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The Antacid Efficacy of Maalox in Comparison to a Range of Antacids

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Abstract

This review has comprehensively reviewed the literature relating to the use of antacids in the treatment of the symptoms of heartburn, regurgitation and indigestion and the findings of gastro-esophageal reflux (GER) including defining the onset and duration of action of some key antacids available in the global market place. The rate and duration of neutralization was determined using a modified Rossett and Rice test. The review also investigated the frequency of use of antacids, common antacid drug interactions, common antacid side effects and the efficacy of antacids in daily use. As well as the efficacy of antacids on the symptoms, endoscopic findings and gastric pH in clinical studies. Antacids are cheap, easily available, over the counter (OTC) remedies that target mild symptoms of heartburn and indigestion associated with GER. They should be inexpensive, safe and palatable for use in the self-medication /OTC market place. They are widely used and in 2017 antacid sales were reported to be worth $10 billion worldwide. The ideal antacid needs to be efficacious with a rapid onset of action in neutralizing stomach contents and a long duration of action maintaining a prolonged reduction in stomach acidity preferably in both the fasted and full stomach in an acidic and a weak acidic environment. The review particularly investigated the efficacy of Maalox Tablet products and Maalox Suspension products to compare the products in terms of onset of action to neutralize stomach contents and the duration of neutralization.

Keywords: Antacid, Maalox, Neutralization, Onset of action, Duration of action, Efficacy, Drug interactions, Side effects

Introduction

Antacids are often the first line of treatment for combating the bothersome symptoms of heartburn and indigestion associated with gastro-esophageal reflux (GER). They are cheap, easily available, over the counter (OTC) remedies that target mild symptoms and they are considered to be fast acting. Antacids act to neutralize the acid in the gastric juice and increase the pH of the stomach thus putatively reducing the impact on the esophagus when gastric juice is refluxed but may also neutralize acid in the esophagus. Since the action of an antacid is dependent upon neutralization of acid their action is limited in the background of continuous physiological acid secretion and sustained relief of heartburn will require repeat dosing [1]. The ideal antacid needs to be efficient (small dose to control large amounts of acid), efficacious (control symptoms) and safe, but also inexpensive and palatable which are important drivers within this self-medication / OTC arena [2].

There is no global definition, but the US FDA define an antacid in relation to acid neutralizing capacity (ANC), which must be greater than 5 mEq of H^+ per lowest dose. There are many different antacid formulations and the formats are generally chewable tablets or liquids. There

are almost as many brand names as there are different antacid formulations which are broadly classified into the following types, although mixing within formulations is common:

- Aluminium & magnesium containing
- Bicarbonate/carbonate containing
- Alginic acid containing (not raft-forming)
- Complexes (e.g. Hydrotalcite)
- Bismuthcontaining

Antacids are nothing new and have been around for many years and in fact the first mention of the antacid goes as far back as 3500 years ago. The ancient Sumerians observed the ability of alkalines to relieve stomach upsets and the first recorded example was a combination of milk and peppermint mixed with carbonates [3]. It wasn't long before the Sumerians chose sodium bicarbonate as the preferred carbonate for their antacid preparation. It was a long time before a new form of antacid hit the scene. In 1829 Sir James Murray made his own liquid magnesia antacid preparation which was patented shortly after his death in 1873 and given the name Milk of Magnesia [3,4]. The established formulation we know today for the suspension of magnesium hydroxide was developed by Charles Henry Phillips in 1880. Since then there has been an explosion of new antacids, formulations and brands.

Antacids are widely used and in 2017 antacid sales were reported to be worth $10 billion worldwide. In the UK the upper GI market [5] was on a slow decline and the whole indigestion market was estimated at £92.5 million in 2010. However, the gastrointestinal remedies market is forecast to be valued at an expected £308 million in 2018. An indigestion relief product is purchased annually by one in four people with an average annual spend of £8.26 [5]. The latest data from IMS Health states that global antacid spend was $1.28 billion in 2011 which increased by 4.6% to total global sales of $1.33 billion in 2012.

Aim

The aim of this review is to comprehensively review the literature relating to the use of antacids in the treatment of symptoms and findings of GER. These include defining the onset and duration of action, investigating the frequency of use and dosing, detailing side effects and drug interactions. The efficacy of antacids on symptoms, endoscopic findings and gastric pH in published clinical trials will also be reviewed.

Methods

1. Literature searches to identify papers relating the treatment of GER with antacids were carried out in PubMed with English language papers reviewed in full and English abstracts only of foreign language papers. The brand name and formulation details of antacids are described where possible and are described in detail in Table 1 along with maximum daily dose permitted and acid-neutralizing capacity (ANC) where available.

All discussion relates to pure antacid formulations designed to provide bulk neutralization of stomach acid. As such it does not include alginate-based raft forming reflux suppressants, which have a distinct mode of action (raft-forming) and are not classified as antacids, or formulations that include anti-spasmodics. However, simethicone containing formulations were included.

Since this review is related to GER and symptoms of heartburn, regurgitation and indigestion it should be noted that papers relating to treatment of duodenal and gastric ulcers are not included.

2. Using a modified Rossett and Rice test [6] to determine the rate of neutralization and the duration of neutralization. Figure 1 shows a typical set up for the Rossett and Rice method.

The antacid components of the Maalox formulation will influence the products speed and duration of neutralization which are both important aspects of the products efficacy. Maalox has been formulated to maximise the products neutralizing capacity and designed in such a way to ensure that the hydroxides continue reacting with the protons produced in the stomach.

The rate is determined separately to the duration to enable assessment of the short-term antacid activity, which is important for the relief of pain directly after chewing and swallowing.

The reaction vessel is maintained at 37 °C throughout the experiment. A minimum recommended dose (1 Maalox Plus Tablet, 2 Maalox Tablets, 5 ml of Maalox Plus Oral Suspension and 5 ml of Maalox Oral Suspension) of the formulation is added to the reaction vessel containing 70 ml of deionised water. This is mixed for 15 minutes.

For the rate of neutralization, the specified acidic environment is then added directly to the mixed sample

Table 1: List of antacids described in this review.

Brand Name	Manufacturer, Country	Details of Antacid Formulation	ANC (per stated dose)	Maximum Daily Dose	Reference
Alka-Seltzer Gold	Bayer Consumer Care Division,	1050 mg sodium bicarbonate	32 mEq	8 tablets	13
	USA	1000 mg citric acid			
		344 mg potassium bicarbonate			
		Per tablet			
Almax	Galenicum Health S.L.	1.5 g Almagate	~42.5 mEq*	8 tablets	8
	Spain	(magnesium carbonate aluminium hydroxide)		(500 mg)	
		In 70 ml water			
Aluminium Hydroxide B.P.		500 mg aluminium hydroxide	~11mEq*	12 tablets	61
		per tablet			
Asilone Gel (Suspension)	Thornton & Ross Ltd,	420 mg aluminium hydroxide	~ 12 mEq*	40 ml	68
	UK	135 mg simethicone			
		70 mg magnesium oxide			
		per 5 ml dose			
Eno	GlaxoSmithKline Consumer Healthcare,	2.32 g Sodium bicarbonate	~22 mEq	30 ml	11
	USA	2.18g citric acid			
		0.5 g anhydrous sodium carbonate			
		Per 5 g sachet			
Extra Strength Maalox	Sanofi Aventis,	400 mg magnesium hydroxide	NA	60 ml	15
	UK	400 mg aluminium hydroxide dried gel			
		40 mg simethicone			
		Per 5 ml dose			
Gastrocote	Thornton & Ross Ltd,	200 mg alginic acid	NA	8 tablets	69
	UK	80 mg aluminium hydroxide			
		40 mg magnesium trisilicate			
		70 mg sodium bicarbonate			
		per tablet			
Gaviscon	GlaxoSmithKline,	200 mg alginic acid	NA	8 tablets	22, 58
	USA	80 mg aluminium hydroxide			
	Marion Laboratories Inc,	20 mg magnesium trisilicate			
	USA	70 mg sodium bicarbonate			
		per tablet			

