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Comparative efficacy and efficiency profile of some commercially available antacids in the Nigerian pharmaceutical market.

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ABSTRACT

Background: Antacids are the substances most commonly used by the patients to obtain fast symptomatic relief from dyspepsia. They are weak bases which neutralize the gastric acid and raise the pH of the gastric contents. The potency of antacids depends on their acid neutralizing capacity (ANC). The ANC varies from one product to the other depending on their formulations.

Objectives: This study evaluated rate and extent of acid neutralization of some antacid formulations available in the Nigerian market.

Methods: Ten liquid formulations were sampled from pharmacies, stored according to manufacturer's recommendations before analysis. All samples were coded by an independent researcher (blinding) and studied for their acid neutralizing capacity. Both acid neutralizing capacity and the neutralizing efficiency was studied for all sampled antacids using the British Pharmacopoeia 2013 method. Constituents were also noted for pharmacotherapy review. Analysis was carried out in triplicates and data analysed using analysis of variance.

Results: Six of the ten antacid preparations satisfied all the conditions stipulated for an efficient and efficacious antacid in the BP. The ANC among the liquid formulations was highest for ANCS 1g 27.51±0.05 and lowest for ANCS 1j 20.13± 0.17 antacid formulations. Two products failed the efficiency test while two others failed to neutralize the acid at both 10 and 20 minutes as recommended in the official reference.

Conclusion: Six of the antacids passed the official test for effectiveness and efficiency while the remaining four either failed one or both tests.

Key-words: Antacids; acid neutralizing capacity; titration; efficiency; efficacy.

Profil comparatif d'efficacité et d'efficience de certains antiacides disponibles dans le commerce sur le marché pharmaceutique nigérian.

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RESUME

Contexte: Les antiacides sont les substances les plus couramment utilisées par les patients pour obtenir un soulagement symptomatique rapide de la dyspepsie. Ce sont des bases faibles qui neutralisent l'acide gastrique et augmentent le pH du contenu gastrique. La puissance des antiacides dépend de leur capacité de neutralisation de l'acide (ANC). L'ANC varie d'un produit à l'autre en fonction de leurs formulations.

Objectifs: Cette étude a évalué le taux et l'étendue de la neutralisation acide de certaines formulations d'antiacides disponibles sur le marché nigérian.

Méthodes: Dix formulations liquides ont été échantillonnées dans des pharmacies, stockées selon les recommandations du fabricant avant l'analyse. Tous les échantillons ont été codés par un chercheur indépendant (aveuglement) et étudiés pour leur capacité de neutralisation de l'acide. La capacité de neutralisation des acides et l'efficacité de neutralisation ont été étudiées pour tous les antiacides échantillonnés utilisant la méthode de la pharmacopée britannique 2013. Les constituants ont également été notés pour l'examen de pharmacothérapie. L'analyse a été effectuée en trois exemplaires et des données analysées à l'aide de l'analyse de la variance.

Résultats: Six des dix préparations d'antiacides ont satisfait à toutes les conditions stipulées pour un antiacide efficace dans lapharmacopée britannique. L'ANC parmi les formulations liquides était le plus élevé pour ANCS 1g 27,51±0,05 et le plus bas pour ANCS 1j 20,13±0,17 des formulations d'antiacides. Deux produits ont échoué au test d'efficacité tandis que deux autres n'ont pas réussi à neutraliser l'acide à la fois 10 et 20 minutes comme recommandé dans la référence officielle.

Conclusion: Six des antiacides ont réussi le test officiel d'efficacité et d'efficience tandis que les quatre autres ont échoué à l'un ou aux deux tests.

Mots-clés: Antiacides ; capacité de neutralisation de l'acide ; titration ; efficience ;efficacité.

INTRODUCTION

Antacids are medications used for alleviating some gastrointestinal disorders which may be due to functional defect in the GIT or associated with identifiable pathology such as esophageal reflux, peptic ulceration or gastritis.[1] Antacids are formulations of weak bases which react stoichiometrically with gastric acid to increase the pH of the stomach and the duodenum, thereby reducing gastric acidity and the attendant gastric pain and discomfort.[2] The symptomatic relief of pain produced is mainly as a result of the reduction in stomach acidity and partly by relief of muscle spasm. Reduction in the acidity also inhibits the activity of pepsin and its associated effect on ulcers. Antacids also increase the tone of the lower esophageal sphincter and hence reduce gastroeosophageal reflux which is the spillage of acid and gastric contents into the esophagus.[3] The need for antacids may be as a result of hyperacidity of the stomach, reflux oesophagitis, gastric ulcer, acidosis, dyspepsia, indigestion or bloating.

