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# AN *IN-VITRO* INVESTIGATION INTO THE DOSE-DEPENDENT ACID-NEUTRALIZATION EFFECT OF ANTACID FORMULATIONS ON THE GHANAIAN MARKET

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**Keywords:**

Antacid, Acid-neutralizing capacity, Dose, Suspension, Tablet, Granule

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**ABSTRACT:** The recommended doses of antacids by some manufacturers are in ranges. However, dosing decisions on antacids should be based on acid-neutralizing capacities (ANCs). This study evaluated the ANCs of different doses of antacids. Twenty-two antacids (3 granular, 5 tablet and 14 suspension formulations) were evaluated for their ANCs at half, minimum, and double their recommended adult doses. All the products complied with the minimum ANC recommendation (5 mEq/dose), although ANCs were significantly different from each other ($p < 0.0001$). The ANC range for minimum recommended doses for all products was 12.417−38.817 mEq. There were no significant differences in ANCs ($p = 0.1662$) based on dosage form. A dose-dependent effect was observed when minimum recommended doses were halved or doubled, with significant differences in ANCs at each dose level ($p < 0.0001$). The ANC range for doubled doses was 19.817-71.133 mEq. The ANCs at half-doses (7.583−20.417 mEq) were also compliant with the regulatory requirement. The findings show that doses smaller than recommended amounts could be indicated for mild hyperacidity conditions, whereas double doses could be restricted to severe cases. Regulation is required for an upper limit of ANC for antacids. Manufacturers should also indicate ANCs on product details to guide prescribing.

**INTRODUCTION:** Antacids are drugs taken orally to neutralize gastric acid to form salt and water. They are basic in nature and their action within the gastrointestinal tract very often leads to the alleviation of symptoms related to hyperacidity conditions such as indigestion, heartburn, gastroesophageal reflux disease and gastric and duodenal ulcers [1]. By this effect, they prevent acid corrosion and peptic digestion of ulcerated parts of the gastrointestinal tract [2].

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Most antacid formulations contain one or more of inorganic salts of magnesium, aluminium and calcium. Others, especially the effervescent antacids, contain sodium bicarbonate. These products usually present as chewable tablets, suspensions and effervescent solids. Antacids are classified as over-the-counter (OTC) medicines, and this makes them easily accessible and susceptible to abuse in self-medication practices.

One study reported that about 60% of patients who experienced symptoms of heartburn chose to self-medicate with OTC medications, which included antacids [3]. In other studies, antacids have constituted one of the most used and/or abused group of medicines in self-medication practices; only falling short (in terms of ranking) to antipyretics and analgesics [4] in some cases and to

analgesics and antimicrobials in other cases [5, 6]. Although it is held that antacids are generally safe at recommended doses and usually present with few side effects due to their low systemic absorption [7], their continuous abuse have been associated with some reported adverse effects. For example, there has been a report of acute pancreatitis secondary to hypocalcaemia from the abuse of calcium-containing antacids [8]. Additionally, when large doses of antacids are taken for long periods of time, significant adverse effects may occur especially in patients with underlying conditions such as chronic renal failure [7, 9]. Antacids are also known to be less desirable due to their numerous drug interactions.

That notwithstanding, antacid use is widespread. In the United States of America alone, the annual expenditure on antacids and other indigestion products exceeds $ 1.2 billion [10]. This trend of patronage may not be different from the situation in sub-Saharan Africa, although the necessary data is not available. There is an increase in the demand for antacids, with a wide array of options for the consumer. This is due to the increasing popularity of antacids through commercials, increasing prevalence of gastrointestinal conditions and growing trend of self-medication [11]. Owing to the sheer numbers and regulatory status of antacids, their purchase by clients is mostly influenced by medical marketing [12].