Gelofalk	Dr Falk Pharma	smectite	135 mEq	NA	59
	Germany	aluminium hydroxide	(per day)		
		magnesium hydroxide			
Link	Apothekernes Laboratorium AS,	1100 mg aluminium hydroxide +	30 mEq	4 tablets	56
	Norway	magnesium carbonate			
		co-dried gel			
		(hydrotalcite)			
		per tablet			
Maalox	Sanofi Aventis,	200 mg Magnesium hydroxide	27 mEq	80 ml	20
	UK	200 mg aluminium hydroxide dried gel			
		20 mg simethicone			
		Per 5 ml dose			
Maalox tablet	Sanofi S.p.A,	400 mg Magnesium hydroxide	24mEq	8 tablets	
	Italy	400 mg aluminium hydroxide			
		Per tablet			
Maalox Plus tablet	Sanofi S.p.A	200 mg Magnesium hydroxide	20 mEq	16 tablets	
	Italy	200 mg aluminium hydroxide			
		25 mg simethicone			
		Per tablet			
Maalox Plus Oral suspension	Sanofi Aventis,	200 mg Magnesium hydroxide	13mEq	80 ml	
	Ireland	175 mg aluminium hydroxide			
		25 mg simethicone			
		Per 5 ml dose			
Maalox Oral suspension	Sanofi Aventis,	200 mg Magnesium hydroxide	13mEq	80 ml	
	Ireland	175 mg aluminium hydroxide dried gel			
		Per 5 ml dose			
Maalox Plus	Rhone-Poulenc Rorer	1000 mg aluminium hydroxide	58 mEq	40 ml	15
		900 mg magnesium hydroxide			
		80 mg simethicone			
		Per 10 ml dose			
Maalox Therapeutic Concentration	William H. Rorer,	600 mg aluminium hydroxide	27 mEq	80 ml	62
	USA	300 mg magnesium hydroxide			
	Novartis Consumer Heath,	Per 5 ml dose			
	Switzerland				

Mylanta	Johnson & Johnson,	400 mg magnesium hydroxide	~19 mEq*	80 ml	10
	UK	400 mg aluminium hydroxide			
		40 mg simethicone			
		Per 10 ml dose			
Mylanta Double Strength	Johnson & Johnson	800 mg magnesium hydroxide	50mEq	40 ml	15, 16
	UK	800 mg aluminium hydroxide			
		80 mg simethicone			
		Per 10 ml dose (or per two tablets)			
Mylanta II	Johnson & Johnson,	400 mg magnesium hydroxide	~19 mEq*	40, 60 or 80 ml	66, 67
	UK	400 mg aluminium hydroxide			
		30 mg simethicone			
		per 5 ml dose			
Nacid	Shionogi,	500 mg magnesium aluminium hydroxyl carbonate	NA	8 tablets	63
	Japan	(hydrotalcite)			
		per tablet			
Novaluzid	Meda AB,	Aluminium hydroxide	85 mEq	40 ml	65
	Sweden	Magnesium hydroxide			
		Magnesium carbonate			
		Per 10 ml dose			
Pepto Bismol	Norwich Eaton Pharmaceuticals Inc,USA	16.7 mg/ml (525 mg) bismuth subsalicylate	NA	240 ml	24
	Procter & Gamble, USA	per 30 ml dose			
Rennie	Bayer Consumer Care Division,	680 mg calcium carbonate	15 mEq	16 tablets	6, 7
	USA	80 mg magnesium carbonate			
		per tablet			
Rennie Liquid	Bayer Consumer Care Division,	1.36 g calcium carbonate	30mEq	80 ml	25
	USA	160 mg magnesium carbonate			
		per 10 ml dose			
Riopan Gel	Takeda	800 mg Magaldrate anhydrous oral suspension	NA	40-80 ml	6, 21
		per 10 ml dose			
Rivolox	Rivopharm SA,	349 mg aluminium hydroxide	~18 mEq*	80 ml	23
	Switzerland	399 mg magnesium hydroxide			
		per 10 ml dose			
Surpass antacid chewing gum	Wrigley Healthcare,	450 mg calcium carbonate	~8mEq*	17 pellets	14
extra strength	USA	per pellet			

Surpass antacid chewing gum	Wrigley Healthcare,	300 mg calcium carbonate	~5mEq*	26 pellets	14
regular strength	USA	Per pellet			
Talcid	Bayer Healthcare	500 mg hydrotalcite	13 mEq	12 tablets	19
	Germany	per tablet			
Talcid Forte	Bayer Healthcare	1000 mg hydrotalcite	26 mEq	6 tablets	18, 64
	Germany	per tablet			
Titralac	3M,	420 mg calcium carbonate	15 mEq*	19 tablets	17
	USA	168 mg elemental calcium			
		per tablet			
Topaal	Pierre Fabre Ltd,	200 mg alginic acid	NA	12 tablets	63
	UK	40 mg magnesium hydrocarbonate			
		30 mg aluminium hydroxide			
		per tablet			
Tums	GlaxoSmithKline,	500 mg calcium carbonate	10 mEq	16 tablets	14
	UK	per tablet			
Tums E-X	GlaxoSmithKline,	750 mg calcium carbonate	15 mEq	15 tablets	13, 16, 57, 70
	UK	per chewable tablet			
unknown		400 mg aluminium hydroxide	~19 mEq*	NA	9
		400 mg magnesium oxide			
		per tablet			

ANC = Acid Neutralization Capacity; mEq = Milliequivalents, * ANC estimated by calculation,
Maximum Daily Dose = over 24 hours
NA = not available

and the pH against time is recorded.

For the duration of neutralization, after 1 minute of adding the acidic environment, 0.1M HCl is added at a rate of 4 ml/min. The pH against time is recorded from the time of addition of the acidic environment.

The rate of neutralization and duration of neutralization will be determined in the following environments:

Fasted stomach, strong acid (25 ml 0.1M HCl)
Full stomach, strong acid (100 ml 0.1M HCl)
Fasted stomach, weak acid (25 ml 0.0001M HCl)
Full stomach, weak acid (100 ml 0.0001M HCl)

The presence of food in the stomach (full stomach) influences the absorption and speed of transit of products as well as the resting gastric pH. It is important to compare how a product behaves in terms of its effect on gastric pH and speed of onset between an empty and a full stomach, as both gastric volumes and gastric pH will be different in these states. The two models have been designed in such a way as to mimic the extremes in these conditions. This is important in terms of determining when is the best time to administer the product.

Results

Onset of action

The time to the onset of action of antacids was assessed through a comprehensive review of the published literature which included objective assessment of intra gastric and intra esophageal pH as well as patient perception of symptoms of GER.

Sulz et al. [7] evaluated speed of onset of action by assessing the impact of two antacids (Rennie and Riopan Gel) upon intragastric pH in 24 healthy volunteers. Baseline pH was approximately pH 1.0 and the median time to reach a pH of greater than 3.0 for at least 10 consecutive minutes was determined. This was rapid in both cases with a median time to onset of 2.5 min for Rennie and 4.2 min for Riopan Gel (> 30 min for control). In a similarly designed earlier study Netzer et al. observed that the median lag time to reach an intragastric pH > 3.0 was 5.8 minutes for a dose of Rennie in 16 healthy volunteers [8]. Some studies have used a cut off of intragastric pH > 4.0 and the onset of action was 4.1 minutes for Almagate [9],

2 minutes for aluminium hydroxide/magnesium oxide [10], but most interestingly a 200 ml glass of water acted in 1.5 minutes to increase gastric pH [10].

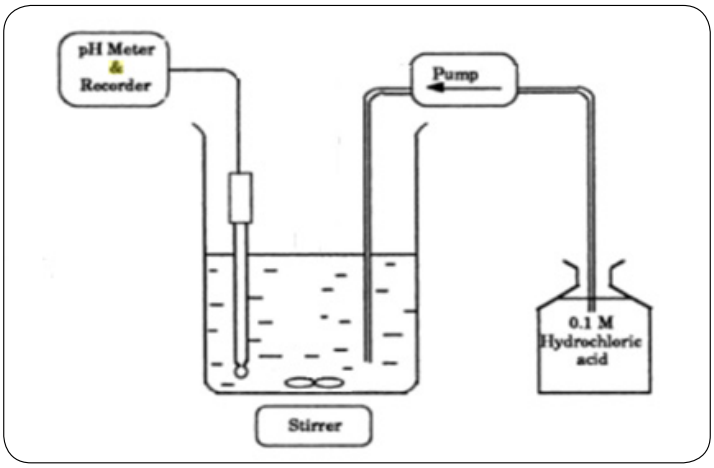

Figure 1: Rossett and Rice method.