The pH of an empty stomach is between 1.5 and 2.5 but rises to between 5.0 and 6 after food ingestion. The low pH is maintained by the presence of endogenous hydrochloric acid which is always present under physiological conditions.[4] Peptic ulcers are believed to result when there is an imbalance between aggressive factors such as *Helicobacter pylori*, anti-inflammatory drugs, gastric acid and protective factors such as mucin, bicarbonate and prostaglandins.[5:6] Other risk factors include alcohol intake, smoking, eating habits, stress, pregnancy, obesity and ageing.[5:7-9]

Antacids use predates written history as chalk (calcium carbonate) has been chewed for the relief of dyspepsia and it is still in use till date. Antacids were the only useful drugs for dyspepsia until the arrival of cimetidine, the first H_2 antagonist.[4] The treatment of peptic ulcer disease, gastro-oesophageal reflux disease (GERD) and functional dyspepsia still utilize antacid.

Hydroxides of metallic ion are the most common bases used as antacids although, trisilicates, carbonates and bicarbonates are also used. The therapeutic efficacy and the adverse effects depend upon the metallic ion with which the base is combined. The metallic ions commonly combined with the bases are aluminum, magnesium, calcium or sodium.[10] Some of the components of common antacids include the following compounds: sodium bicarbonate, aluminum hydroxide, aluminum phosphate, dihydroxy-aluminum ammonium acetate, dihydroxy-aluminum sodium carbonate, calcium carbonate, tribasic calcium phosphate, magnesium oxide, magnesium phosphate and magnesium trisilicate.

Antacids can be classified as systemic antacids and non-systemic antacids. Systemic antacids are antacids that undergo complete systemic absorption following oral ingestion, like sodium bicarbonate and carbenoxolone sodium. Non-systemic antacids are those that do not undergo systemic absorption following oral ingestion, such as aluminium hydroxide, aluminum phosphate, magnesium trisilicate,[11] magnesium hydroxide, magnesium carbonate and calcium carbonate.[12:13] The systemic antacid most commonly used is sodium bicarbonate. It is white in colour, water soluble and a completely absorbable antacid. It reacts with the gastric acid to form sodium chloride, water and carbon dioxide. It is an effective and rapid acting antacid. The carbon dioxide liberated during the process of acid neutralization often gives a sense of relief from the abdominal discomfort. The adverse effect of sodium bicarbonate as a systemic antacid is systemic alkalosis. The sodium chloride formed may result in the retention of fluid and the carbon dioxide liberated may cause the feeling of nausea, belching, flatulence, fullness and rupture of the prior formed peptic ulcer.[14]

Aluminium hydroxide, a non-systemic antacid, reacts with the gastric acid to form aluminium chloride. Additional advantage of aluminium hydroxide is that it has astringent and demulcent properties by which it forms a protective coating over the ulcer crater. It may also adsorb toxins, bacteria and gases. Constipation is however a major adverse effect of aluminium containing antacids. Aluminium containing antacids also prevent the absorption of phosphate from the intestine causing osteomalacia.[15] Patients with chronic renal failure may have high serum aluminium concentration following ingestion of aluminium antacids which in some rare cases cause encephalopathy; also the deposition of aluminium in bones may cause osteodystrophy.[16] Another commonly used non systemic antacid is magnesium hydroxide. It is available as Milk of Magnesia, containing 7 to 8.5% of magnesium hydroxide. The major adverse effect of magnesium hydroxide is diarrhoea.[17] Calcium carbonate occurring as a white powder with chalky taste is also used as non-systemic antacid. It reacts with the gastric acid to form calcium chloride. The major side effect of the calcium carbonate is that it increases the gastrin and rebound acid secretion.[18] There is no systemic absorption of the bases among non-systemic antacids, because the salt formed with combination of the gastric acid combines with the bicarbonate in the intestine to form the original base which will be excreted in the faeces.[19]

Alginic acid is usually combined with antacids to encourage the adherence of the antacid to the mucosa and it also acts like a protective raft to the gastric mucosa. Simethicone or dimethicone are included in the antacids as a foaming agent to reduce flatulence by lowering the surface tension and allowing the small bubbles of froth to coalesce into large bubbles that can be more easily passed up from the stomach or down from the colon.[20]

The characteristics desired of an ideal antacid are that it should be inexpensive, long acting, unabsorbable, not causing systemic alkalosis or rebound hyperacidity, palatable, and should not interfere with the absorption of food and other digestive processes.[21]

