

## Review Article

# Anaesthetic antacids: a review of its pharmacological properties and therapeutic efficacy

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**Received:** 13 December 2017

**Accepted:** 27 December 2017

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## ABSTRACT

Anaesthetic antacids, combination of antacids (Aluminium hydroxide, Magnesium hydroxide) with an anaesthetic (oxethazaine), is becoming a choice of physicians and is re-emerging across all types of GI disorders (esophagitis, peptic ulcer, duodenal ulcer, heartburn, gastritis, functional dyspepsia), despite the discovery of potent and efficacious acid suppressants like H<sub>2</sub> receptor blockers and proton pump inhibitors (PPIs). The reason being that anaesthetic antacids increase the gastric pH and provide relief from pain for a longer period of duration at considerably a lower dosage. Furthermore, it significantly increases the duration between the time of medication and the peak pH as compared to antacid alone. Oxethazaine, an anaesthetic component, produces a reversible loss of sensation and provides a prompt and prolonged relief of pain, thereby broadening the therapeutic spectrum of antacids. Antacids vary widely in their in vitro acid neutralizing capacity (ANC), which measures the potency. Among marketed brands in India, Digecaine has shown the highest potency with maximum mean ANC value (28.84 mEq). The expert panel has recommended the inclusion of oxethazaine-antacid/alginate-antacid as complementary to the proton pump inhibitors in the management algorithm of gastroesophageal reflux disease. The present review summarizes the pharmacokinetic and pharmacodynamic of different components of anaesthetic antacids and its clinical use across different gastrointestinal indications, for generalists and specialists, based on existing evidences.

**Keywords:** Aluminium hydroxide, Anaesthetic antacids, Hyperacidity, Magnesium hydroxide, Oxethazaine, Peptic ulcer

## INTRODUCTION

Antacids are used in the treatment of gastric acid related disorders for a long time and grew in popularity during early 19<sup>th</sup> century. They provided good symptomatic relief from hyperacidity and other associated conditions by directly neutralizing the gastric acid and thereby raising the pH of the gastric contents, restoring acid-base balance, attenuating the pepsin activity and increasing the bicarbonate and prostaglandin secretion.<sup>1</sup>

Despite the discovery of potent and efficacious acid suppressant (anti-secretory) agents such as histamine H<sub>2</sub> receptor blockers and proton pump inhibitors (PPIs), the

long-term safety of antacids remains unsurpassed. Notably, both the acid suppressant classes were reported to have certain disadvantages which could limit their use in the long run. Postprandial acid control and tachyphylaxis are commonly observed side effects of long-term use of H<sub>2</sub> blockers.<sup>2</sup>

Moreover, recent studies have highlighted numerous side effects, ranging from an altered gut environment and impaired nutrient absorption to an increased risk for cardiovascular events, kidney disease, and dementia, with the use of PPIs, despite being safe and a choice of medication for most gastric-related problems.<sup>3</sup> Antacids are commonly prescribed for non-ulcer dyspepsia,

duodenal ulcer, gastric ulcer, stress gastritis, gastroesophageal reflux disease (GERD), pancreatic insufficiency, bile acid-mediated diarrhea, biliary reflux, constipation, urinary alkalisation, and chronic renal failure. The key therapeutic advantage of antacids is their rapid onset of action, thereby providing rapid relief of gastric discomfort within minutes.

Antacids are divided into two classes; the first class includes those antacids that work by chemical neutralization of gastric acid, most notably sodium bicarbonate; and the second class of antacids act by adsorption of the acid (non-absorbable antacids), such as calcium and magnesium salts. Antacids include carbonate and bicarbonate salts (e.g., sodium bicarbonate, calcium or magnesium carbonate), alkali complexes of aluminium and/or magnesium (e.g., aluminium and magnesium hydroxides), aluminium and magnesium phosphates, magnesium trisilicate, and alginate-based raft-forming formulations (Table 1).

As highlighted above, conventional antacids offer less symptomatic relief from gastric related problems and therefore, their use has declined with the availability of efficacious anti-acid secretory medications ( $H_2$  blockers and PPIs). However, in the light of recent studies highlighting the use of PPI and the risk to human health with their use, has led to a new debate on revising the use of antacids in gastric related problems.

Anaesthetic antacid, prepared by combining the local (topical) anaesthetic (oxethazaine) with aluminium hydroxide and magnesium hydroxide, is one such formulation that promises to offer better control of gastric related problems. Aluminium and magnesium hydroxide react chemically to neutralize the acid and increases gastric pH. Oxethazaine exerts a prolonged topical anaesthetic action. It is prescribed for rapid and effective relief in gastritis, esophagitis, hiatus hernia, heartburn and peptic ulcer. The anaesthetic/antacid combination is used at a considerably lower dose which reduces the risk of adverse effects as compared to antacids, per se. In some of the antacid formulations, alginate acid has been added to promote adherence of the antacid to the gastrointestinal (GI) mucosa, and it also acts as a protective covering to the gastric mucosa.

Given the fact that the pathogenesis of GERD is not attributed, solely, to the acid secretion, the new algorithm has recommended the use of antacids and alginate-antacid combination in conjunction with the PPIs, as an additional option (as adjuvant therapy) in patients with GERD.<sup>4</sup> The improved therapeutic profiles of anaesthetic antacids as compared to the usual short-lasting simple acid neutralizing antacids, hopes to compete with currently established medications for gastric related disorders. The present review aims to assess and provide an insight on the pharmacological properties and therapeutic efficacy of anaesthetic antacids in various GI disorders.