Using a cut-off of intragastric pH > 3.5 Mylanta suspension was able to significantly increase gastric pH compared to cimetidine within the first hour but more specific time information was not provided [11]. Using the same pH > 3.5 cut-off Regular Eno was able to elevate intragastric pH to this level within 1 minute (41 seconds) in 24 fasted healthy volunteers, which was also significant compared to a placebo [12]. However, abnormally fast time of action is seen in fasted subjects that are not seen in fed states [13].

Robinson et al. [14] carried out a complex crossover study in 20 heartburn patients, all of which underwent gastric and esophageal pH monitoring on 8 occasions to evaluate three different antacids at varying doses after a refluxogenic meal. The onset of action was defined as the time when the pH was significantly different to placebo. Reflux into the esophagus was clearly demonstrated after the refluxogenic meal. All antacids tested (Tums E-X chewable $CaCO_3$, swallowable $CaCO_3$ or Alka Seltzer bicarbonate solution) exhibited a significant change in pH in the esophagus and stomach 30-35 minutes after dosing.

Intragastric pH was compared against a placebo and three treatment arms which were regular and extra strength antacid chewing gums comprised of calcium carbonate and also chewable calcium carbonate antacid (Tums) [15]. Onset of action was within 5 minutes for both regular and extra strength chewing gum and within 10 minutes for Tums.

Decktor et al. evaluated 3 antacids versus placebo in 24 heartburn patients given a refluxogenic meal and in which intra-esophageal and intra- gastric pH were measured [16]. Patients were dosed with either 20 ml Mylanta Double Strength, 20 ml Maalox Plus or 30 ml Maalox Plus (or placebo) in a crossover fashion. The impact upon esophageal pH was more rapid than that on gastric pH. An elevation of esophageal pH (significantly different to the placebo) was seen within 5 minutes of dosing regardless of antacid but within 30 minutes for gastric pH elevation. Another similar study by the same research group evaluated tablet antacids, namely Tums E-X and Mylanta Double Strength (2 tablets) [17] in a larger population (n=83). Significant elevation of esophageal pH over placebo was seen in 10 minutes with both antacids. However, Tums E-X was not able to produce a significant increase in gastric pH compared to the placebo, but Mylanta Double Strength achieved this within 15 minutes.

Robinson et al. evaluated both onset of symptom relief and esophageal and gastric pH (integrated pH), in comparison to a placebo, after induction of postprandial reflux and treatment with Titralac [18]. Onset of action determined by a significant impact on heartburn severity was 45 minutes post dosing. There was no significant impact on gastric pH but the effect on esophageal pH was significantly different to the placebo 30 minutes after dosing.

Other studies considering the speed of onset of action of antacids have documented the impact on relief of heartburn. A single dose of Talcid was able to improve symptoms of heartburn substantially (by 2 points on a 4 point scale) and the approximate median time to response was 15 minutes [19]. A second study using Talcid demonstrated onset of symptom relief at 10 minutes [20]. Faaij used a 100 mm visual analogue scale (VAS) with an electronic diary to accurately monitor heartburn symptoms and noted that the median time to symptom relief was 19 minutes with Maalox [21].

In contrast to the very rapid speed of onset shown by Riopan Gel with intragastric pH monitoring methods [7] a much slower action (44 minutes) was seen when evaluating complete disappearance of heartburn symptoms [22]. Symptom relief was observed by the majority of patients (67%) within 15 minutes after treatment by an alginic acid-containing antacid [23]. A standard Al/Mg antacid demonstrated an onset of action by symptom relief in the majority of patients between 15-30 minutes [24]. Bismuth subsalicylate was able to completely relieve symptoms of the first episode of indigestion in a median time of 60

minutes but 90 minutes for all episodes evaluated in the study [25].

The Collings et al. Study [15] evaluated onset of symptom relief after a refluxogenic meal in healthy volunteers in addition to esophageal and gastric pH (previously discussed). All three treatments showed improvement in heartburn symptoms within 5 minutes (Tums, Surpass Regular, Surpass Extra) by both a VAS and Likert scale compared to a placebo arm.

The time of onset of action (rate of neutralization) of the Maalox Tablet and Maalox Plus Tablet in a fasted stomach and a full stomach in a strong acidic environment. In a fasted stomach Maalox Plus Tablet takes on average between 40 to 50 seconds to reach pH 3 compared to on average between 50 to 60 seconds observed for Maalox Tablets. In a full stomach with a strong acidic environment, Maalox Plus Tablets take on average between 70 to 80 seconds to reach pH 3 compared to on average between 120 to 130 seconds observed for Maalox Tablets using the modified Rossett and Rice method (Figure 2a).

The time of onset of action of the Maalox Tablet and Maalox Plus Tablet in a fasted stomach and a full stomach in a weak acidic environment. Both products had a weaker pH than pH 3 on addition to the stomach environment (Figure 2b).

The time of onset of action of the Maalox Plus Oral suspension and Maalox Oral suspension. In a fasted stomach and a full stomach in a strong acidic environment. In a fasted stomach Maalox Plus Oral suspension takes on average between 60 to 70 seconds to reach pH 3 compared to on average between 80 to 90 seconds observed for Maalox Oral suspension. In a full stomach with a strong acidic environment Maalox Plus Oral Suspension takes on average between 120 to 130 seconds to reach pH 3 compared on average between 130 to 140 seconds observed for Maalox Oral Suspension. Using the modified Rossett and Rice method (Figure 2c).

The time of onset of action of the Maalox Plus oral Suspension and the Maalox Oral Suspension in a fasted stomach and a full stomach in a weak acidic environment. Both products had a weaker pH than pH 3 on addition to the stomach environment (Figure 2d).