The efficacy of antacids is determined by the acid neutralizing capacity (ANC) of the antacids. Since antacids are mostly admixtures of inorganic salts, their safety is dependent on the safety and limitations of the component salts. The characters of the salts may also affect the safe administration of the antacids in some pathological conditions. Antacids are administered mostly without prescriptions and with liberal dosing regimens, necessitating a study of the efficiency, efficacy and safety of the antacids in the Nigerian market space. The potency of the different antacids depends upon the ANC of the individual antacid. ANC of an antacid is defined as the number of milliequivalents (mEq) of 1N hydrochloric acid (HCl) that is brought to the pH of 3.5 in 15 minutes by a unit dose of the antacid preparation.[22]

Presently, the Nigerian pharmaceutical market has many antacid preparations which are available in different formulations. The present study was conducted to identify the antacid neutralizing capacity of different formulations. The aim of this study is to evaluate both the rate and extent of acid neutralization of different formulations available in the Nigerian market in order to help pharmacists and practicing physicians to choose the best or optimal formulation among a very large number of formulations.

METHODS

Ten branded antacid preparations were purchased from pharmacy outlets in Ibadan, in the southwestern Nigeria after ascertaining that all these brands were available in fifty (50) outlets in a previous survey (data not shown). The antacid preparations were coded to provide ethical research climate and prevent bias from the different handling. The coding was done by an independent but experienced researcher and the researchers were not aware of the codes. The constituents of the antacids were documented for a review of the safety of the salts especially contraindications in some pathological conditions (Table 1.). Each antacid preparation was subjected to ANC tests as stated in the BP[23] and data in triplicate were analyzed to establish both the efficiency and efficacy of the antacids.

The liquid antacid bottles were shaken well for one minute and 5g of the preparation was poured into a 250mL glass beaker. 100mL of de-ionized water was added and the content heated to 37°C. 100mL of 0.1M hydrochloric acid, which was previously heated to 37°C, was added with continual stirring with a paddle stirrer, while maintaining the temperature at 37°C. The pH of the suspension at 37°C was measured and recorded after 10 and 20 minutes of stirring. Thereafter, 10 mL of 0.5M hydrochloric acid which was previously heated to 37°C was added and the mixture stirred continuously for 1 hour, while maintaining the temperature at 37°C. The mixture was then titrated with 0.1M *sodium hydroxide* to pH 3.5. The volume of 0.1M *sodium hydroxide used was subtracted* from 150 to obtain the number of mL of 0.1M *hydrochloric acid VS* required for the neutralization. The weight per ml of the mixture was determined, and hence the volume of 0.1M hydrochloric *acid* required to neutralize 5mL of the mixture was calculated.

RESULTS

Two parameters were tested in the ten liquid antacids in this study. The neutralizing capacity denoting efficacy and the neutralizing efficiency which is time bound. Antacids are required to bring the pH of the experimental medium to 2 and above in ten minutes and below 4 in twenty minutes. From the study, eight (8) samples passed the pH test at 10 minutes while two (ANCS 1f and ANCS 1b) failed the test (Table 2). Four samples (ANCS 1d, ANCS 1a, ANCS 1f and ANCS 1b) failed the pH test at 20 minutes. The results of the ANC show that all the samples passed the minimum requirement of the value for efficacious antacid i.e ANC of 20.The product with the minimal ANC is ANCS 1j, with ANC of 20.13 while the product with the highest ANC is ANCS 1g with ANC of 27.52.. The order of efficacy is ANCS 1j < ANCS 1e < ANCS 1d < ANCS 1a < ANCS 1k < ANCS 1c < ANCS 1f < ANCS 1b < ANCS 1h < ANCS 1g.