## INDIVIDUAL COMPONENTS OF ANAESTHETIC ANTACIDS

### *Oxetacaine (Oxethazaine)*

Oxetacaine (N,N-bis-(N-methyl-N-phenyl-t-butyl-acetamide)-beta-hydroxyethylamine) is a potent local anaesthetic agent, exceeding by far the potency of either cocaine, procaine, lidocaine or dibucaine. It acts by producing a reversible loss of sensation by preventing or diminishing the conduction of sensory nerve impulses near the site of its application. Unlike other local anaesthetic compounds, it is chemically a glycine amide instead of benzoate or aminobenzoate. It is given orally (usually in combination with an antacid) for prompt and prolonged relief of pain associated with peptic ulcer disease or esophagitis. When applied to the mucous membranes, it produces a more potent anaesthesia of longer duration than either cocaine hydrochloride or lidocaine hydrochloride. *In vitro*, oxethazaine produces antispasmodic action on smooth muscle and blocks the action of serotonin on smooth muscle, though the clinical relevance of this effect remains to be established. It shows its action after 5 minutes and the duration of action ranges from 2 to 3 hours. In the stomach, it increases the pH and neutralizes the gastric acid, which further relieves the symptoms of hyperacidity problems. Unlike most other local anesthetics, it does not break down under strongly acidic conditions. Hence, it is particularly suited in combinations antacid formulations which are intended to provide additional gastric pain relief besides neutralization of the gastric acid. A combination of the oxethazaine hydrochloride in aluminium and magnesium hydroxide gel is available in the market for commercial use. It also has a large margin of safety when administered intragastrically and has proven to be useful clinically to control pain due to a variety of gastric disorders. Some of the conditions for which oxetacaine is indicated include GERD, hemorrhoidal pain, symptoms of hyperacidity symptoms, eructation, nausea, vomiting, stomach discomfort, esophagitis, gastritis, gastric/duodenal ulcer, local anaesthetic, heart burn in, etc.

### *Simethicone/Dimethicone*

Simethicone is an orally administered antifoaming agent, used to reduce gas from the digestive tract in patients complaining of recurrent flatulence. It is a mixture of dimethicone (polydimethylsiloxane) and hydrated silica gel (silicon dioxide). It shows effect locally in the digestive tract and not absorbed into the blood stream. It is being used as an effective adjunct therapy in conditions where excessive gas is aggravating the symptoms in conditions such as dyspepsia, peptic ulcer, post-operative gaseous distention and irritable colon. Moreover, the drug is used as a self-medication to relieve symptoms commonly referred to as gas, including upper digestive tract bloating, pressure, fullness, or stuffed feeling.

**Table 1: Important antacids and their features.**<sup>1,5</sup>

Antacids	Acid neutralizing capacity <sup>#</sup>	Advantages	Disadvantages	Clinical conditions
Calcium carbonate	58	Potent and rapidly acting	GI distress Nausea/vomiting Hypercalcemia Hypo-phosphatemia milk-alkali syndrome	Heartburn Acid indigestion Upset stomach
Magnesium trisilicate	Low	Slow but prolonged action laxative (at larger doses)	Low solubility and reactivity, Absorbed systemically (problem in renally compromised patients)	Dyspepsia Heart burn Hyperacidity Constipation
Magnesium carbonate	Low used in combination with other products		GI distress, Electrolyte imbalances Hypotension Neuromuscular blockade hypotension	Hyperacidity and peptic ulcer dyspepsia heartburn GERD Constipation
Magnesium hydroxide	35	Reacts with HCl Promptly and is an efficacious antacid, low systemic absorption	Low water solubility, no systemic alkalosis (mg is poorly absorbed from gut)	Constipation, digitalis toxicity Gastric acidity Hypomagnesaemia Peptic ulcer Pre-eclampsia
Magaldrate	33	Good oral antacid with prompt and sustained neutralizing action	Diarrhea Constipation Intestinal pain	Gastritis Hyperacidity Reflux esophagitis
Carbaldrate (dihydroxy aluminium sodium carbonate)	20	One of the most effective antacid substances Rapid neutralization of gastric acid	Uraemic aluminium on long-term use Associated with dementia	Indigestion and heartburn GERD Duodenal ulcer Gastric ulcer ZES
Aluminium hydroxide	29	Raises the pH of the gastric juice, Adsorbs pepsin	Efficient, low systemic absorption, Decreases phosphate excretion via kidney	Chronic diarrhoea hyperparathyroidism Hyper-phosphatemia (in renal failure), nephrolithiasis, peptic ulcer, reflux esophagitis, stress ulcers
Sodium bicarbonate	17	Most rapidly acting antacid	Metabolic alkalosis with urine alkalinisation, Intake of large doses	Heartburn Alkalinisation of urine Acidosis

Acid neutralizing capacity (mEq/15mL of a commercially available product); Al<sub>2</sub>Cl<sub>3</sub>: Aluminium chloride; CO<sub>2</sub>: CaCl<sub>2</sub>: Calcium chloride; Carbon dioxide; GERD: Gastroesophageal reflux disease; HCl: Hydrochloric acid; MgCl<sub>2</sub>: Magnesium Chloride; MgSO<sub>4</sub>: Magnesium sulfate; NaCl: Sodium chloride; SiO<sub>2</sub>: silicon dioxide; NaHCO<sub>3</sub>: Sodium bicarbonate; ZES: Zollinger Ellison Syndrome; <sup>#</sup>The potency of an antacid is generally expressed in terms of its acid neutralizing capacity (ANC) which is defined as the number of mEq of 1N HCl that are brought to pH 3.5 in 15 min (or 60 min in some tests) by a unit dose of the antacid preparation.