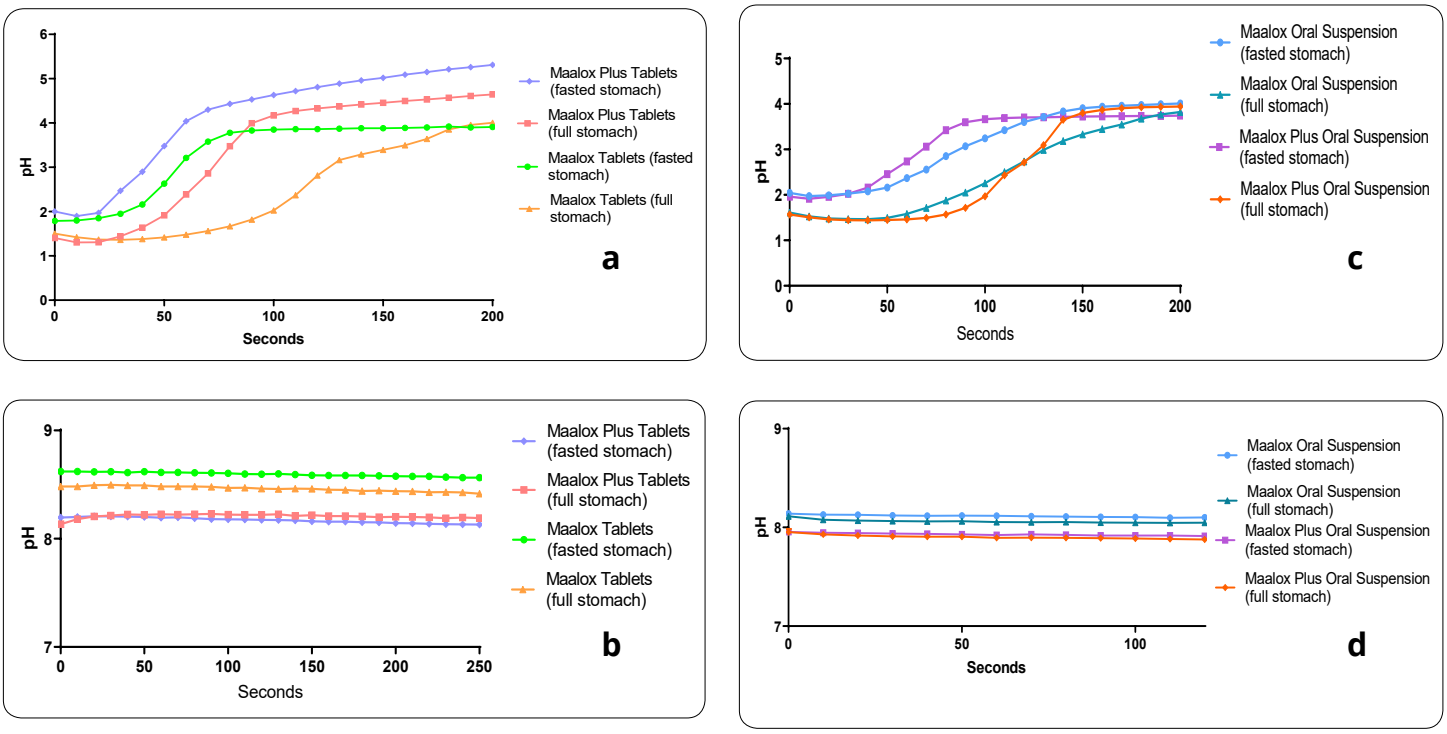

Figure 2: The Onset of Action (Rate of Neutralization) for Maalox Tablets (Tablet and Plus Tablet) and Maalox Suspensions (Plus Oral Suspension And Oral Suspension).

a)Tablets Rate of Acid Neutralization Profile on a Fasted and Full Stomach in a Strong Acidic Environment (N=6).
b) Tablets Rate of Acid Neutralization Profile on a Fasted and Full Stomach in a Weak Acidic Environment (N=6).
c) Suspensions Rate of Acid Neutralization Profile on a Fasted and Full Stomach in a Strong Acidic Environment (N=6).
d) Suspensions Rate of Acid Neutralization Profile on a Fasted and Full Stomach in a Weak Acidic Environment (N=6).

Duration of action

Here we review the data regarding the length of time that antacids can have an impact. Based on intragastric pH studies the data suggests that antacids have a short duration of action. The study described previously by Sulz et al. [7] indicated rapid onset of action but also clearly showed that this action was of very short duration. Intragastric pH was only maintained at pH > 3.0 for 12.7 min and 10.3 min for Rennie and Riopan Gel respectively (control 2.7 min). Based on a statement by Netzer et al. that 10.3% of the recording time was pH < 3.0 with Rennie it can be interpreted that the duration of effect was 25 minutes [8]. Rey et al showed that Almagate maintained intragastric pH > 4.0 for 61.3 minutes in post-prandial conditions but was considerably shorter in fasting conditions (19.4 min) [9]. The study by Karamanolis et al. showed a short duration of action on intragastric pH > 4.0. The antacid had duration of action of 12 minutes and a glass of water had duration of action of 3 minutes [10]. With multiple doses of Mylanta in 20 healthy volunteers gastric pH > 3.5 was over 25% of the time for 4 hours [11]. Robinson et al. using symptoms and integrated gastric and esophageal acidity showed that the duration of action of Titralac on heartburn symptoms was only 15 minutes but persisted for an hour on measuring intra-esophageal acidity [18].

The study by Robinson et al. [14] that tested seven antacids against a placebo noted that swallowable calcium carbonate antacids had a short duration of effect of 10-15 minutes in the esophagus and 5-35 minutes in the stomach, depending on the dose. High dose chewable calcium carbonate antacid lasted for 40 minutes in the esophagus and 180 minutes in the stomach. The effect of Alka Seltzer lasted for 40 minutes in the esophagus and 100 minutes in the stomach. The acid neutralizing effect of Rennie Liquid and Maalox Liquid was 79.7 minutes and 83.5 minutes respectively as determined by the time a pH rise caused by the antacid was no longer different to the placebo according to Hurlimann et al. [26].

The study by Decktor et al. with 3 liquid antacids (Maalox 20 ml and 30 ml and Mylanta 20 ml) [16] noted that the elevation of esophageal pH (compared to placebo) lasted for 25 minutes with 20 ml Maalox and 75 minutes for 20 ml Mylanta and 30 ml Maalox. Similarly, the duration of effect on raised intra-gastric pH was shorter for 20 ml Maalox (100 min) but 150 minutes for the 2 other doses/antacids. The study with antacid tablets by Decktor showed that the duration of effect in the esophagus was 60 minutes for Tums E-X and 82 minutes for Mylanta, but Mylanta Tablets had a duration of action of 26 minutes in the stomach (Tums E-X did not have an effect on intragastric pH) [17].

Chevrel assessed the duration of action as either, less than 2 hours, 2-4 hours, or greater than 4 hours. The median duration of action for the Al/Mg antacid in this study was between 2-4 hours by continued relief of symptoms [24]. The Talcid antacid in the study by Holtmeier et al. [20] highlighted that 70% of subjects still had symptom relief 3 hours after dosing which was significant against placebo. But also 82% of subjects claimed to be symptom free after 6 hours post-dosing. The duration of action of Talcidin a second study by Konturak et al. was noted as 120 minutes, in relation to significance against famotidine, but this may be slightly longer if this was related to a placebo arm instead [19].

It was suggested by Giannini et al. that the duration of action of the Riopan Gel was a very extensive median time of 12.7 hours, but this may be an indication of frequency of symptoms rather than action of antacid [23]. In comparison to a placebo arm three treatments were able to reduce heartburn symptoms in response to a refluxogenic meal using two scoring systems for a duration of 120 minutes (Tums, Surpass Regular, Surpass Extra) [15].

In summary, Figure 3 summarizes the median time of duration of action of the range of different antacids tested in the studies described in detail above. In general, studies that objectively measured gastric or esophageal pH tended to indicate a very short duration of action of the antacids (average 78 minutes) (Figure 3a). But on the whole if you consider the patients' symptoms the duration onset was longer (average 122 min) (Figure 3b). Duration of action between 1-2 hours would seem to be the consensus and a calculated mean of the 22 antacid tests (irrespective of method or study size) was 92 minutes.

Duration of action of the Maalox Tablet and Maalox Plus Tablet. In a fasted and a full stomach strong acidic environment. Maalox Plus Tablets take on average between 1920 to 1980 seconds to drop below pH 2 compared to on average between 3270 to 3330 seconds observed for Maalox Tablets in the fasted stomach. In a full stomach strong acidic environment. Maalox Plus Tablet takes on average between 840 to 900 seconds to drop below pH 2 compared to on average between 2340 to 2370 seconds observed for Maalox Tablets using the modified Rossett and Rice method (Figure 4a).

Duration of action of the Maalox tablet and Maalox Plus Tablet. In fasted and full stomach weak acidic environment. Maalox Plus Tablet takes on average between 3420 to 3480 seconds to drop below pH 2 compared to on average between 3720 to 3780 seconds observed for Maalox Tablets in the fasted stomach. In a full stomach weak acidic environment, Maalox Plus Tablet takes on average between 2520 to 2580 seconds to drop below pH 2 compared to on average between 4260 to 4320 seconds observed for Maalox Tablets using the modified Rossett and Rice method (Figure 4b).

Duration of action of the Maalox Plus Oral suspension and Maalox Oral suspension. In a fasted and a full stomach strong acidic environment. Maalox Plus Oral suspension takes on average between 1620 to 1680 seconds to drop below pH 2 compared to on average between 1740 to 1800 seconds observed for Maalox Oral suspension in the fasted stomach. In a full stomach strong acidic environment, Maalox Plus Oral suspension takes on average between 600 to 660 seconds to drop below pH 2 compared to on average between 540 to 600 seconds observed for Maalox Oral suspension using the modified Rossett and Rice method (Figure 4c).

Duration of action of the Maalox Plus Oral suspension and Maalox Oral suspension in a fasted and a full stomach weak acidic environment. Maalox Plus Oral suspension takes on average between 2040 to 2100 seconds to drop below pH 2 compared to on average between 1980 to 2040 seconds observed for Maalox Oral suspension in the fasted stomach. In a full stomach weak acidic environment, Maalox Plus Oral suspension takes on average between 2160 to 2220 seconds to drop below pH 2 compared to on average between 2040 to 2100 seconds observed for Maalox Oral suspension using the modified Rossett and Rice method (Figure 4d).

