.28	2.14	1.48	1.44

KEY:

DMPS – DIMETHYL POLYSILOXANE, AMP - ACTIVATED METHYL POLYSILOXANE

MGD- MAGALDRATE, SMT- SIMETHICONE.

Analysis of nineteen (19) commercially available antacid formulation brands found in Nigerian markets was carried out using back-titration techniques which has been applied for the evaluation of antacids in other countries.^{4,6,8} The shelf life of a pharmaceutical product is defined as the time at which the average drugs characteristic (potency) remains within an approved specification after manufacture. (FDA 1987) The shelf life of each product varies from one 1- 3 years for antacid suspensions and 2- 5 years for antacid tablets. This is because of the higher moisture content of the suspension formulation, since water makes the suspension to be liable to hydrolysis and host of some other reactions which subsequently reduce the suspension shelf life when compared to the tablet dosage form. Among other factors, the shelf life of a drug also depends on some other formulation factors. Thus, explaining why the selected antacid tablets having higher shelf lives.

With exception of sample AA and AK, which do not have the NAFDAC registration number, the remaining antacid brands used in this study were registered with NAFDAC. Brands AA and AK may have been imported either as an orphan drug or their registration formality is not yet complete.

The organoleptic properties (colour and flavour) and sign of imperfections were tested for. All the antacids studied were either white or off-white [Milk of magnesia[®](AA), Gaviscon[®] (AB), Gestid[®](AD), Relcer gel[®] (AF), Gascol[®] (AG), Juhel-Mistmag[®] (AJ) Maalox[®](AK), Antasil[®](BA), Krisacid[®] (BB), Danacid[®](BC), Sodamint[®](BF), Julisil[®](BG)] except Ulgicid[®] (AC) and Getosil[®] (BB), which are yellow in colour; Gestid[®] (AD), Grenocid[®] (AE), Rulox[®] (AH), Jawasil[®] (AI) and Polygel[®] (BA) which had pink colour, most of the antacids had no flavour while the rest were flavored with peppermint except brand AK with citrus lemon flavor. The variation in colour, and presence or absence of flavour has no correlation with the other physicochemical properties investigated in this study; this may imply that the colour and flavor of the antacid were merely for aesthetic value and identification purposes. None of the brands show any form of imperfection.

From the average pH values (Tables 1 & 2) of the antacids assayed, none of the product's pH is significantly different from the average value (pH = 7.12) obtained for different brands. There is no correlation between the obtained pH values, cost effectiveness and their ANCs. The antacid suspension (AA) with the highest product pH of 7.96 neither had the highest nor lowest values for cost effectiveness or ANC. The above observation may be due to the difference between the pH of stomach content and the pH of the antacid.

The specific gravity of an antacid suspension is not a major determining factor for the effectiveness of an antacid suspension. As seen in Table 1, Brand AK has the lowest specific gravity value (1.021) but not the highest ANC value while brand AI with the highest specific gravity (1.205) is not have the brand with the lowest ANC value. The above observation may be due to inclusion of dimethyl polysiloxane (DMPS): a surface acting agent and other active ingredients in sample AI which may have increases its specific gravity and indirectly the viscosity of the

preparation, thereby affecting the rate and extent of contact between the antacid formulation and the gastric acid content.

The effectiveness of the antacids chemical composition was also looked out for as suggested by Grishpan *et al*⁹. Similar trends in terms of specific gravity, pH and ANC were followed by different brands with similar active ingredients such as we have in brands “AC & AI”, “AD, AE & AF” for suspension, “BB & BD”, “BC, BE, BG & BH” for tablet formulation. These physico-chemical properties are different within the group. This may be the result of formulation factors employed in the manufacturing of the products. Brand AA which contain only a single antacid as the active ingredient: Mg(OH)₂ had the highest ANC when compared to other Antacid suspension. This may be as a result of this brand having the lowest specific gravity, which translates to higher surface area for the suspended magnesium hydroxide particles in the suspension, better flowability and thus better contact with the stomach acid. On a closer look at brand AG without any chemically classified antacid component but purely anti-foaming agents, also exhibit a relatively high ANC value. Formulations with both anti-foaming agents and antacids as their component were observed to have low ANC value. (Table. 1 & 2) The possible reasons may be because the antacids in the combined formulations in an acidic environment may have reacted with only the excess stomach acid that cannot be sequestered by the gel formed by the anti-foaming agents, thus explaining the reason why they had low ANC values when compared with preparation containing only anti-foaming which sequester the acid better.