Regardless of the commercial and aesthetic presentation of any antacid, its efficacy is dependent on its ability to increase intragastric pH above 3.5, otherwise termed acid-neutralizing capacity (ANC) [13]. ANC is expressed in millequivalents (mEq) [10] and it remains one of the vital parameters by which objective decisions about the choice of antacids should be made. The United States Food and Drugs Administration (USFDA) recommends that an antacid possess a minimum ANC of 5 mEq/minimum dose and that the ANC of antacids should be made available to health professionals in making decisions on their dosing regimen [14]. In the absence of this information (which is usually the case), most decisions on the dosing of antacids have been centered on the manufacturers' recommended dosage regimen. Previous studies carried out in Ghana [15, 16] and other parts of the world [10, 17, 18] show that most antacids comply with the USFDA requirement of 5 mEq/minimum doses [14] and that most of these products possess ANCs far in excess of this requirement. It is also shown that these products exhibit ANCs significantly different from each other, with some recording twice and three times the magnitudes of others for similar doses and compositions. While some of these observations have been attributed to differences in compositions, others have made cases for the effects of other physicochemical properties of the products such as sedimentation rate and viscosity [19]. Largely, the dose of an antacid is a major contributor to the ANC of the antacid and with the observance of different manufacturers' recommended dosage regimens; the ANCs of respective products could be significantly impacted. This project was therefore undertaken as an exploratory study, to assess the effect of dose adjustment on the ANCs of selected antacids. It is the aim of the authors that the outcome of the current investigation could help initiate an academic discussion on the dosing of antacids by key stakeholders in the medicine manufacturing and regulatory industries.

## MATERIALS AND METHODS:

**Chemicals and Reagents:** The chemicals and reagents used for the investigations were of analytical grade. These included hydrochloric acid (HCl) (VWR International SAS, Fontenay-sous-Bois, France), sodium hydroxide (NaOH) pellets (Eurostar Scientific Ltd., Liverpool, England), sulfamic acid (Eurostar Scientific Ltd. England) and anhydrous sodium carbonate (Eurostar Scientific Ltd. England).

**Antacid Samples:** A total of 22 different antacid products were randomly selected in a systematic manner from a compiled list of all the antacids available in retail community pharmacies in the Ho Municipality of the Volta Region of Ghana. The products were labeled A−V. The details of the samples collected are showed in **Table 1**. The products after collection were handled according to respective manufacturers' recommended handling and storage conditions.

**Sample Preparation for Analysis:** The samples were prepared according to the procedures described in the United States Pharmacopeia and National Formulary (USP-NF) [20].

For the suspensions, first, each bottle was well shaken until its contents were uniform. An accurate volume of the uniform suspension equivalent to the minimum dose indicated on the label claim was then transferred into a 250 mL beaker. Water was added to the sample to obtain a 70 mL mixture, which was then stirred on a magnetic stirrer for 1 min. For the tablets, 20 dosage units were weighed, after which the average tablet weight was determined.

The tablets were ground to a fine powder and mixed to obtain a uniform mixture. An amount of the powder equivalent to the minimum labeled dose was accurately weighed into a 250 mL beaker, to which 70 mL of water was added. The mixture was then stirred on the magnetic stirrer for 1 min. For the granules, an amount of the formulation equivalent to the minimum labeled dose was accurately weighed and transferred into a 250 mL beaker. Next, 10 mL of water was added to the granules and the beaker was gently swirled while allowing the reaction to subside. Another 10 mL of water was added and the beaker was swirled gently. The walls of the beaker were then washed with 50 mL of water, after which the mixture was stirred on the magnetic stirrer for 1 min.

**Determination of ANC:** ANC was determined according to the procedure described in the USP-NF. All volumetric solutions (VS) used for the potentiometric determinations were standardized with appropriate primary standards before use. An accurate volume of 30 mL of 1.0 N HCl (VS) was added to the prepared samples, followed by stirring for 15 minutes. An additional 30 mL of the same 1.0 N HCl (VS) was added to samples that had pH ≥ 3.5 after the first addition of HCl. The excess HCl was titrated against 0.5 N NaOH (VS) until a pH of 3.5 was obtained. The procedure was repeated using half and double the minimum doses recommended by the product manufacturers. Triplicate determinations were performed for each sample. The number of millequivalents (mEq) of acid consumed by each antacid at the three dose levels was calculated using the following equation:

$$\text{Total mEq} = (V_{HCl} \times N_{HCl}) - (V_{NaOH} \times N_{NaOH})$$

Where $N_{HCl}$ and $N_{NaOH}$ are the normalities of HCl and NaOH, respectively, and $V_{HCl}$ and $V_{NaOH}$ are the volumes of HCl and NaOH, respectively.