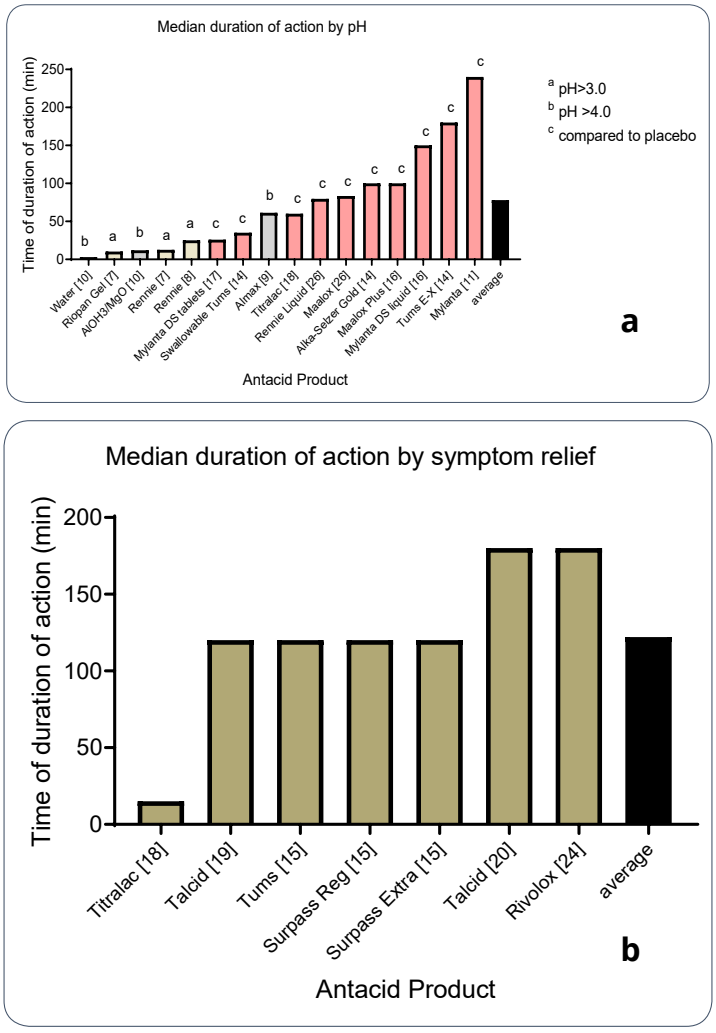

Figure 3: Duration of Antacid Action for Both Antacid Tablet and Suspension Products.

a) Assessed By Intragastric Ph. B) Assessed By Symptom Relief

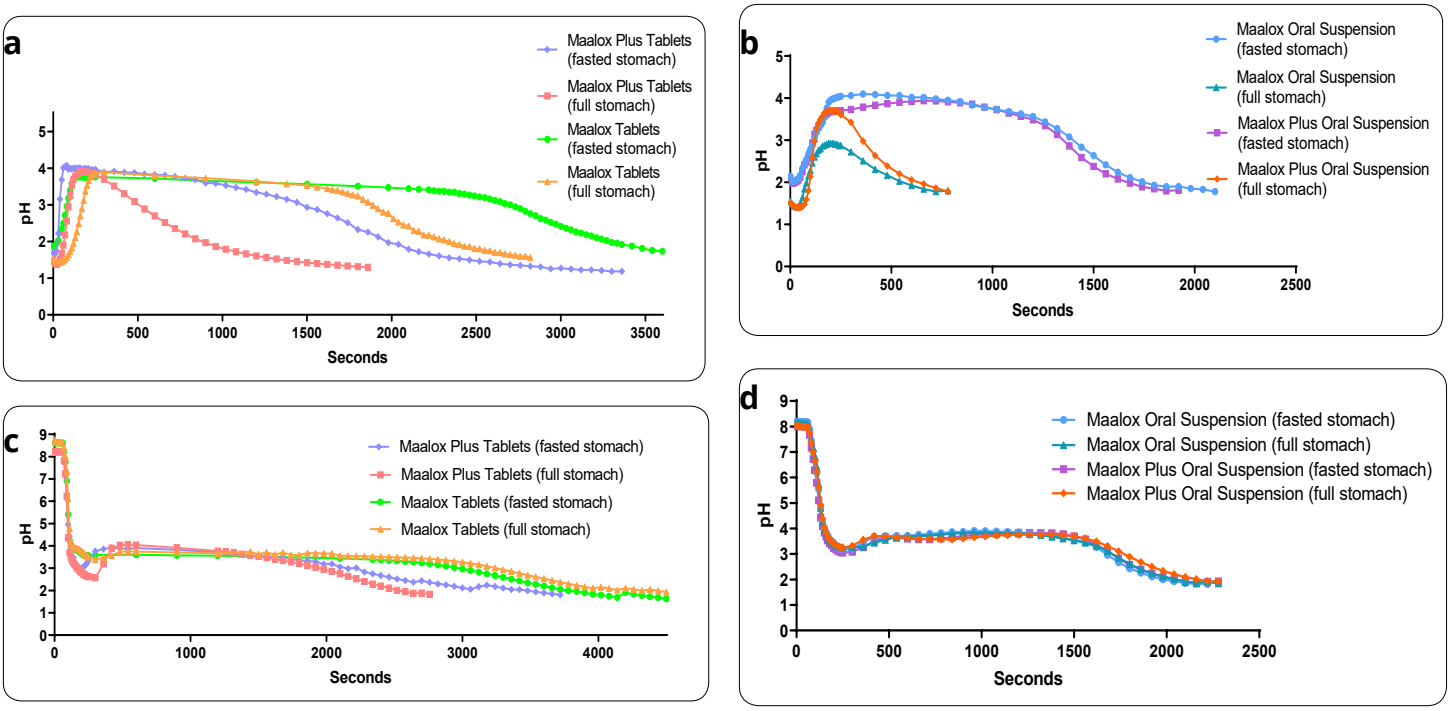

Figure 4: Duration of Action (Duration of Neutralization) For Maalox Tablet Products (Tablet and Plus Tablet) and Maalox Suspension Products (Plus oral Suspension and oral Suspension).

a) Duration of Acid Neutralization Profile on a Fasted and Full Stomach in a Strong Acidic Environment (N=6).
b) Duration of Acid Neutralization Profile on A Fasted and Full Stomach in a Weak Acidic Environment (N=6).
c) Duration of Acid Neutralization Profile on a Fasted and Full Stomach in a Strong Acidic Environment (N=6).
d) Duration of Acid Neutralization Profile on a Fasted and Full Stomach in a Weak Acidic Environment (N=6).

Frequency of use

The recommended daily doses of common antacids are described in Table 1 and relate to large numbers of tablets or volumes of liquid each day. However, these maximal doses should not be maintained for longer than 2 weeks. It is difficult to obtain real life profiles of OTC antacid habits, but it would not be unexpected that prolonged infrequent use is common but that in symptomatic periods very frequent dosing could be likely.

Analysis of prescription records in Spain [27] identified that antacid use was prolonged (10-14 weeks) with a mean of 73 days for women and 93 days for men but that older adults (>65 years) maintained antacid use for on average 101 days. However, the doses were not excessive based on the main antacid used, namely Almagate in this Spanish population.

The purchasing habits of OTC antacids in pharmacies and drugstores in the Netherlands were investigated using a questionnaire of 63 persons buying antacids [28]. The majority of antacid users took them 1-3 times per week but 7.5% were taking them on a daily basis. Extrapolation of estimated spend on OTC antacids suggested that 10% of antacid users were purchasing large amounts of antacids for long-term use as 6% were spending 50-100 Euros per year and 4% were spending >100 Euros per year [28]. Excessive lengths of antacid use for persistent symptoms was noted by Conn in her review of 186 adults >65 years of age [29].

Considering the potential excessive use of readily available antacid medication a comprehensive review of the side effects and drug interactions of antacids is warranted.

Side effects

It needs to be stressed that side effects from antacid use are very common and are predominately bowel habit changes but some of these are serious metabolic disorders which are described in Table 2. The use of antacids should not be taken lightly in those with underlying conditions, particularly those with renal disease. Most antacids are warned to not be taken at the indicated doses continuously for longer than 2 weeks.