It has also been used for the gastroscopy to enhance visualization and prior to radiography of the intestine to minimize gas shadows. Although there is gastroscopic evidence that simethicone aids in the elimination of gas from the digestive tract and reduces postoperative gas pains, the relationship of gas accumulation to what patients commonly refer to as symptoms of gas under

ordinary conditions is not clear; however, the drug also has been shown to be effective in relieving these symptoms. Simethicone has been reported as an effective antilflatulent agent but there is currently no conclusive evidence available to demonstrate that immediate postprandial upper abdominal distress (IPPUAD) is caused by excessive gas, despite the fact that a majority

of patients related symptoms of the distress to gas. In addition, more data is needed to confirm the efficacy of simethicone to show that it provides the symptomatic relief from IPPUAD, a complex symptom that commonly occurs within 30 minutes after a meal and consists of sensations of bloating, distention, fullness, or pressure with upper abdominal discomfort but not aerophagia or hyperacidity.

Dimethicone is a silicone polymer, also known as polydimethylsiloxane (PDMS) having viscoelastic properties. Dimethicone is used as a surfactant, antifoaming agent, and carminative in various products such as medical devices, food products, and lubricants. It has been reported as a common additive to antacids, although its value in the treatment of reflux esophagitis is unproven. A double blind clinical study has investigated its efficacy comparing the effect of a dimethicone-containing antacid gel (Asilone Gel) with a simple antacid gel in patients with reflux esophagitis. The inclusion of dimethicone in the antacid gel formulation was reported inefficacious in terms of conferring any benefit of symptomatic pain relief, however, it conferred a small advantage with regard to objective markers of esophageal inflammation, indicating that a dimethicone-containing antacid could be of value in the treatment of symptomatic gastro-esophageal.<sup>5</sup>

#### **Alginate-antacid**

Alginates are natural polysaccharide polymers isolated from brown seaweed (*Phacophyceae*) which upon coming in contact with gastric acid precipitates into low density viscous gel of near neutral pH within few seconds (*in vitro*) or a few minutes (*in vivo*). It forms a protective barrier and increases the viscosity and adherence of mucus to the esophageal mucosa. Therefore, formulations containing alginates have a quite different mode of action than antacids. Alginate-based raft-forming formulations usually contain sodium or potassium bicarbonate. In the presence of gastric acid, the bicarbonate is converted to carbon dioxide which becomes entrapped within the gel precipitate, converting it into foam that floats on the surface of the gastric content, providing a relatively pH-neutral barrier.<sup>6</sup>

### **PHARMACOKINETIC PROPERTIES OF COMPONENTS OF ANAESTHETIC ANTACIDS**

#### **Magnesium hydroxide**

Nearly 15%-50% of magnesium hydroxide is absorbed very slowly through the small intestine. Its peak action and distribution are reported as variable, and it does not bind with plasma proteins. A very little amount is absorbed in the intestine unless the patient has hypomagnesemia. Overall, about 15%-50% of the magnesium hydroxide suspension is absorbed systemically which does not undergo any metabolism as it is rapidly excreted in the urine via kidney. Since the

kidneys play a major role in its clearance, individuals with renal failure are at risk of hypermagnesemia with long-term consumption due to deficient magnesium excretion. The acid neutralization capacity (ANC) of each mg of  $Mg(OH)_2$  is expected to be 0.0343 mEq.

#### **Aluminium hydroxide**

Aluminium hydroxides found to be absorbed, in only relatively small amounts, into the digestive tract. Approximately 17-30% of the  $Al_2Cl_3$  formed in the stomach is absorbed. The onset of action of aluminium hydroxides ranges from 5-10 minutes and its action lasts for about 100 minutes. It is eliminated fast, chiefly via renal route. The ANC of each mg of  $Al(OH)_3$  is expected to be 0.0385 mEq.

#### **Oxetacaine (Oxethazaine)**

10 mL of alumina gel with magnesium hydroxide containing 20 mg oxetacaine (oxethazaine), the peak oxethazaine plasma level of approximately 20 ng/mL was reached after about one hour after dosing following oral administration. Oxethazaine has been reported to undergo rapid and extensive hepatic metabolism which results in a short plasma half-life ( $T_{1/2}$ ) of approximately one hour. Less than 0.1% unchanged oxethazaine was found to be recovered in the urine within 24 hours.

Beta-hydroxy-mephentermine and beta-hydroxy-phentermine have been identified as the primary metabolites of oxetacaine. Mephentermine and phentermine were found in the plasma in pharmacologically insignificant amounts and only 0.1% of the dose administered was excreted in the urine after 24-hour of the duration.<sup>7</sup>

#### **Simethicone**

Simethicone is pharmacologically inert. It is not absorbed from the digestive tract and does not interfere with gastric secretion or absorption of nutrients. Following oral administration, the drug is excreted unchanged in feces. As, it is not absorbed by the body into the bloodstream and is therefore considered relatively safe.