**Data Analysis:** GraphPad Prism for Windows (version 8.0.2; GraphPad Software, Inc., La Jolla, CA, USA) was used for the data analysis. Student's *t*-test and analysis of variance were used to assess differences in the ANCs of the products.

## RESULTS AND DISCUSSION:

**Description of Products:** The details of all the antacid products analyzed are presented in **Table 1**. The products investigated were tablets (n = 5), suspensions (n = 14) and effervescent granules (n = 3). The antacids were manufactured in Italy (4.5%), the United Kingdom (18.2%), India (18.2%), and Ghana 59.1%. The liquid products were packaged in plastic or glass bottles that were amber-colored or plain. The tablets were packaged in aluminum foil (1 sample) or blister-packed.

All the granular samples were packaged in sachets with foil linings. Samples K, M and T did not have any batch numbers indicated on them, which does not conform to good manufacturing practices; as such products cannot be traced. One of the granular formulations (sample T) did not have an expiry date or a batch number indicated on its label. This is unacceptable as the product may be consumed after it has expired, which could have attendant safety issues. The prices of the products were GHS 3.00-42.00 per bottle (100-200 mL) for the liquids, GHS 1.00-28.60 per package (6-24 units) for the tablets and GHS 0.60 per 5 g sachet for the granules. Generally, the least expensive products were produced in Ghana.

**Table 2** shows the compositions of the antacids. The active ingredients listed on the products were aluminum hydroxide, calcium carbonate, magnesium carbonate, magnesium hydroxide, magnesium trisilicate and sodium bicarbonate, which are all specified active ingredients permitted in antacid products for OTC human use [14]. The granules contained only sodium bicarbonate (2280 or 2277 mg/sachet) as the active ingredient. They also contained magnesium sulphate (932.5 or 930.5 mg), as the other indication for the products is constipation. It was indicated on sample U that the product can be dispersed in water and drank as a refreshing tonic, without any warning on the maximum number of sachets that can be ingested in a day. Considering that sodium bicarbonate is a systemic antacid because it is highly soluble in

aqueous media and the freely available proportions rapidly absorbed from the gastrointestinal tract after consumption, its side effects, such as metabolic alkalosis, may be enhanced when large doses are ingested [21]. This requires the direction for using the product as a drink to include the maximum daily dose.

Other ingredients in the sampled productswere sodium alginate, oxethazaine (local anesthetic agent) and simethicone (antifoaming agent). It was noted that 72.7% of the products were flavored with mint, clearly pointing to the flavor as the most commonly used in antacids. The other flavors used were lemon, pineapple, orange and citric acid.

One product contained both orange and citric acid flavors. The minimum adult dose ranges for the products were 5-30 mL for the liquids, 1-2 units for the tablets and 1 sachet (5 g) for the granules.