The most commonly noted side effects are constipation with aluminium containing antacids and

diarrhoea with magnesium containing antacids caused by an osmotic laxative effect [2]. It is because of these opposing effects that antacids are frequently formulated to include both magnesium and aluminium salts. The impact of constipation by aluminium salts has been known to cause intestinal obstruction particularly in the elderly or other vulnerable groups (with decreased bowel motility, dehydration or restricted fluids) [2]. The impact of magnesium salt induced diarrhoea may be fluid and electrolyte depletion [2].

Magnesium salts are cleared rapidly by the kidneys but especially in those with renal disease, magnesium may accumulate and hypermagnesemia may be the outcome [30-35]. There are serious consequences of hypermagnesemia including hypotension, depressed reflexes, muscle paralysis, respiratory depression and even coma. In extremely high levels magnesium is cardiotoxic and causes cardiac depression which may lead to coma and death [31]. Magnesium containing antacids need to be avoided at all costs in those with renal disease.

Aluminium containing antacids can also have repercussions in those with renal disease in a way that is exploited pharmacologically, phosphate binding, but in those without renal disease aluminium will also bind phosphate leading to hypophosphatemia even as rapidly as after 2 weeks of therapy. The phosphate depletion can then cause release of calcium from bone resulting in hypercalciuria, osteomalacia and osteoporosis [36-38]. This impact on bone metabolism seems particularly common when used in infants [39-42].

Systemic alkalosis and milk-alkali syndrome are potential side effects with sodium bicarbonate antacids and, to a lesser extent, calcium carbonate antacids, especially when taking large doses of antacids [43-49]. The sodium levels in sodium bicarbonate antacids need to be a concern for those on low-salt diets and in pregnancy or other sensitive groups [50].

Drug interactions

Many drugs rely on the pH of the stomach for their pharmacokinetics. It could be that they are soluble or absorbed only at specific pHs or that they have an enteric coat that permits their safe passage through the acidic environment [2,51,52]. Changes in the gastric pH caused by antacid use may affect concomitantly used drugs either by increasing or decreasing their bioavailability by several possible mechanisms giving an unpredictable outcome for a standard dose. The most common group of medications that seem to be affected the most by antacids are the infection fighters namely antibiotics, antibacterial and antifungal drugs and these are summarized in Table 3.

An increase in gastric pH will reduce absorption of weak acid drugs as more is ionised and thus not permeable across the cell membrane. In contrast, weak base drugs are less ionised and therefore more can be absorbed. This is the main cause of antacid-drug interactions and affects numerous weakly acidic drugs including indomethacin, nalidixic acid, nitrofurantoin, penicillin, isoniazid, pentobarbital and the sulphonamides with pseudoephedrine as an example of a weakly base drug. It has been suggested that co-administration of antacid (magnesium hydroxide) with ibuprofen enhances ibuprofen absorption in a manner that could be exploited to give rapid onset of pain relief [53].

Some drugs are dependent on low pH to enable the dosage form to dissolve or disintegrate and a rise in pH will hinder this and decrease bioavailability (e.g. ketoconazole). In contrast drugs that are usually degraded in acidic environments are protected and as such a greater dose makes it through (e.g. penicillin, amoxicillin). An increased gastric pH may fool an enteric coat in which case it may dissolve prematurely and cause the drug to be absorbed in the wrong location (e.g. enteric-coated aspirin [51]). Other drugs are affected by changes in gastric emptying. (e.g. levodopa, digoxin and beta-blockers). The example of Levodopa is a good one to highlight the clinical significance of the antacid-drug interaction. It is absorbed up to three-times as much in the presence of antacids, primarily due to more rapid absorption in the small intestine from an increased rate of gastric emptying. In a Parkinson's disease patient who is well controlled on levodopa the addition of an antacid may cause toxicity whereas removal of an established co-administered antacid will reduce the titre and symptoms may recur [2].

Some antacids can alter urinary pH which impacts on drug clearance. Some have decreased renal clearance while other drugs result in increased clearance. A wide range of drugs are affected in this way including the groups amphetamines, sympathomimetics, salicylates and sulphonylureas and the specific drugs quinidine, tetracycline, methotrexate, lithium, aspirin, methenamine and mecamylamine.

Table 2: Side effects of antacids in healthy users.

Side Effect	Antacid Type				
	Mg^{2+} salts	**Al^{3+} salts**	**Calcium Carbonate**	**Sodium Bicarbonate**	**Bismuth**
Constipation		☑ Common	☑ Disputed		
Laxative/Diarrhoea	☑ Common		☑ Disputed		
Flatulence			☑	☑	
Gastric Distension (leading to perforation)				☑ effervescent salts	
Intestinal Obstruction		☑ consequence of constipation			
Black Stools					☑ common
Black Tongue					☑
Systemic Alkalosis			☑	☑ with prolonged use	
Milk-Alkali Syndrome			☑	☑	
Sodium Overload				☑ with prolonged use	
Hypercalcaemia			☑		
Hypermagnesemia	☑				
Hypophosphataemia		☑			
Renal Stones	☑ infrequent Trisilicate salt		☑ possibly		

Some antacids are believed to interact physically with some drugs and bind them up to reduce absorption (e.g. phenytoin, benzodiazepines, chloroquine digoxin and phenothiazines). Others act by ionic chelation or forming complexes to hinder absorption (e.g. isoniazid, penicillamine and tetracycline).

All of these factors make for erratic actions of co-administered drugs such that a greater or reduced effect per dose may be seen or perhaps a lack of effect altogether if the drug is destroyed or absorbed in the wrong location. All of these potential antacid-drug interactions are of course more likely in the case of poly-pharmacy when many medications are utilised by an individual [54]. Since antacids are typically self-administered OTC products the healthcare professional is generally unaware of their use and therefore unable to advise on appropriate dosing regimens to ensure safe and efficacious prescription drug use. An interesting study by Sleath et al. [55] carried out detailed interviews of patients after audio-recorded visits to their GP. It showed that 36% of patients did not tell their GP about OTC medication use. With respect to antacid use 27 patients were using OTC antacids but only 9 (33.3%) informed the GP about this.

It is suggested that antacids must be administered at least 3 hours after tetracycline [2] and similar regimens (taking antacid at a different time) are warranted for other drug interactions when antacids are undoubtedly needed [52].

Table 3: Drug interactions by antacids (adapted from Appendix 1 of the British National Formulary (BNF).

Drug Group	Specific Drug	Mechanism
ACE Inhibitors	captopril, enalapril, fosinopril	↓absorption
Acid Suppression	lansoprazole	↓absorption
Anaemia therapy	deferasirox	↓absorption (Al)
Anaemia therapy	oral iron	↓absorption (Mg) by chelation
Analgesics	aspirin	↑urinary excretion
Antibacterials	azithromycin, cefaclor, cefpodoxime, ciprofloxacin, isoniofloxacin, rifampicin, moxifloxacin, nitrofurantoin, norfloxacin, ofloxacin, penicillin, amoxicillin,	↓absorption
Antibacterials	penicillin, amoxicillin	↑ absorption
		↓acid labile degradation
Antibacterials	tetracyclines	↓absorption by chelation
		↑urinary excretion
Antiepileptics	gabapentin, phenytoin	↓absorption by direct binding
Antifungals	itraconazole, ketoconazole	↓absorption
Antihistamines	fexofenadine	↓absorption
Antimalarials	chloroquinine, hydroxychloroquine, proguanil	↓absorption
Antiplatelet Drugs	dipyridamole	↓absorption
Antipsychotics	phenothiazines, sulpiride	↓absorption
Antipsychotics	lithium	↑urinary excretion
Antivirals	atazanavir, fosamprenavir, tipranavir	↓absorption
Bisphosphonates	bisphosphates	↓absorption
Cardiac Glycosides	digoxin	↓absorption by direct binding ↑gastric emptying
Corticosteroids	deflazacort	↓absorption
Cytotoxins	erlotinib	↓absorption
Emergency Contraception	ulipristal	↓absorption
Immunosuppressants	mycophenolate	↓absorption
Lipid Regulating Drugs	rosuvastatin	↓absorption
Platelet Disorders Drugs	eltrombopag	↓absorption
Rheumatic Disease Drugs	penicillamine	↓absorption by chelation
Thyroid Hormones	levothyroxine	↓absorption

↓ = decreased ; ↑ increased

Efficacy

There are numerous randomised controlled clinical trials in which antacids are included in at least one arm of a study to control the symptoms and findings of heartburn or GER. However, it is often that the antacid arm is the 'control' to another test product which is important to note given the large placebo-effect seen in reflux disease and a general natural history that pertains to intermittent outbreaks and remission. These clinical efficacy studies range from evaluation of single doses or reflux episodes to 12 weeks of antacid intake. Patient numbers range from 10-490 in the extreme cases, but the majority of studies utilise less than 100 patients. Studies that examined the effect of antacids on short term events (single reflux events, stimulated reflux events, <1 day) were discussed earlier in the sections relating to onset of action and duration of action. Here we concentrate on longer term efficacy studies from 2 weeks to 12 weeks treatment.