#### **Dimethicone**

Information on the pharmacokinetic properties of dimethicone remains less studied. However, dimethicone has been reported to influence pharmacokinetic of several other drugs.<sup>8</sup>

Dimethicone has been reported to improve GI tolerability of non-steroidal anti-inflammatory drugs (NSAIDs). A study investigating the alleviation of the NSAIDs induced epigastralgic effects, dimethicone did not affect the efficacy of the ketoprofen treatment and altered other pharmacokinetic parameters but it did not significantly change the bioavailability of ketoprofen.



## PHARMACODYNAMIC PROPERTIES OF COMPONENTS OF ANAESTHETIC ANTACIDS

### *Magnesium hydroxide*

Magnesium hydroxide suspension neutralizes gastric acid by reacting with hydrochloric acid in the stomach to form magnesium chloride and water. It is practically insoluble in water and does not have any effect until it reacts with the stomach acid. There, it decreases the direct acid irritant effect and increases the pH in the stomach leading to inactivation of pepsin. Magnesium hydroxide enhances the integrity of the mucosal barrier of the stomach as well as improving the tone of both the gastric and esophageal sphincters. Unabsorbed magnesium salt cause osmotic diarrhea and aluminium salts cause constipation, hence these two are commonly administered together in a ratio of 2:1 to minimize the impact on bowel function. As a laxative, it works by increasing the osmotic effect in the intestinal tract and drawing water in. This creates distension of the colon resulting in an increase in peristaltic movement and bowel evacuation.

### *Aluminium hydroxide*

Aluminium hydroxide is the one of the compounds amongst the many different aluminium salts, used most commonly in antacid formulations more often in combination with magnesium hydroxide and used rarely alone as a single substance. It dissolves slowly in the stomach and forms polymers of varied compositions. Together with phosphate and bile salts, it forms an insoluble compound. It has a weaker effect and is a slower acid-neutralizer as compared to magnesium salts. Aluminium ion causes the relaxation of the GI smooth muscle, which can postpone gastric emptying and can cause constipation. Aluminium hydroxide inhibits pepsin activity by increasing pH and through adsorption and exerts cytoprotective effects through increases in bicarbonate ion and prostaglandins. It also binds dietary phosphate in patients with chronic renal failure. This reduces phosphate load and decreases the hyperphosphataemia seen in patients with chronic renal failure.

### *Oxetacaine (Oxethazaine)*

Oxethazaine, has been reported as the most potent local anaesthetic (amide type), and is claimed to be 2000 times more potent than lignocaine and 500 times more potent than cocaine as assessed in rabbit's eyes.<sup>7</sup> Currently, oxethazaine is used in an antacid preparation for the topical relief of pain in conditions such as hiatus hernia, where the local pH is very low. It produces a reversible loss of sensation by preventing or diminishing the conduction of sensory nerve impulses near the site of its application. This also decreases the permeability of the nerve cell membrane to sodium ions (membrane stabilizing effect). In the stomach it increases the pH and neutralizes the gastric acid, which relieves the

hyperacidity problems. It acts as a vasoprotective with antacids, and has antispasmodic actions.

### *Dimethicone*

Activated dimethicone has been used to relief excessive gas (flatulence) by dispending and preventing formation of mucus surrounding gas pockets in the gastro-intestinal tract. It lowers the surface tension of the gas bubbles and bringing together all the small bubbles of gas (coalesce) to form a large bubble, which is then expelled. Thus, the gas is released by belching or passing flatus. Antiflatulents have been combined to an antacid gum coating to be effective antigas materials and eliminate trapped gas. The most common antigas material is dimethicone and when mixed with silicone dioxide becomes simethicone.

### *Simethicone*

Simethicone is a liquid dimethicone activated with finely divided silicon dioxide to enhance the defoaming properties of the silicone. It acts by decreasing the surface tension of gas bubbles, thus facilitating their coalescence and expulsion as flatus or belching. It also prevents the formation and accumulation of mucus-enclosed pockets of gas in digestive tract. Simethicone also facilitates the passage of gas through bowel lumen and allows patients to excrete a greater volume of gas at one time, thereby reducing the number of flatus events. Thus, less residual gas is present to cause uncomfortable or painful pressure in the stomach and intestines.

## INDICATIONS OF ANAESTHETIC ANTACIDS

Antacids were commonly prescribed in multiple gastrointestinal disorders like hyperacidity, peptic ulcer, GERD, irritable bowel syndrome, functional dyspepsia, flatulence and abdominal distension blotting.

Hyperacidity is a set of symptoms caused by an increased level of acid formation in the stomach. The currently used drugs for treatment of hyperacidity include acid blockers (which reduce gastric acid secretion for a prolonged duration), PPIs, antacids (neutralize gastric acid), protecting agents and antibiotics caused due to *Helicobacter pylori* (*H. pylori*) infection.<sup>9</sup> Oxethazaine, also produces antispasmodic action, is used in combination with aluminium and magnesium hydroxide for symptomatic relief of hyperacidity associated with peptic ulceration, gastritis, esophageal reflux, and gastric hyperacidity.<sup>10</sup> The results from different studies showing improved treatment and pain alleviation with oxethazaine containing antacids likely to increase its use in future.

