Comparison of Seven Oxethazaine Containing Antacids Available in the Indian Market

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Abstract

Objective: This in-vitro study was designed to measure the quantity of acid neutralized by a suspension of a commercial antacid available in Indian markets at a labeled dose and to test the concept of the relative effectiveness of 7 different commercial antacids containing Oxethazaine.

Methods: A simple back titration methodology was used to determine the acid neutralization capacity (ANC) of antacids.

Results: It was observed that different antacids vary widely in their in vitro ANC. There was also a batch to batch variation noted for each brand of antacid. The analysis indicated that there was a significant difference of ANC in favor of AD versus other antacids studied.

Conclusion: Comparison of relative effectiveness indicates that AD has highest ANC in vitro amongst other antacids. However, the present study being in vitro, the effects of antacid may vary in vivo, as individual variations also contribute to the ultimate effectiveness of an antacid.

Abbreviations: M: Molar; HCL: Hydrochloric Acid; NaOHa: Sodium Hydroxide; H2CO3: Carbonic acid; CO2: Carbon dioxide; CaCO3: Calcium carbonate; Na2CO3: Sodium Carbonate; meq: mili-equivalents; ANC: Acid neutralizing capacity; GERD: gastro-oesophageal reflux disease; OTC: over the counter; USP: United States Pharmacopeia; ANOVA: Analysis of variance

Introduction

Antacids are commonly used world over as over the counter (OTC) or prescribed medications. They have been used as the mainstay of treatment for peptic ulcers, gastritis, gastro-oesophageal reflux disease (GERD), and functional dyspepsia. Approximately 8% of the population in the United Kingdom visits their general practitioner each year with dyspeptic symptoms, and 50% of gastroenterology referrals are attributed to these symptoms. Although there is no published evidence about the exact cost of dyspepsia to the Indian community, it represents a considerable burden to the health care services.

Antacids mostly consist of magnesium and aluminium salts and sodium/calcium carbonate in various compounds or combinations. Antacids act by neutralising the hydrochloric acid (HCl) secreted by the gastric parietal cells and thereby elevating the gastric pH. When the pH is raised above 3 most of the gastric HCl is neutralised and the proteolytic activity of pepsin (which is capable of digesting the gastric mucosal membrane) is reduced.

An effective antacid is characterised by its ability to react rapidly with acid, buffer in the pH range of 3 to 6, have a high acid neutralising capacity (ANC), and cause few or minimal side effects. Besides these, a physician also needs to consider the following factors; the antacid should neutralise the greatest amount of acid per unit cost; should be both palatable and conveniently consumed by the patient, its sodium content, its constipating or diarrheogenic effects, and its physical form. Antacids are available in both liquid suspensions as well as solid dosage forms. Liquid antacids are generally preferred as they have a higher neutralization capacity which is attributed to their smaller particle size resulting in a greater surface area.

Besides the aluminium and magnesium salts, some antacids also contain oxethazaine. Oxethazaine, or 2,2’-(2-hydroxyethylimino) bis[N-(l,l-dimethyl-2-phenylethyl)-N-methylacetamide], a glyicine amide resembling lidocaine, is a potent, safe local anaesthetic agent. Following topical application, it provides prolonged anaesthesia of mucous membranes. Its salient feature includes its ability to remain un-ionised even at a pH of 1, unlike most of the other local anaesthetics. There have been many published reports in recent years of the prompt and prolonged relief of pain obtained by Oxethazaine plus antacid combination in patients with esophagitis, gastritis, and peptic ulcers. Some investigators have shown that, in addition to providing symptomatic relief, this medication produced an increase in gastric pH above 3.5 for varying time periods.

Various in-vitro tests have been developed to evaluate the performance of antacids which are intended to reflect their in-vivo efficacy. The measurement of ANC is one such widely used test. Other tests are pH-stat test, monitoring the reaction rate, and measuring the performance under conditions intended to resemble the in vivo environment. In 1973, Fordtran and co-workers established the methods and evaluated the ANCs of antacids available at that time. Since then, their published results have served as a guide for physicians prescribing antacids. Several antacids are marketed in India, with a wide variability in their ANC. A study was conducted by Gadad et al., to assess the effects of various disintegrating agents on the ANC of antacid tablets. However, the liquid Indian antacid products have not yet been studied independently to determine their ANC, and labels on antacid products do not include this information.

The objective of this in-vitro study was to determine the ANC of seven Oxethazaine containing antacid suspensions (AD, AM, AU, AS, AC, AO, and AT) which were randomly
selected commonly prescribed brands, commercially available in the Indian market and to test the concept of their relative effectiveness, wherein the ANC of AD was compared with the ANC of the other products. As Oxethazaine commonly features in antacids having local anaesthetic action, hence Digeicaine containing Oxethazaine was considered as the reference drug for this study.