**TABLE 1: DETAILS OF SAMPLED PRODUCTS**

| Sample | Indicated Adult Doses | Source | Color | Batch Number | Manufacturing Date | Expiry Date | Flavor |
|---|---|---|---|---|---|---|---|
| A | 30 mL | UK | Cream | 646W1 | 09/2018 | 09/2021 | Peppermint |
| B | 10 mL | India | White | 011P912X | 07/2019 | 07/2022 | Orange |
| C | 15 mL | Ghana | Cream | 0312U | 12/2018 | 12/2021 | Peppermint |
| D | 10–20 mL | Ghana | White | 0403W | 03/2020 | 03/2023 | Peppermint |
| E | 10–20 mL | UK | Off-white | 917186 | 06/2019 | 06/2021 | Peppermint |
| F | 5–10 mL | India | Pink | ML 1652 | 03/2019 | 02/2022 | Peppermint/Spearmint |
| G | 5–10 mL | Italy | White | 727 | 02/2019 | 01/2022 | Lemon |
| H | 10 mL | India | Yellow | RE-19107 | 01/2018 | 12/2020 | Pineapple |
| I | 5–10 mL | India | Off-white | 9EL06158 | 04/2019 | 03/2022 | Mint |
| J | 15 mL | Ghana | Deep pink | C-303 | 05/2020 | 04/2022 | Peppermint |
| K | 15 mL | Ghana | White | N/A | 08/2019 | 07/2021 | Peppermint |
| L | 15 mL | Ghana | White | MMT 005 H9 | 08/2019 | 08/2022 | Peppermint |
| M | 15−30 mL | Ghana | White | N/A | 04/2020 | 03/2023 | Peppermint |
| N | 15 mL | Ghana | White | A055 | 03/2020 | 03/2022 | Peppermint |
| O | 1–2 tablets | Ghana | White | AL35C | - | 10/2022 | Peppermint |
| P | 2 tablets | Ghana | Off-white | 0305V | 05/2019 | 05/2023 | Peppermint |
| Q | 2–4 tablets | UK | White/pink | 925401 | - | 08/2021 | Mint |
| R | 1 tablet | Ghana | Off-white | 19055 | 07/2019 | 07/2023 | Peppermint |
| S | 2 tablets | UK | Off-white | N1A046 | 01/2019 | 01/2022 | Spearmint |
| T | 1 sachet | Ghana | White | - | - | - | Citric acid |
| U | 1 sachet | Ghana | Light orange | 751019 | 10/2019 | 10/2021 | Orange/Citric acid |
| V | 1 sachet | Ghana | White | 230320 | 03/2020 | 03/2022 | Citric acid |

**TABLE 2: ACTIVE INGREDIENT COMPOSITIONS (MG PER MINIMUM DOSE)**

| Sample | Aluminum Hydroxide | Magnesium Hydroxide | Magnesium Carbonate | Magnesium Trisilicate | Sodium Bicarbonate | Calcium Carbonate |
|---|---|---|---|---|---|---|
| A, L, M | - | - | 750 | 750 | 750 | - |
| B | - | 240 | - | 100 | - | 800 |
| C | 300 | 300 | - | - | - | - |
| D | 500 | 500 | - | - | - | - |
| E | - | - | - | - | 213 | 325 |
| F, I | 250 | 250 | - | - | - | - |
| G | 225 | 200 | - | - | - | - |
| H | 500 | 500 | - | - | - | - |
| J | 750 | 750 | - | - | - | - |
| K | - | - | 750 | 750 | 37.5 | - |
| N | - | - | N/A | N/A | N/A | - |
| O | 500 | - | - | - | - | - |
| P | 500 | 500 | - | - | - | - |
| Q | - | - | - | - | 213 | 375 |
| R | 400 | 400 | - | - | - | - |
| S | - | - | 160 | - | - | 1360 |
| T | - | - | - | - | 2280 | - |
| U, V | - | - | - | - | 2277 | - |

**Description of the ANCs of the Products:** The ANCs as determined based on the minimum recommended doses of the products under investigation are illustrated in **Fig. 1**. The ANCs of all the products ranged from 12.417 ± 0.325 mEq to 38.817 ± 2.457 mEq, with a mean value of 24.124 ± 8.991 mEq. All the products had ANCs that were significantly greater than the minimum recommended value of 5 mEq [14] ($F_{21, 44} = 128.0$, $p < 0.0001$; **Fig. 1.**

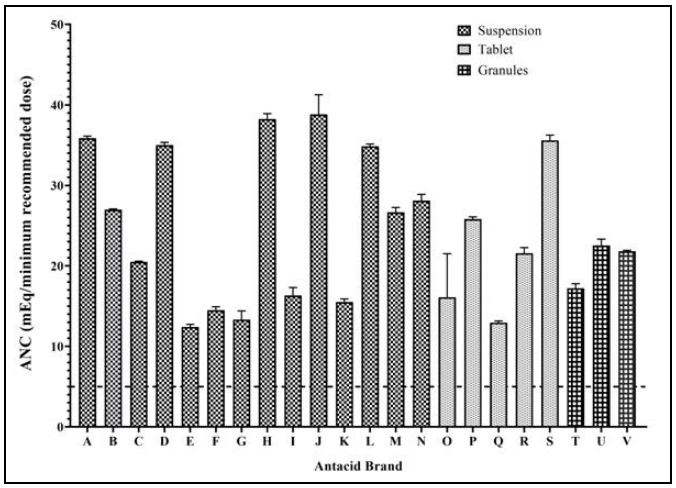


**FIG. 1: ANCS DETERMINED FOR THE MINIMUM DOSES INDICATED ON PRODUCT LABELS. THE MINIMUM RECOMMENDED ANC OF 5 MEQ IS INDICATED AS THE BLACK BROKEN LINE. ALL PRODUCTS HAD ANCS HIGHER THAN THE MINIMUM RECOMMENDED VALUE**