Peptic ulcer is characterized by disruption in the mucosal lining of the stomach or duodenum, with depth to the submucosa, by more than 5 mm. PPIs and H<sub>2</sub> blockers afford effective ulcer healing in most patients with uncomplicated gastric and duodenal ulcers. For patients

in which peptic ulcer is caused by *H. pylori*, initial management includes complete eradication of *H. pylori* and subsequent withdrawal of offending drugs and contributing factors. Among antacids, both systemic and non-systemic antacids are used in the management of peptic ulcer of either gastric or duodenal origin. Aluminium-containing antacids show constipation as a most common side effect, which may progress to intestinal obstruction, faecal impaction and development of haemorrhoids and anal fissures. In addition, the most frequent adverse effect of magnesium containing antacids is diarrhoea, which is due to poor absorption of the relatively insoluble magnesium salts and subsequent osmotic effect in the bowel, and these antacids components have been combined to counteract each other weaknesses.<sup>2</sup> Oxethazaine containing antacids relieves the pain by producing numbing effect at considerably, lesser dose in patients with oesophagitis, gastritis, and peptic ulcer.<sup>11</sup> This combination produced rapid rise in PH, a significantly higher peak PH, a greater period of anacidity from the time of medication until the PH returned to the acid range. Unlike other local anaesthetic, oxethazaine has proven successful as it remained nonionized in acidic medium and increased the gastric pH above 3.5 for varying length of time. Furthermore, it easily penetrates the lipid membrane of myelin sheath and produce satisfactory and prolonged anaesthesia. Antacid combinations utilising oxetacaine has given satisfactory relief of ulcer pain and reduced the pain episode as compared to antacids alone.<sup>12</sup> These impressive features of anaesthetic antacids have led it as one of the most promising candidate for treating peptic ulcer.

Gastroesophageal reflux is a normal physiological process, normally of short duration, often remain asymptomatic, and limited to the distal part of esophagus.<sup>13</sup> The American College of Gastroenterology defined GERD as, "chronic symptoms or mucosal damage produced by the abnormal reflux of gastric contents into the esophagus".<sup>14</sup>

The management of GERD includes antacids and alginate, prokinetic drugs, sucralfate, H<sub>2</sub> blocker and PPIs. Antacids neutralize stomach acid to cut down on heartburn, sour stomach, acid indigestion, and stomach upset. Some antacids also contain simethicone that helps to get rid of gas from the body. A recent meta-analysis concluded that the relative benefit increase was up to 60% with alginate/antacid combinations, and 11% with antacids as compared with the placebo response.<sup>15</sup> In summary, there are insufficient data supporting a recommendation for anaesthetic antacids as a treatment option for symptomatic heartburn. However, alginate/antacid combinations appear to be superior to the per se use of antacid in patients with GERD.

Irritable bowel syndrome (IBS) is a chronic functional disorder defined by the presence of abdominal pain or discomfort, with altered bowel habits.<sup>16</sup>

The treatments of IBS include addressing abdominal symptoms such as pain, cramping, bloating, or bowel symptoms, including diarrhea and constipation. In IBS patients with predominant diarrhea along with pain and bloating, antispasmodics, particularly hyoscine, and peppermint oil, should be used as first line therapy. Other anti-diarrheal agents, such as loperamide, improve stool form and frequency in IBS patients. Antidepressants should be used in patients failing antidiarrheal drugs. In a study on IBS patients, around one in five patients self-medicated inappropriately and the antacid class had the highest incidence of inappropriate medication use.<sup>17</sup> A similar study on 374 patients in Sweden showed that acid-suppressive agents were the most commonly used drugs for abdominal complaints by IBS patients, for non-abdominal complaints, 13.3% of IBS patients self-medicated with antidepressants.<sup>18</sup> According to a previous study, antacids were regularly prescribed during the high-dose steroid therapy to prevent gastritis, and in this context, oxethazaine-antacid is expected to provide greater pain relief and control of symptoms in gastritis. Given the fact that IBS has broad range of physiological and psychological alterations, the optimal treatment strategy for its management has yet to be identified. However, the existing treatment is largely focused on the symptomatic control in which anaesthetic antacids can play a vital role. Further research with the role of anaesthetic antacids is necessarily recommended.

Functional dyspepsia is a chronic or recurrent pain or discomfort centered in the upper part of the abdomen. Antacids have been commonly prescribed as the first line treatment which patient try before consulting a physician. However, many patients get satisfied with antacids and they get relief from commercial (especially the liquid) formulations during episodes. This may be attributed to mucoprotective effect or to the antiflatulent agents (simethicone) that are often combined in these formulations, but independent of the acid neutralizing effect.<sup>19</sup> The oxetacaine-antacids may provide additional benefits of pain suppression besides acid neutralization.

Flatulence is a buildup of gas causing discomfort and distress in the digestive system. Probiotics and rifaximin (Xifaxan) have been shown to reduce total number of flatus episodes and associated discomfort. Simethicone has been recommended for treatment of flatulence and bloating; however, no benefit has been shown for common flatulence.<sup>20</sup>

A combination of simethicone and loperamide (Imodium Advanced) is effective in relieving abdominal bloating and gas associated with acute diarrhoea (more than either treatment alone); however, it has not been studied in nondiarrhoea-associated flatus.<sup>21</sup>

Bloating is more commonly seen in patients with IBS, whereas distension is more readily seen in patients with constipation and pelvic floor dysfunction in whom plethysmographic studies confirm an increase in

abdominal girth of as much as 12 cm. Fortunately, new therapies involving dietary manipulation (low-FODMAP diet) have proved highly successful in relieving symptoms of bloating and abdominal distension, with

efficacy rates well exceeding those of drug therapies, such as antibiotics and prokinetic agents. The role of anaesthetic antacid in various indications has been presented in Table 2.