Table 1. Particulars of the tested antacids

No	Code of Antacid	Contents
1.	ANCS 1a (with simethicone) 200mL	Aluminium magnesium silicate BP- 300mg Magnesium trisilicate BP- 250mg Magnesium carbonate BP- 250mg Sodium bicarbonate BP- 250mg Simethicone BP- 20mg
2.	ANCS 1b (pepper mint) 200mL	Sodium Alginate BP-500mg Sodium bicarbonate PH EUR- 267mg Calcium carbonate PH EUR- 160mg
3.	ANCS 1c (200mL)	Dried Aluminium hydroxide gel USP equivalent to Aluminium hydroxide 306mg. Magnesium hydroxide USP- 100mg Simethicone Emulsion USP equivalent to polydimethylsiloxane 125mg.
4.	ANCS 1d (200mg)	Dried Aluminium hydroxide gel BP- 600mg Magnesium trisilicate BP 300mg Magnesium hydroxide BP- 200mg Dimethyl polysiloxane USP- 50mg
5.	ANCS 1e (mint flavor) 200mL	Alginic acid BP- 200mg Magesium hydroxide- 250mg Dried aluminium hydroxide- 250mg Magnesium trisilicate B.P-250mg Dimethicone BP 125mg
6.	ANCS 1f (100mL)	Activated Methylpolysiloxane- 125mg Magnesium hydroxide- 100mg Aluminium Hydroxide gel- 4.75mL
7.	ANCS 1g	Simethicone USP- 50mg Magesium Hydroxide USP- 250mg Dried Aluminium hydroxide gel USP 250mg.
8.	ANCS 1h (180mL	Aluminium hydroxide gel USP equivalent to Aluminium hydroxide- 365mg. Magnesium hydroxide paste USP equivalent to magnesium hydroxide 80mg. Simethicone USP-100mg Deglycyrrhizinatedliquorice equivalent to Liquorice 400mg
9.	ANCS 1j (100mL)	Sodium Bicarbonate BP -250mg Light Magnesium carbonate BP -250mg Magnesium Trisillicate BP -250mg Suspending Agents Q.S
10.	ANCS 1k (200mL)	Alginnic acid BP -200mg Magnesium hydroxide BP- 250mg Dried aluminium hydroxide BP -250mg Magnesium trisilicate BP-250mg Activated Dimethicone BP -125mg

Table 2. Results showing the values used for determination of ANC

S/N	Code of Sample of antacid	S/ml Wt./ml	pH at 37 ˚C		Vol. (mL) of NaOH To pH 3.5	mL 150-V NaOH	mL Vol of 0.1M HCl =5ml mix	Acid Neutralizing Capacity (ANC) Meq/5ml	Remarks
			10mins	20mins					
1	ANCS 1j	1.2	2.6 2.8	3.6 3.4	50 47	100 103	108.7 111.9 110.3	20.13	Passed
2	ANCS 1e	1.1	2.9 2.7	3.5 3.2	51 48	99 102	110.0 113.3 111.7	20.39	Passed
3	ANCS 1d	1.2	3.2 3.2	*5.0 *4.8	48 45	102 105	121.4 125.0 123.2	22.48	Failed pH at 20mins>4.0
4	ANCS 1a	1.3	3.5 3.7	*4.4 *4.6	46 40	104 110	126.8 134.1 130.5	23.82	Failed pH at 20mins>4.0
5	ANCS 1k	1.2	2.6 2.6	2.9 3.0	38 41	112 109	133.3 129.8 131.6	24.02	Passed
6	ANCS 1c	1.3	2.9 2.9	3.6 3.2	40 44	110 106	134.1 129.3 131.7	24.04	Passed
7	ANCS 1f	1.4	*4.2 4.0	*4.6 *4.6	50 54	100 96	138.9 133.3 136.1	24.84	Failed pH at 10mins and pH 20mins>4.0
8	ANCS 1b	1.3	*1.6 *1.6	*2.1 *2.3	38 38	112 112	147.4 147.4 147.4	26.90	Failed pH at 10mins <2.0, pH at 20mins<2.4
9	ANCS 1h	1.4	2.5 2.8	3.4 3.9	42 46	108 104	154.2 147.2 150.7	27.50	Passed
10	ANCS 1g	1.4	2.9 2.6	3.5 3.8	46 49	104 101	149.4 152.2 150.8	27.52	Passed

Notes to Table 2: * Significant difference from the standard pH values at both 10 and 20 minutes.

pH values for a good antacid must be higher than 2 at 10 minutes and less than 4 at 20 minutes.

DISCUSSION

The tests showed the relative efficiency and efficacy of ten of the antacid brands marketed in Nigeria. The efficiency was defined by their acid neutralizing profile at both ten and twenty minutes while the efficacy was determined by the acid neutralizing capacity after back titration as stated in the BP.[23] From this study, ANCS 1j, ANCS 1e, ANCS 1k, ANCS 1c, ANCS 1h and ANCS 1g can be regarded as efficient while all the products are all adjudged to be efficacious.[23]

Antacids are prescribed for symptomatic relief of hyperacidity associated with peptic ulcer, gastritis, gastric hyperacidity etc., which on ingestion react with HCl of the gastric juice to lower the acidity of the gastric contents. From this study all the ten antacids will produce symptomatic relief of hyperacidity but with different efficiencies with ANCS 1g appearing to be the most efficient and apparently the most efficacious. Different antacid formulations are widely available in the market containing different combinations of active ingredients in varying concentrations and in different brand names. In the context of the contents of the antacids (Table 1), all the antacids except ANCS 1b and ANCS 1j contain aluminum metal either as hydroxide or dried gel of the hydroxide. Since the antacids that are both efficient and efficacious contain aluminum salt, aluminum may not contribute to the failure of efficiency or low efficacy (Table 2). It should be noted that aluminum salts can cause constipation but which may be advantageous in counteracting the diarrhoeaic effect of magnesium. Aluminum also confers protection against bacterial infection as they adsorb toxins and bacteria.[16] Aluminum

may however prevent the absorption of phosphate from the intestine causing osteomalacia. Patients with chronic renal failure may have high serum aluminum concentration following ingestion of aluminum antacids which in some rare cases cause encephalopathy; also the deposition of aluminum in bones may cause osteodystrophy.[16]