Materials and Methods

Materials

Seven antacids in suspension form containing oxethazaine were procured from the market. Sodium hydroxide (NaOH), HCl, and sodium carbonate (Na2CO3) anhydrous of GR grade used for back-titration were obtained from Merck.

Methods

Principle

A strong acid-strong base titration was used to test the capacity of various commercial antacids to neutralise an acidic environment (simulated acidic stomach). For studying the batch to batch effect, three batches of each antacid were evaluated. Six trials from each batch ensured reproducibility of the experiments. Antacid samples were dissolved in the solution containing a known amount and concentration of the HCl solution. The amount of excessive HCl (non reacted acid) that remained in the solution was determined by back-titration of the solution to neutrality with a standardised solution of NaOH. The amount of NaOH solution required was used to estimate the amount of HCl which was neutralised by each antacid. Hence the ANC (nSample) was calculated by the following equation:

\[
\text{nSample} = \text{NA} - \text{NB}
\]

Where

\[
\begin{align*}
\text{NA} & \quad \text{the number of moles of HCl used for dissolving the antacid sample} \\
\text{NB} & \quad \text{the number of moles of NaOH needed to back-titrate the excess HCl} \\
\text{nSample} & \quad \text{the number of moles neutralized by the sample}
\end{align*}
\]

In the present study, United States Pharmacopeia (USP) ANC was studied for antacids and the results were expressed in milliequivalents (mEq) of HCl consumed, as Indian Pharmacopeia doesn’t specify ANC in terms of mEq of HCl consumed.10

As per the final protocol, 10 mL of antacid sample was to be used for the process of titration. To each sample 30 mL of 1N HCl was to be added to determine the neutralising capacity of the sample. It was assumed that upon taking 30 mL acid, there will always be some excess left after neutralising the antacid, and that can be quantified by back-titration. The amount of acid reacted would therefore give the neutralizing capacity for the antacid sample. Following the same analysis with each antacid sample would finally provide the variation in the ANC of the antacids under study. All experiments were carried out at a controlled laboratory temperature (25°C ± 5°C). Standardization of NaOH and HCl solutions was carried out as per USP method.11

<table>
<thead>
<tr>
<th>Antacid</th>
<th>AD</th>
<th>AM</th>
<th>AU</th>
<th>AS</th>
<th>AC</th>
<th>AO</th>
<th>AT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grand mean (mEq) of antacid</td>
<td>28.84</td>
<td>16.81</td>
<td>13.29</td>
<td>14.26</td>
<td>17.12</td>
<td>18.7</td>
<td>14.43</td>
</tr>
</tbody>
</table>

Table 1: Grand mean of ANC of all antacids

Table 2: Relative Effectiveness of Commercially available Antacid Brands with respect to AD

<table>
<thead>
<tr>
<th>Antacid</th>
<th>Grand Mean of ANC (mEq)</th>
<th>S.D.</th>
<th>C.V.</th>
<th>Relative Effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD</td>
<td>28.84</td>
<td>0.4212</td>
<td>1.460</td>
<td>100</td>
</tr>
<tr>
<td>AM</td>
<td>16.81</td>
<td>0.5505</td>
<td>3.275</td>
<td>58.28</td>
</tr>
<tr>
<td>AU</td>
<td>13.29</td>
<td>3.377</td>
<td>25.40</td>
<td>46.08</td>
</tr>
<tr>
<td>AS</td>
<td>14.26</td>
<td>0.090</td>
<td>0.6361</td>
<td>49.44</td>
</tr>
<tr>
<td>AC</td>
<td>17.12</td>
<td>0.3579</td>
<td>2.090</td>
<td>59.36</td>
</tr>
<tr>
<td>AO</td>
<td>18.70</td>
<td>0.9127</td>
<td>4.879</td>
<td>64.84</td>
</tr>
<tr>
<td>AT</td>
<td>14.43</td>
<td>0.080</td>
<td>0.5600</td>
<td>50.03</td>
</tr>
</tbody>
</table>

S.D= Standard deviation; C.V = Coefficient of Variance

Results

When 10 mL antacid as sampling volume was used as per protocol, it was observed that some samples neutralised the entire 30 mL HCl added, leaving no excess. Thus back-titration was not possible unless the initial quantity of acid added was
increased to a higher value. Therefore to get ANC values for all the brands, the next option chosen was to use 5 mL of antacid samples to initiate further analysis of ANC for all antacids. This change in methodology was not expected to result in any measurement bias, and would in fact improve the yield of valid results for ANC.