**Table 2: Advantages of anaesthetic antacids across different indications.**

Author, year	Type of study	Study characteristic	Finding
<b>Hyperacidity</b>			
Bhoir and Bhagwat, 2013 <sup>22</sup>	<i>In-vitro</i>	Compared the ANC of 7 anaesthetic antacids	Anaesthetic antacid, digecaine has the highest ANC amongst all marketed antacids
<b>Duodenal ulcer</b>			
Siffert, 1972 <sup>23</sup> (n=34)	Double-blind clinical study	Arm 1: Antacid + Oxethazaine Arm 2: Antacid only	Less dose of anaesthetic antacid is required for symptom control
Pontes et al., 1975 <sup>13</sup> (n=17)	Double blind clinical study	Arm 1: Antacid + Oxethazaine Arm 2: Antacid only	Less dose of anaesthetic antacid is required for ulcer pain control
Novaes et al., 1975 <sup>11</sup> (n=20)	Double-blind crossover study	Arm 1: Antacid + Oxethazaine Arm 2: Antacid only	Increased anacidity period with anaesthetic antacid combination
Zanni et al., 1986 <sup>24</sup> (n=40)	Double-blind clinical study	Arm 1: Antacid + Oxethazaine Arm 2: Antacid only	Reduction in the doses of medication needed to achieve adequate symptomatic relief
<b>Gastroesophageal reflux disease (Heartburn)</b>			
Carne, 1964 <sup>25</sup> (n=36)	Double-blinded clinical study	Patients took anaesthetic antacids and antacids only on alternate days	Majority showed preference for anaesthetic antacids and also these patients reported complete relief from heartburn
Kovacs et al., 1990 <sup>26</sup> (n=50)	Double-blind parallel study	Arm 1: Antacid + Oxethazaine Arm 2: Antacid only Arm 3: Placebo	Anaesthetic antacids relieved symptoms of heartburn better than antacid used alone
<b>Functional dyspepsia</b>			
Holtmann et al., 2002 <sup>27</sup> (n=185)	Double-dummy placebo controlled study	simethicone (105 mg t.d.s.) Arm 2: Cisapride (10 mg t.d.s.) Arm 3: placebo (t.d.s.)	Simethicone is efficacious in functional dyspepsia treatment compared to cisapride and placebo

ANC: Acid Neutralizing Capacity; t.d.s: thrice a day

## CLINICAL STUDIES INCLUDING *IN VITRO* AND *IN VIVO* STUDIES

The measurement of ANC remains one of the most widely known *in vitro* tests used to evaluate the efficacy of antacids intended to reflect their *in vivo* efficacy. A strong acid-strong base titration has been used to test the capacity of various commercial antacids to neutralize an acidic environment (simulated acidic stomach).

In 2013, Bhoir and Bhagwat conducted an *in vitro* study to compare the ANC of seven randomly selected, commonly prescribed oxethazaine containing antacid suspensions from India.<sup>22</sup> The study tested the concept of the relative effectiveness and batch-to batch variations of different antacids formulations, wherein the ANC of reference antacids AD\* (with oxethazaine as local anaesthetic feature) was compared with the ANC of the other available products. To ensure reproducibility of the result, the study undertook six trials from each batch of antacids. 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 standardized solution of NaOH. The amount of NaOH solution required was used to estimate the amount of HCl which was neutralized by each antacid. The study observed a significant variation in the *in vitro* ANC of different antacids including a batch to batch variation for each brand of antacid which reflected that all the seven commercially marketed antacids containing oxethazaine were different in terms of their relative efficacy. However, it should be noted that, the effects of antacid might significantly vary *in vivo*, as individual variations also contribute to the eventual efficacy of an antacid. Antacids having a higher ANC is generally considered to be more efficacious requiring the lowest dosage volume. The study utilized the relative effectiveness as a parameter to compare potency of antacids. In the study, antacid formulation which was found to have higher ANC was indicated to be efficacious (Table 3) and hence,

such antacids would require lower dosage volume compared to other antacids to neutralize the acid. From the table, reference antacids AD\* was highly efficacious antacid followed by antacids in the following order: reference antacids AD\* > 5 > 4 > 1 > 3 > 2. (\* stands for Digecaine).

**Table 3: Relative effectiveness and ANC of different antacid formulation used by the study of Bhoir and Bhagwat, 2013.<sup>22</sup>**

Antacid	ANC (mEq)	Relative effectiveness
Digecaine (known antacid)	29.0	100
Antacid 1 (unknown)	17.0	58.3
Antacid 2 (unknown)	13.3	46.1
Antacid 3 (unknown)	14.5	49.4
Antacid 4 (unknown)	17.1	59.4
Antacid 5 (unknown)	18.7	64.8
Antacid 6 (unknown)	14.4	50.0

ANC: Acid neutralizing capacity

Another *in vivo* study compared four different antacids in term of their ANC, bile salt binding capacity, cost, and patient acceptance. The antacid preparations were reported to differ significantly in ANC and bile acid binding capacity, as well as cost. It was observed that dimethicone containing antacid demonstrated the highest ANC and bile acid binding capacity. The study concluded that individuals requiring antacid therapy should be allowed to choose from a range of preparation, in order to achieve maximize compliance.<sup>28</sup> Another *in vivo* study has suggested that addition of dimethicone in the antacid formulation would be of value the treatment of symptomatic gastroesophageal reflux.