The ANC ranges for the suspensions, tablets and granular formulations were 12.417 ± 0.325 − 38.817 ± 2.457 mEq, 12.950 ± 0.218 − 35.600 ± 0.654 mEq and 17.217 ± 0.577−22.533 ± 0.791 mEq, respectively. However, it was observed that there were no significant differences in the ANCs of the products in terms of dosage form type ($F_{2, 50} = 1.860$, $p = 0.1662$; **Fig. 2.**

The suspensions showed the highest average ANC of 25.508 mEq, followed by the tablets (22.410 mEq) and then the granules (20.522 mEq), possibly showing that antacid suspensions have a better neutralizing effect. Nonetheless, it is worth noting that all the granular and tablet antacids showed better ANCs than the sample that produced the lowest ANC, which was a suspension (sample E). Liquid antacids are usually preferred in the management of hyperacidity-related symptoms because their active ingredients are usually in a fine state, which can improve acid neutralization after administration [22]. However, in the current study, the ANCs of the liquids were comparable to those of the tablets and granules as per the manufacturers' dose recommendations, barring the effects of dosage form factors. An example of such factors is disintegration for the tablets since they were ground to a fine powder before the test. Therefore, patients must be counseled that chewable antacid tablets must be chewed into a fine powder to maximize acid neutralization. In effect, the ANCs of the products were not influenced by their physical forms.

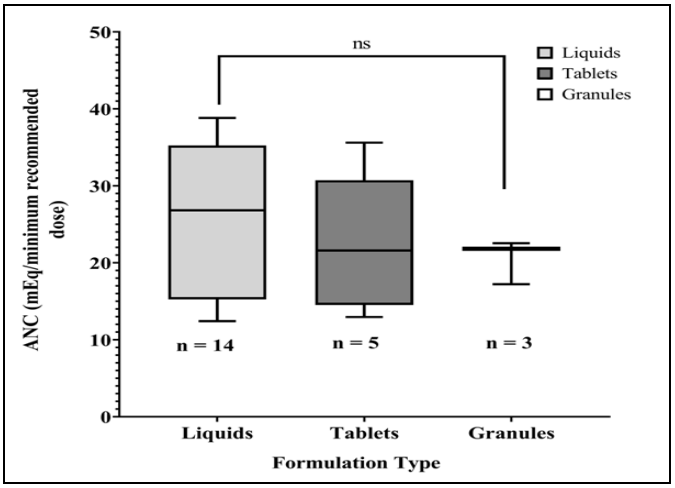


**FIG. 2: COMPARISON OF THE ANCS OF THE PRODUCTS BASED ON DOSAGE FORM TYPE**

**Relationship between Antacid Dose and ANC:** As discussed above, all the products had ANCs higher than the minimum level required. In our investigations, it was observed that when the manufacturers' recommended minimum doses were halved, the ANCs of the products reduced by a ratio of 1.231−3.926 **Table 3** to values ranging from 7.583 mEq to 20.417 mEq (mean = 13.384 ± 3.827 mEq). These values were also greater than the minimum recommended value of 5 mEq **Fig. 3**.

Additionally, at half the recommended doses, 100% of the granule products, 92.8% of the suspensions, and 60% of the tablet brands had ANCs ≥ 10 mEq, which is double the recommended value. Overall, 86.4% of all the products had ANCs ≥ 10 mEq at half dose. As such, it may be argued that administering half the doses recommended by the manufacturers could still achieve desirable acid-neutralizing effects as they exceed the minimum ANC of 5 mEq. Please delete this. It is the caption for the table.