Magnesium is contained in 90% of the antacids studied. Only ANCS 1b does not parade magnesium in its composition. ANCS 1b failed the efficiency test but it is among the most efficacious antacids (Table 2). Fifty per cent (50%) of the antacids parade two magnesium salts in the formulations possibly indicating the usefulness of magnesium in antacid formulations. Magnesium is presented either as a carbonate, hydroxide or a trisilicate salt. Sodium bicarbonate is contained in three (30%) of the antacids investigated. It is worthy of note that antacids with sodium salts may not be advisable or safe with patients with cardiovascular issues. Because of the liberal dosing frequency of antacids, exceeding the tolerable sodium level in cardiovascular patients with a need for antacid is a possibility that put such patients at more risks. Sodium containing antacids are best avoided in such patients. The carbenoxolone sodium experience and its eventual withdrawal from the formulary for ulcer treatment is instructive of the challenges of sodium in generous dosing as we have with antacids. Calcium content of antacids pose challenges for patients on thiazide diuretics. The milk-alkali syndrome is a challenge with antacids[24] containing calcium as hypercalcemia is a major concern; therefore pregnancy and lactation that are conditions predisposing to dyspepsia and use of antacids should avoid antacids containing calcium.[22] One of the antacids (ANCS 1h) has deglycyrrhizinated liquorice equivalent to Liquorice-400mg as a component. This poses challenges in lactation, pregnancy, obesity, and may lead to cardiovascular challenges all due to its ability to cause sodium retention, potassium depletion and depression of the renin-angiotensin-aldosterone level. The ability of liquorice to inhibit 11-beta-hydroxysteroid dehydrogenase leads to increased cortisol levels in the kidneys and in other mineral ocorticoid selective tissues.[25]

Three of the samples (ANCS 1a, ANCS 1j and ANCS 1f) did not carry leaflet insert for detailed education of the patients. The classification of antacids as over the counter medicament should recognize residual medical conditions and co-morbidity in patients. Antacid interaction with co-administered drugs is not the only important issue, the possibility of contraindication of some of the constituents of antacids necessitate full information on a leaflet. A statement on the ANC of the antacid may also be useful as was once advocated in a work that addressed the Canadian antacid market.[26]

Six of the ten antacid preparations satisfied all the conditions stipulated for an efficient and efficacious antacid in the BP.[23] Two products failed the efficiency test as they could not neutralize the volume of acid at 20 minutes by bringing the pH of the acid to 4 or below; two others failed to neutralize the acid at both 10 and 20 minutes by bringing the pH of the medium to 2 and not more than 4 respectively. However, all the products passed the efficacy test as the ANC showed values that comply with the BP standard.[23] Supermag®, Megacid®, Ulgicid®, Gestid®, Relcer® and Polygel® all passed the efficiency tests while Jawasil® and Emtrisil® failed to neutralize the medium at 20 minutes. Polyfort® and Gaviscon® failed to neutralize at both 10 and 20 minutes.

The researchers recognize that minor variations exist in the same brand, within and between batches. Raw material quality and formulation factors may influence the antacid activity. The researchers tried to eliminate this error with reasonable effort. The researchers also recognize that while invitro ANC correlates with invitro efficacy and efficiency, other factors e.g. mucoproteins, gastric emptying time, etc may moderate this relationship. This is even more significantly so for $Al(OH)_3$ containing antacids.

CONCLUSION

The acid neutralizing capacity tests showed the relative efficiency and efficacy of ten antacid brands marketed in Nigeria. Six of the antacids passed the official test for effectiveness and efficiency while the remaining four either failed one or both tests. The order of efficacy is ANCS 1j < ANCS 1e < ANCS 1d < ANCS 1a < ANCS 1k < ANCS 1c < ANCS 1f < ANCS 1b < ANCS 1h < ANCS 1g. The participating antacids, in no particular order are Megacid®, Emtrisil®, Polyfort®, Polygel®, Gaviscon®, Supermag®, Ulgicid®, Relcer®, Gestid® and Jawasil®.

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