The Sodium content per dose was calculated as suggested by Adriana Sales *et al*.¹⁰ Sodium was present as NaHCO₃ in three of the brands tested; brands AB (73.11mg/dose), AJ (68.45mg/dose), BF (82.14mg/dose). Thus, it is important that these brands are not recommended for patients on a Sodium restricted diet for example hypertensive patients.

The ANC of the most potent antacid (AA) was found to be thirteen times that of the least potent (BD). This difference in their ANC is not reflected on the labels of the various antacid products assayed. The acid neutralizing capacity of an antacid is $\geq 5\text{mEq}$ per dose (FDA). The ANC of brand AA (13.55mEq) per 5ml of the suspension was found to be highest while brand AF (1.73mEq) had the lowest. Meanwhile, for the antacid tablets, brand BA was found to have the highest ANC of 3.17mEq and brand BD with lowest ANC value of 1.10mEq. This literally means that that 5ml of Milk of magnesia will neutralize an equal amount of acid as eight tablets of Polygel. Mary *et al*⁴ suggested that liquid antacids were better compared to chewable tablets and this study has proven same. The possible reason for this observation is that the antacid particles in the suspension exposes more surface areas (fine powders) than the tablet formulation which is compressed from granules. The nineteen antacid formulations were classified into three groups according to their ANC's as suggested by Duffy *et al*; those with a high ANC (13.55 – 9.51 mEq), those with an intermediate ANC (5.48 – 3.17 mEq) and those with a low ANC (2.98 – 1.10 mEq). According to this categorization, it was observed that antacid suspensions mostly fell under the high and intermediate class while the tablet formulation belong mostly to low class antacid in terms of ANC.

The unit price of Antacid suspension was found to be between ₦5 - ₦50 per 5ml dose, while that for the tablet antacids was found to be between ₦1 - ₦15/tablet, thereby making the tablet to be cheaper than the suspension. The most expensive antacid suspension was Maalox[®] with unit price of ₦10/ml while the cheapest brand is Juhel-Mist Mag[®] ₦1/ml. For the chewable tablets, Getosil[®] was the most expensive brand at ₦15/tablet while the cheapest brand, Julisil[®] chewable antacid tablet goes for ₦1/tablet. This study reveals no correlation between the unit price and the ANCs of the antacids. These prices vary from one Pharmacy to another and the price is determined by different factors such as how and where the products were sourced and also the product mark-up which varies from one pharmaceutical premise to another. Thus there is need for both health care provider and the patient come to an agreement and select the appropriate Antacid considering both the effectiveness as well as the price.

The cost effectiveness of an Antacid is interplay between the ANC and the unit cost of the antacid. Milk of magnesia[®] and Antasil[®] have the highest unit cost of ₦ 8/ml and ₦5/tablet respectively (Table 1 & 2), the highest ANC with the least cost effectiveness. Although both brands are not one of the cheapest, but they have the lowest cost effectiveness in terms of the dose required for treatment.

In choosing the best antacids for the treatment of hyperacidity, certain parameters such as which of the antacid formulations best controls the symptoms, Speed of relief, potency and their adverse effects has to be taken into consideration.

CONCLUSION

Parameters such as ANCs, Sodium content and price of the antacid formulations play an important role in the selection of appropriate antacids that would suit the patients' needs. It was observed that brands AA and BA consumed the highest volume of 0.1M HCl (135.5ml and 31.67ml respectively) per unit dose and thus with highest Acid neutralizing capacity's (13.55mEq and 3.17mEq respectively) per unit dose. Despite the obvious high volume of acid consumed and consequent high values of ANC obtained, brands AA and BA were the most cost effective antacid brands rather it was brand AJ and BF interestingly manufactured by the same Nigeria Company (JUHEL). When an efficacious antacid therapy is required for the treatment of peptic ulcer disease, antacids with a high or an intermediate ANC with most cost effectiveness brands should be the most preferred brands as these products will provide the highest neutralization capacity with the lowest dose and price. As a function of their cost, this study has been able to show that the effectiveness of an antacid is not a function of the price but on its acid neutralizing capacity. This work strengthened the common perception that the quality of a product is directly related to its quality and that it is also applicable to antacid formulations.

CONFLICT OF INTEREST

This work was not supported by any organization. The authors fully sponsor this work. We declare that there is no conflict of interest.

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