**TABLE 3: ANCS OF THE ANTACIDS AT DIFFERENT DOSE LEVELS**

| Product | ANC (mEq) | | | Minimum Dose/Half Dose | Double Dose/Minimum Dose |
|---|---|---|---|---|---|
| | Half Minimum Dose | Minimum Recommended Dose | Double Minimum Dose | | |
| A | 18.250 ± 0.377 | 35.867 ± 0.257 | 63.817 ± 3.601 | 1.965 | 1.779 |
| B | 13.500 ± 0.050 | 26.983 ± 0.104 | 48.217 ± 1.097 | 1.999 | 1.787 |
| C | 11.800 ± 0.265 | 20.517 ± 0.076 | 26.400 ± 0.377 | 1.739 | 1.287 |
| D | 18.317 ± 0.176 | 35.000 ± 0.350 | 56.783 ± 1.373 | 1.911 | 1.622 |
| E | 7.583 ± 0.506 | 12.417 ± 0.325 | 21.117 ± 0.189 | 1.637 | 1.701 |
| F | 10.083 ± 0.629 | 14.500 ± 0.436 | 56.933 ± 0.176 | 1.438 | 3.926 |
| G | 10.000 ± 0.436 | 13.333 ± 1.075 | 26.950 ± 0.350 | 1.333 | 2.021 |
| H | 20.417 ± 0.454 | 38.250 ± 0.673 | 71.133 ± 1.500 | 1.873 | 1.860 |
| I | 11.433 ± 1.285 | 16.317 ± 0.993 | 28.783 ± 0.333 | 1.427 | 1.764 |
| J | 17.733 ± 0.379 | 38.817 ± 2.457 | 58.583 ± 0.493 | 2.189 | 1.509 |
| K | 11.483 ± 0.076 | 15.500 ± 0.397 | 41.050 ± 0.173 | 1.350 | 2.648 |
| L | 19.533 ± 1.373 | 34.867 ± 0.275 | 69.117 ± 1.721 | 1.785 | 1.982 |
| M | 13.367 ± 0.293 | 26.650 ± 0.608 | 51.350 ± 1.176 | 1.994 | 1.927 |
| N | 15.217 ± 0.275 | 28.100 ± 0.786 | 57.600 ± 1.011 | 1.847 | 2.050 |
| O | 8.217 ± 0.161 | 16.100 ± 5.414 | 19.817 ± 1.381 | 1.959 | 1.231 |
| P | 15.383 ± 0.431 | 25.817 ± 0.275 | 50.067 ± 1.563 | 1.678 | 1.939 |
| Q | 8.250 ± 0.529 | 12.950 ± 0.218 | 22.567 ± 0.115 | 1.570 | 1.743 |
| R | 11.400 ± 0.173 | 21.583 ± 0.702 | 39.133 ± 0.939 | 1.893 | 1.813 |
| S | 16.967 ± 0.189 | 35.600 ± 0.654 | 64.850 ± 1.311 | 2.098 | 1.822 |
| T | 10.583 ± 0.454 | 17.217 ± 0.577 | 32.550 ± 0.482 | 1.627 | 1.891 |
| U | 13.050 ± 0.654 | 22.533 ± 0.791 | 42.367 ± 1.025 | 1.727 | 1.880 |
| V | 11.883 ± 2.004 | 21.817 ± 0.126 | 43.050 ± 2.079 | 1.836 | 1.973 |
| Minimum recommended ANC = 5 mEq | | | | | |