In the past, a battery of clinical studies involving oxethazaine, reported effective management of esophagitis, peptic ulcer and esophagitis, duodenal ulcer and hiatus hernia, and gastritis.<sup>11,29,30</sup> All these studies have highlighted the efficacy of oxethazaine in gastric diseases. The clinical studies showing advantage of anaesthetic antacids across different indications were presented in Table 2.

Antacids have been fast and effective at relieving the symptoms of heartburn and are therefore, preferred by patients because of immediate relief from symptoms. It has been reported that about 30-50% of women required only antacids to ease their heartburn of pregnancy. Further, magnesium, aluminium, or calcium containing antacids have been reported to have no teratogenic risk, and also magnesium and aluminium hydroxide containing antacids were reported safe during lactation. A recent European consensus conference have recommended Ca/Mg-based antacids for pregnant women because of their safety profile.<sup>31</sup> Additionally, according to the experts, calcium based antacids have added benefit of increasing calcium supplementation to prevent the hypertension and pre-eclampsia associated with

pregnancy. The similar results were reported from a large, randomized placebo-controlled trial demonstrating that magnesium sulphate supplementation halves the risk of eclampsia compared with placebo, and could also reduce the risk of maternal death, with no serious short-term side-effects.<sup>32</sup>

A clinical study has also reported the efficacy of oxethazaine in the treatment of hemorrhoids suggesting that treatment with anaesthetic antacid could go beyond GI tract.<sup>33</sup> A meta-analysis by Tran et al. (2007) reported efficacy of OTC medications in treating symptomatic GERD. They reported that the relative benefit increase was up to 41% with H<sub>2</sub> blockers while with alginate/antacid combinations and antacids, alone were 60% and 11%, respectively.<sup>15</sup>

### ADVANTAGES OF ANAESTHETIC ANTACID OVER ANTACIDS

In the light of the above discussed *in vitro*, *in vivo* and the available clinical studies, it may be strongly advocated that therapeutic efficacy of oxethazaine-antacid formulations far exceeds than that of older antacid mixtures. The anaesthetic component of the oxethazaine-antacid formulations helped them gain an important place in therapeutic algorithm of GERD and other gastric related disorders. The prominence of oxethazaine containing antacids can be measured from the fact that these formulations are being recommended as complementary to PPIs in GERD and related disease. Thus, anaesthetic antacid now has clear-cut advantages over older simple antacid mixtures. The older antacid formulation primarily consisted of calcium and magnesium and aluminium-salts in various combinations and had acceptability problem including debated long-term use. The topical local anaesthetic agent helps relieve the pain caused due to hyperacidity and aluminium and magnesium hydroxides react with stomach acid to neutralize it. Oxethazaine is a strong local anaesthetic allowing it to be used in very dilute solutions. It acts in a number of ways to numb the walls of the stomach and relieve the pain. Antacids provided good alternative for quick symptomatic relief, but they presumably have little long-term effect and on overall disease progression, and the development of potent efficacious medication such as H<sub>2</sub>-blockers and PPIs led to the significantly decline in their use clinically for duodenal and gastric ulcers and GERD. Also, their use was reported as controversial in the management of nonulcer dyspepsia or nonsteroidal anti-inflammatory drug related upper GI mucosal damage. The therapeutic spectrum of anaesthetic antacid will increase manifold, if also contains antifatulent agents (dimethicone/simethicone) beside the local anaesthetic component. Thus, the greater acceptability of anaesthetic-antacid compared to usual antacid combinations. Over the recent years, several double blind clinical studies have reported complete pain relief with the use of anaesthetic antacid. The dose of anaesthetic antacid was also significantly reduced in comparison to



antacid mixtures which also helped reduce side effects encountered with these antacids that taken mostly in large dose and more number of times. Some investigators have reported that oxethazaine containing antacid produces persistent increase in gastric pH to 3.5 or above.<sup>22</sup>

## TREATMENT ALGORITHM

Acid reflux is one of the single most important components in the GERD pathogenesis and acid suppression has remained cornerstone pharmacological therapy.<sup>34</sup> PPIs constitute as the main medication in the classical treatment algorithm for this condition. According to the expert consensus panel, the treatment of GERD requires a symptom-based approach in the beginning followed by a pathogenesis-based approach, where symptoms that respond to adequate acid suppressant therapy confirm the role of acid reflux and symptoms nonresponsive to acid suppression confirm the role of other factors. In 2007, Tran et al. reported a meta-analysis covering the period 1972 to 2005. They concluded that over-the-counter (OTC) medications were effective in treating symptomatic GERD, and antacids and alginate-antacids were effective in treating of gastric symptoms which most often appear after a meal.<sup>15</sup> Further, the revised algorithm, somehow, considerably maximized the satisfaction of patient and the disease management. It has tried to optimize the management of symptoms by dividing symptom management into three levels of care: self-care, primary care and secondary care. While, at the primary care level, PPIs remains the mainstay therapy for most the stomach acid-related pathologies, which, however, take much longer time to work and even longer than the H<sub>2</sub> blockers. Further, accumulating evidence from newer clinical studies reported that PPIs were ineffective in treating some patients including PPI-refractory GERD patients.<sup>35</sup> This formed the basis for the expert panel to recommend antacids, alginate-antacids, among others at the self-care level besides PPIs. Also, at all the levels of GERD treatment, antacids or alginate-antacids got a more prominent place both independently and in combination with acid suppressive therapies (H<sub>2</sub> blockers and PPIs). The most palpable difference between antacids and PPIs (including H<sub>2</sub> blockers) is the rapid onset of action, and antacids and alginate-antacids have shown a rapid and adequate relief from symptoms of GERD.<sup>36</sup> The formation of a raft-like structure in the acid pocket by alginate-antacids treatment have reduced the injury caused by pepsin and bile acids.<sup>37</sup> In patient refractory to treatment with PPIs, in GERD, the expert panel recommended combining antacids or alginate-antacids among other complementary therapy with PPIs. In 2013, a survey on primary care in Spain have been carried out to assess “the perceptions of primary care physicians on the effectiveness of the isolated use of PPI in controlling symptoms in GERD patients, as well as to know the degree of implementation of use of combined therapy (PPI plus antacid) and utilization patterns of this therapy to achieve a better control of symptoms in such patients.”