2 weeks treatment

Chevrel assessed the impact of an antacid comprising

349 mg aluminium hydroxide and 399 mg magnesium hydroxide gelon the symptoms of GERD in a 2-way crossover trial in 44 patients (the antacid was the control arm for Liquid Gaviscon) for 2 weeks (10 ml 4 × daily) [24]. After 2 weeks treatment the efficacy of the antacid was deemed good or very good (self-assessment) in only 23% of patients but the majority (52%) noted a moderate improvement with 25% stating no improvement at all.

A multicentre parallel group study evaluated Riopan Gel 10 ml4 × daily (control arm for Gaviscon Advance) in 98 patients over 2 weeks [22]. Patients' intensity of symptoms (heartburn and regurgitation) was recorded on a diary card using a 4-point scale and the change in total symptom score compared to baseline was determined. Symptomatic improvement was seen after one day with slow continued improvement with continued dosing and absence of symptoms was seen in 74% of patients after 2 weeks of treatment.

Patients with endoscopically confirmed esophagitis (n=47) were recruited to a 2-way crossover study of Link antacid (1 tablet 4 × daily) compared to placebo over 2 weeks [56]. A global assessment of reflux symptoms was recorded on a 100 mm visual analogue scale (VAS). There was a significant reduction in global symptom score with antacid tablets compared to placebo (16.9 mm vs 6.3 mm) with 79% of patients improved to some extent with antacid compared to 55% on placebo (but note the high placebo effect, real effect 24%) although the authors indicate that the symptomatic improvement was 'not impressive'.

A small parallel study (n=15 per arm) in pregnant women [57] screened volunteers having 4 or more reflux events despite having 1 week of treatment with Tums E-X (2 tablets 4 × daily). Even so there was a significant improvement in heartburn score (10-point scale) from 7.9 to 6.5. The volunteers were then randomised to either antacid (Tums E-X) alone or antacid plus ranitidine and a greater effect was seen with addition of ranitidine (to 3.7) but antacid alone was also able to further significantly improve heartburn intensity compared to baseline.

4 weeks treatment

A multicentre study carried out by McHardy was a 2-arm parallel group trial of 2 antacids over 4 weeks [58]. Treatment was with US formulation Gaviscon (2 tablets 4 × daily) against a matched antacid (details not stipulated) and the patient population had endoscopically confirmed esophagitis. Presence of heartburn (incidence and severity and calculated composite score) was recorded in diary form on a weekly basis. There were no differences between the two test products in this study but there was clear improvement in frequency of heartburn. There was negligible improvement of heartburn intensity with US Gaviscon but there was a noticeable improvement with the antacid. The composite heartburn score was substantially improved by both treatments over 4 weeks. The McHardy study also assessed the extent of esophagitis by endoscopy at baseline and post-treatment. Significant improvements (in friability, erosions and ulceration) were seen after 4 weeks of treatment. Both treatments had the same outcomes.

A 4-week study in 97 gastritis or esophagitis patients assessed the impact of Gelofalk and an aluminium hydroxide antacid suspension on symptoms and endoscopic healing [59]. Gelofalk was able to improve pain relief and heartburn symptoms and provide evidence of endoscopic healing and these effects were significantly better than the standard antacid.

Hotz et al. carried out a large study on 686 dyspepsia patients in which 340 were randomised to receive an undefined antacid (control arm to ranitidine) but absence of symptoms was seen in only 13% by 2 weeks and 30% after 4 weeks treatment [60].

In a small study 17 patients with dyspepsia were treated with aluminium hydroxide tablets for 4 weeks (control arm to antacid + antispasmodic) [61]. An improvement in symptoms was observed in 59% of patients from self-assessment and 71% by assessment through the doctor but there were no significant improvements in specific symptoms.

In a small study carried out by Graham & Paterson (1983) in patients with chronic heartburn with esophagitis in which 10 received Maalox antacid (15 ml 7 × daily) and 11 received placebo over a period of 4 weeks [62]. Although there was improvement in heartburn severity and frequency there was no difference between the placebo group and antacid group, nor in the endoscopic improvement seen. The authors suggested that the natural history of symptomatic reflux esophagitis was to improve regardless of treatment choice.

6 weeks treatment

A 2-way parallel group study evaluated two different antacids (alginic acid antacid - Topaal and basic antacid - Nacid) in 121 endoscopy negative reflux disease patients for 6 weeks [63]. The severity of heartburn was noted on

a 100 mm VAS (which was 7.43-7.52 cm at baseline) and after 6 weeks treatment the reduction in VAS was 6.29 cm for Topaal and 4.11 cm for Nacid. There was a significant difference between the two treatments. There were improvements by both treatments (although better with Topaal) in frequency of heartburn, regurgitation and pain but it appears that the maximal effect was seen within 2-3 weeks and no further improvement was evident.

A study carried out in China evaluated 6 weeks treatment with Hydrotalcite (n=25) (with omeprazole (n=20) as the control arm)in endoscopically confirmed esophagitis patients[63]. Symptom scores of heartburn, regurgitation and chest pain improved by week 1 and fell further by week 6 in both study arms. Both study groups decreased the time that the esophagus was exposed to pH < 4 which was classed as normal in 29% of the Hydrotalcite group (77% in the omeprazole group). Endoscopic healing was assessed after 6 weeks and 64% was the healing rate (67% with omeprazole).

A placebo-controlled crossover study in 37 esophagitis patients showed that the antacid Novaluzid (10 ml 7 × daily) was significantly superior to placebo (also compared to ranitidine [64] in providing symptom relief but not on endoscopic or histological findings. These were improved compared to baseline but not compared to placebo [65].

8 weeks treatment

Patients with endoscopically confirmed erosive esophagitis were randomised to 2 parallel groups in which 14 patients received Mylanta II (versus Mylanta + Bethanacol) and took 30 ml 4 × daily for 8 weeks [66]. A composite heartburn score was calculated based on frequency, severity and duration of heartburn and there was also endoscopic assessment. The baseline composite heartburn score was 5.1 and significantly reduced to 2.5 after 8 weeks. However, the data suggests that similar improvement was seen both at 2 weeks and 8 weeks. A composite endoscopic score was 9.1 at baseline and improved significantly to 2.6 after 8 weeks of treatment with antacid and 36% of patients were considered to have complete mucosal healing with the remainder exhibiting partial healing.

A 2-way crossover study in 15 scleroderma patients with symptomatic reflux with endoscopically confirmed esophagitis were recruited and took Mylanta II (30 ml 4 × daily) (compared to cimetidine) [67]. Heartburn was assessed using a 100 mm VAS and there was endoscopic assessment after 8 weeks. After 8 weeks 33% of antacid users became symptom free and the symptomatic improvement seen at 8 weeks was no better than at 4 weeks. In this population there was no overall improvement at all in endoscopic mucosal damage (score 7.9 to 7.5) and only one patient (7%) had complete healing.

A 2-way parallel group study of patients with symptomatic reflux randomised 28 to receive Asilone Gel (10 ml 4 × daily) for 8 weeks and 25 received Gaviscon Liquid (10 ml 4 × daily) for 8 weeks [68]. After 4 weeks 39% experienced noor minimal symptoms, increasing to 57% after 8 weeks of treatment with Asilone Gel. 50% percent of patients were endoscopically free of oesophagitis after 8 weeks of treatment and 18% even had histologically normal mucosa after biopsy.