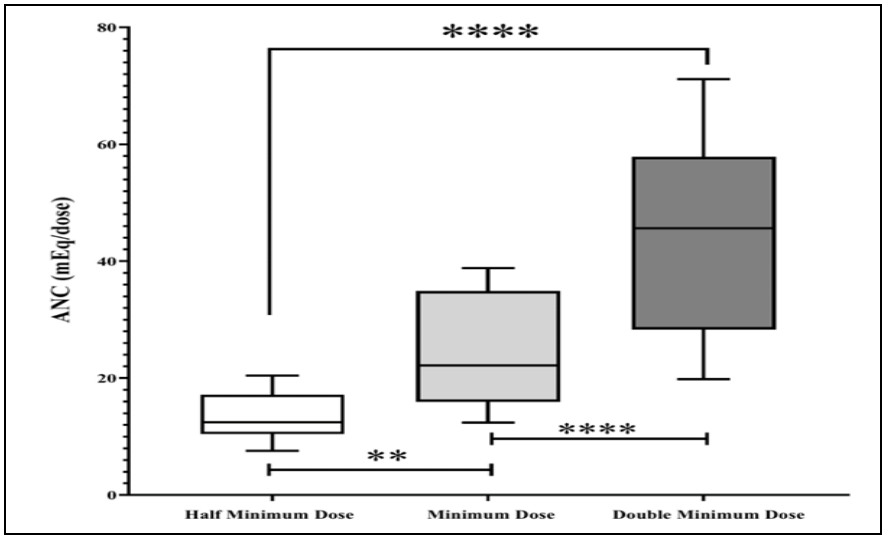


**FIG. 3: DOSE-DEPENDENT EFFECT OF THE PRODUCTS ON ANC**

When the labeled minimum doses were doubled (as seen for some of the dosage recommendations by some of the manufacturers), the ANCs increased by an average ratio of 1.916 **Table 3** to values ranging from 19.817 mEq to 71.133 mEq (mean = 45.102 ± 16.289 mEq). These results show that when the doses of these products are doubled, their ANCs may far exceed what may be required to relieve hyperacidity-related symptoms like indigestion. However, in the management of peptic ulcer diseases, such values may become valuable in the relief of symptoms. Considering the three-dose levels adopted, the ANCs of the products were observed to be dose-dependent, with significant differences at each dose level ($F_{2, 63} = 47.60$, $p < 0.0001$). Thus, recommending a range of doses for administration, as some manufacturers do in **Table 1**, may result in patient's achieving different levels of acid neutralizing effect depending on the dose administered at any point in time.

This may lead to inconsistencies in treatment outcomes, which may be undesirable. Additionally, the dose ranges indicated on product labels may misinform patients that antacids are safe to consume in large doses. This downplays the importance of expert advice in the proper management of conditions that have acid reflux and heartburn as symptoms.

Consequently, in an attempt to improve symptoms with self-treatment, patients could expose themselves to undesirable effects when antacid doses are increased blindly. Since, antacid doses lower than the minimum labeled doses resulted in acceptable ANCs, it may be inferred that manufacturers and/or prescribers may need to reconsider recommending a general and broad range of dosages of such products for consumers or patients and that recommendations must be based on the severity of symptoms. This observation of ANCs being greater than the minimum regulatory requirement is commendable. However, the phenomenon brings up for discussion the subject of the maximum allowable ANC of an antacid, so that as an administered dose maintains its acid-neutralizing effect, it does not predispose the consumer to toxic effects as a result of prolonged product use or short-term intake of high doses [9, 23].

Another issue of importance is that intake of relatively higher doses may increase the cost of treatment. For example, the labeled dose for antacid E, which is commercially available as a 150 mL product and was one of the expensive samples, is 10−20 mL. From the current results, 5 mL (half of the minimum recommended dose) of the antacid produced an ANC of 7.583 ± 0.506 mEq, while 10 mL and 20 mL produced ANCs of 12.417 ± 0.325 mEq and 21.117 ± 0.189 mEq, respectively. Consequently, regular intake of 20 mL of the antacid by a patient would mean only 7.5 doses would be obtained from a bottle, while 15 and 30 dose administrations could be achieved from regular intake of 10 mL and 5 mL, respectively. Thus, the cost implications of different dosage regimens should be considered by the manufacturer.

**CONCLUSION:** The findings of the current investigations show that in as much as manufacturers' recommended doses of antacids achieve the minimum regulatory requirements, halving such doses also achieves similar requirements. This may indicate that at half the labeled doses, some common and acute hyper-acidity symptoms could be managed adequately. Furthermore, the practice of re-commending a range of doses for administration, in which case, the upper limit may likely be twice the lower limit, could lead to irreproducible treatment outcomes. Although antacids are considered safe even at higher doses relative to other classes of medicines, it may be important for medicine regulators to consider setting upper limit specifications for ANCs. This is important because it could reduce the risk of over dosage. Overall, the suspensions had the highest average ANC, followed by the tablets and then the granules.

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**CONFLICTS OF INTEREST:** The authors have no conflict of interest to declare.

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