When the grand mean of all the three batches were calculated per formulation, AD was shown to have the highest mean ANC value (28.84 mEq) in comparison with others (Figure 1) (Table 1). The relative effectiveness of the other antacids was then calculated considering AD as 100 (Table 2). The mean difference in the ANC of AD and the rest of the antacids was statistically significant at 5% level of significance (P = 0).

**Discussion**

In our study we have compared the oxethazaine containing antacid suspensions which are presently commercially available in the Indian markets. Our results clearly demonstrate that, there is considerable variation in the in vitro ANC of equal volumes of different antacids. However, this difference in ability to neutralise acid is not reflected on the labels of antacid products. The actual ANC is not mentioned on the product label, and thus most manufacturers recommend a standard dose of 5 to 10 mL, regardless of the antacid’s ANC.

In our experiment, with 5 mL as uniform dose, all antacids have shown ANC variation with statistically significant difference. The potency varied from 28.84 mEq (AD) to 13.29 mEq (AU). In 1975, Fordtran et al demonstrated that the potency per milliliter of antacids varied 17-fold among different commercial products. The same fact was reiterated in the study by Drake et al, wherein they demonstrated a tenfold difference in the ANC between the least and the most effective preparations. Because of this wide variation in neutralising ability, the product and its ANC must be known, when antacid therapy is being recommended.

The fact to consider is that, the antacids with a higher ANC will provide effectiveness with the lowest dosage volume. In our experiment, relative effectiveness was used to compare potency of antacids. AD having higher ANC is expected to be providing effectiveness at lower dosage volume compared to other antacids in the study.

In our experiment, we have also observed batch to batch variation in the same formulation. Various reasons, such as manufacturing, formulation etc may contribute to variation. Further, this could also be attributed to actual variation in the amount of the active ingredient. As mentioned in Drugs and Cosmetics act: “for Patent or proprietary medicines, the contents of active ingredients, other than vitamins, enzymes and antibiotics, shall be not less than 90 per cent and not more than 110 per cent of the labelled content; however, for enzymes and vitamins, only the lower limit of 90 per cent shall apply.” Thus, it seems that permissible limit ± 10% of active ingredient may be leading to difference in the ANC for different batches. Similar trend in liquid antacids was observed in a study conducted by MacCara et al comparing the lot-to-lot consistency in the ANCs of various new antacids in Canada.

We have compared only the oxethazaine containing antacids in our study which were randomly selected commercially available brands. Several authors have demonstrated the benefits of oxethazaine/antacid combination when compared to antacid alone. In vivo study by Novaes et al showed that oxethazaine/antacid combination when compared to antacid alone produced a more rapid rise in pH, a significantly higher peak pH, and a significantly greater period of an acidity between the time of medication and the peak pH, and a significantly greater overall period of an acidity from the time of medication until the period returned to the acid range. In a study by Pontes et al, significantly fewer doses of oxethazaine/antacid combination than that of antacid alone gave satisfactory relief of ulcer pain and significantly fewer pain episodes occurred in the group treated with the combination than with the antacid alone.

A limitation of this study was that, we only studied the ability of antacids to elevate the pH above 3.5 in the presence of HCl. However, the onset of action, rate of neutralisation, and duration of action are also important factors determining the efficacy of an antacid.

Another limitation of our study was that, it was an in-vitro study. Studies done in this therapeutic area are usually in-vitro studies which simulate an in-vivo environment. Similarly this study was conducted in an in-vitro scenario to compare commercially available antacid-local anaesthetic drug combination. Although in vitro tests can approximate in vivo conditions with respect to acid-consuming capacity, speed and duration of action, and maximum buffering capacity of the antacid, they cannot precisely account for variations in antacid activity due to gastric emptying, variability in the acid secretion rate in the fasting and postprandial states, interaction of antacids with glycoproteins and mucoproteins of gastric juice, coating of the gastric mucosa by antacids, and the effect of antacids on endogenous control of gastric acid secretion.

**Conclusion**

Based on this in vitro experiment, we can conclude that, the seven oxethazaine containing antacid suspensions evaluated in this study, varied in potency as measured in terms of their ANC. This fact may be taken into account when antacid drugs are prescribed.

Comparison of relative effectiveness indicates that AD has highest ANC in vitro amongst other antacids. However, the present study being in vitro, the effects of antacid may vary in vivo, as individual variations also contribute to the ultimate effectiveness of an antacid.

**Acknowledgement and Disclosure**

This study was funded by Abbott India. AD is an oxetacaine containing antacid of Abbott India.
References


12. The Drugs and Cosmetics Act and Rules. (23 of 1940) (As Amended Up To The 30th June, 2005) P-499.