The study concluded that Spanish Primary Care physicians observed that a significant number of patients of GERD continued to suffer from symptoms during PPI treatment alone. They considered that on-demand "combined therapy" (PPI plus antacid) was an efficient option to control reflux symptoms in patients which continued to be troublesome following treatment with PPI treatment alone.<sup>35</sup>

### Self-care

The expert panel has advised on using low-dosed PPIs as a treatment option for GERD patients at the self-care level. However, it was observed that the most important factors determining the choice of OTC therapy should have been the speed of action and onset of symptom relief. Antacids or alginate-antacids offer the most rapid symptom relief and can be taken ‘as required’. The panel believed that antacids or alginate-antacids offered symptom relief more rapidly than alternative treatments and therefore, the panel were of the opinion that antacids or alginate-antacids could be used in combination with acid suppressants to treat remaining or breakthrough symptoms. In comparison to former two types of antacids, oxetacaine-antacid combination would offer great and faster symptom relief. However, patients who presented with alarm symptoms were strongly advised to contact primary care physician for referral to specialist care.<sup>38-40</sup>

### Primary care

The expert panel opined that PPIs should not have been the only drugs of choice for GERD as symptoms of GERD could not be only attributed to the secretion of acid. According to the panel recommendations, antacids or alginate-antacids could be an additional option for patients presenting at primary care with symptoms of reflux, or for patients with ongoing symptoms incompletely controlled with acid suppressants. In this context, therapeutic antacid (oxethazaine-antacid), which contain local anaesthetic component, could particularly benefit patients. Hence, PPI or a combination of alginate-antacid and or oxethazaine-antacid, and acid suppressive therapy could be prescribed with clinical judgement of the physician. As combination therapy, it may potentially be more beneficial than acid suppressive therapy alone.<sup>38-40</sup>

### Secondary care

Specialists at the secondary care level are entrusted with the task of dealing with more complex cases, e.g. patients who are partially or completely unresponsive to treatment. Endoscopic examination has been included in the new algorithm as an option for further therapy (or as method of investigation), because of differing clinical practice in the various countries which represented at the expert panel meeting. In general, patients with GERD who were found to have evidence of erosive esophagitis

on endoscopy should be placed on maintenance PPI due to the high risk of relapse off PPI. However, patients with NERD may achieve symptom control on H<sub>2</sub> blockers or, alternatively, with on-demand PPI. If symptoms persist, maintenance PPI should be considered. According to the advice of the expert panel, at the secondary care level also, the adjuvant therapy (oxethazaine-antacid/alginate-antacid) could complement therapy with PPI.<sup>38-40</sup>

## CONCLUSION

Anesthetic antacids, prepared by combination of a local topical anesthetic (like oxethazaine) with antacids, have almost revived the confidence levels of clinicians to use across all types of GI disorders (duodenal ulcer, GERD or) due to its quick and prolonged relief from gastric related problems at considerably lower dose. The anesthetic component, oxethazaine remains non-ionized at hyperacidic conditions and produces a prolonged anaesthetic effect (numbing effect) on the walls of the stomach, thereby broadening the therapeutic spectrum of antacids, besides the normal process of neutralizing acid. Besides oxethazaine, various other components like dimethicone/simethicone (antiflatulent agent) have also brought a colossal change in therapy with antacids. Though PPIs, since long back, has remained the standard of choice in most of the gastric related disorders, but looking at the enhanced therapeutic efficacy of anaesthetic antacid, in terms of low dosage and side effects, persistent increase in gastric pH and fast and longer duration of pain relief, the expert panel on GERD treatment algorithm has recommended the inclusion of oxethazaine-antacid/alginate-antacid as complementary to the PPI.

Hence, anaesthetic antacids offer better control of gastric-related problems in comparison to antacids alone at considerably lower dosage and has been recommended for different types of GI disorders.

## ACKNOWLEDGEMENTS

Authors would like to thank GCE Solutions Pvt. Ltd. for writing support.

*Funding: Academic research funding from Abbott India Limited.*

*Conflict of interest: None declared*

*Ethical approval: Not required*

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**Cite this article as:** Parakh RK, Patil NS. Anaesthetic antacids: a review of its pharmacological properties and therapeutic efficacy. *Int J Res Med Sci* 2018;6:383-93.