10-12 weeks treatment

A study by Eriksen et al. assessed the impact of 10 weeks treatment with Gastrocote (2 tablets 4 × daily) upon reflux symptoms, endoscopic findings and also esophageal pHmetry [69]. There were 66 patients in this 3-way parallel group study and 21 patients were in the Gastrocote arm (other arms were cimetidine, or cimetidine plus Gastrocote). Improvement to some extent in the severity of heartburn was seen in 71% of patients but on average there were still 5 heartburn episodes per week. There was no impact on esophagealpHmetry parameters with Gastrocote treatment for 10 weeks and only 15% exhibited endoscopic healing but 46% were improved (although this was 44% even at 4 weeks).

A 12-week study was carried by Earnest et al. using swallowable calcium carbonate tablets on demand (control arm to effervescent ranitidine) and evaluated heartburn frequency and severity (only over first week) with endoscopic and histological assessment [70]. There were 78 patients that took calcium carbonate antacid on an 'as needed' policy for 12 weeks and 17% had healing of esophagitis by 6 weeks increasing to 29% by 12 weeks. There was a documented improvement of quality of life with antacid use at 6 week and 12 weeks.

Summary

The clinical studies reviewed showed that there was only moderate control of symptoms of heartburn and reflux. With the percentage of patients with a self-appraised improvement ranging from 13% to 79% but predominated around the 30-40% mark. Endoscopic healing by continuous prolonged use of antacids was

either not seen or was minimal and a 12 week study exhibited 29% healing only [70].

The studies described ranged from 2 weeks to 12 weeks duration at optimal therapeutic dose, but prolonged treatment does not appear to offer any additional advantage. In papers when there was discussion of 2 time points within a study the impact of additional treatment was minimal. Complete disappearance of symptoms was 13% at 2 weeks increased to 30% at 4 weeks [60] or 39% symptom control at 4 weeks rising to only 57% at 8 weeks [68]. Graphical representation of weekly frequency of symptoms scores in the study by Lai et al. clearly showed that the main effect was seen over the first 2 weeks of treatment with no further improvement of a further 4 weeks treatment [63]. The study by Petrokubi & Jefferies stated that symptomatic benefit was seen after 4 weeks and this was sustained for a further 4 weeks [67].

There were only three placebo-controlled trials where antacid was the primary investigation product (Table 4). These trials represent three staggered treatment durations of 2 weeks [56], 4 weeks [62] and 6 weeks [65]. They are relatively small studies (n=21-47) and the parallel group study has only 10 patients in the antacid group and 11 in the placebo group [62] whereas the other two studies are of crossover design [56,65]. Weberg and Berstad [56] showed the extent of the placebo-effect that was frequently seen in GER (55% symptom relief) and although a significant effect was seen by the antacid compared to the placebo (improvement - not complete alleviation) it was minimal. The 4-week study by Graham and Paterson [62] showed no significant difference between placebo and antacid for symptom relief and no significant difference in esophagitis healing. Grove et al. [65] noted a significant effect of antacid over placebo in symptom relief of heartburn only but again no significant healing of esophagitis was seen. This clearly shows the importance of properly placebo-controlled studies and comparison between 2 active treatments does not consider the substantial placebo-effect in this disease population.

Discussion

The purposes of antacids are to provide instant relief of stomach pain and symptoms associated with gastro-esophageal reflux by the control of esophageal and gastric pH because the weak bases in the antacid neutralize the hydrochloric acid. There are a confusing number of different antacids available to consumers over-the-counter both in terms of the fundamental formulations and brands. Due to their innocent nature the consumer does not treat them with the respect that is necessary for a medication. Antacids have aninstruction that usage should not be maintained for longer than 2 weeks but compliance with this is not often upheld. There is non-compliance with these instructions as long-term use is common, as is overuse and abuse. For antacids to be efficacious it is important to take the optimal therapeutic doses (taking too little is likely to be sub-optimal) and at the appropriate time (usually 1 hour after a meal). Studies that review the impact of antacids in fasting conditions therefore provide unrealistic outcomes. The common overuse, and sometime abuse, of antacids increases the likelihood of side effects which may simply be bowel habit changes but could be more serious metabolic conditions or mineral accumulations or deficiencies. There is no one antacid type that does not have some form of side effect and all has many drug-drug interactions, mainly as a consequence of altered gastric pH.

The clinical studies described in this review uses two main methods to assess the impact of antacids. Firstly, there is monitoring of gastric (and sometimes esophageal) acidity using pHmetry technology as a marker for neutralization of acid as this is the mode of action of antacids. However, there are several analysis methods that have been used to interpret the pHmetry data. In a number of studies, a specific pH cut-off point has been used, for example an intragastric pH > 3.0 for 10 consecutive minutes, but also pH > 3.5 and pH > 4.0. Another analysis method of pHmetry data is to compare the intragastric pH trace of patients on antacid with a placebo and to assess statistical significance, which may be a more robust method. Although neutralization of gastric acid is the mode of action of antacids it is not a measure of their clinical effect which is the alleviation of symptoms. Symptoms are assessed by patients for example using questionnaires, diaries, Likert scales and visual analogue scales to note frequency and severity of symptoms. This clinically relevant method is more subjective and perhaps needs larger sample sizes to interpret but it is more relevant to the antacid user. However, there are wide ranges of scoring systems used and these are not robust validated instruments.

Recent research has highlighted the importance of the 'acid pocket' in the stomach during the post-prandial period that may explain acid reflux into the esophagus despite the buffering capacity of food [71]. The acid pocket is more extensive in GER patients [72]. This important development may suggest that 'bulk neutralization' of stomach acid is unnecessary and a targeted approach is

more suitable [73]. This is an area in which new antacid clinical studies, both on impact upon the acid pocket and upon symptoms, are required.

Most of the clinical trials discussed in this review are randomized controlled trials with varying levels of blinding but antacids are frequently not the main investigational target and are predominantly the control/ inactive arm of a study into another drug (for example H_2-receptor antagonists, raft forming alginate suspensions, proton pump inhibitors, anti-spasmodics) and are not self-contained studies. There are only 3 trials with durations greater than 1 day that are placebo-controlled trials in which the antacid was the primary investigational target, but these are old studies. Therefore, there is a lack of good prospective studies of antacid efficacy using modern, validated research instruments. In addition, because of the complex arena of different formulations it is not valid to collate all antacids and there needs to be an awareness that robust data for any-one particular antacid is lacking.

Antacids have a rapid onset of action which was demonstrated generally within 15 minutes with objectively measured neutralization of gastric pH but those that compared intragastric pH against a placebo indicated a slightly longer onset of action highlighting the significance of the placebo response in this population. This can be further illustrated; as a placebo effect as a simple glass of water was able to rapidly act to neutralize intragastric pH to above pH 4.0 in less than 2 minutes. A change in intragastric pH may not relate to symptom relief which indicates that the time of onset is delayed. A time of onset of action was calculated from the 25 antacid values (irrespective of method or study size) and was on average 18 minutes after dosing.

The duration of action of the range of different antacids tested in studies that objectively measured gastric or esophageal pH tended to indicate a very short duration of action but a longer duration of action was observed if assessing patients' symptoms. The glass of water that had a rapid onset of action only had an effect for 3 minutes suggesting that the more persistent action of antacids was real. The duration of action was between 1-2 hours and the calculated mean of the 22 antacid values was 92 minutes after onset of action. This relates nicely to the half-clearance time of radio-labelled antacid measured as 93 minutes in the pH research study by Fisher [13]. Therefore, considering the time of onset and duration of action a therapeutic dose of antacid may last for just less than 2 hours.

The antacid efficacy studies reviewed here ranged from 2 weeks to 12 weeks duration at optimal therapeutic dose, but prolonged treatment does not appear to offer any additional advantage. A standard 2-week treatment is likely to be the ideal duration as further continuous treatment does not offer additional symptom relief and a clear plateau effect was seen. In fact, most of the improvements seen in heartburn and reflux symptoms may really be related to the placebo-effect and intermittent nature of GER. In all probability, these randomized controlled trials demonstrate that antacid use should be symptom driven and taken as and when required for rapid relief and not for long-term use. Consequently, this will help reduce side effects and drug interactions.

The overall conclusion reached in terms of onset of action to neutralise the stomach contents to below pH3 for Maalox Tablets in a strong acidic environment in both a full stomach and a fasted stomach showed the Maalox Plus Tablet to be superior to the Maalox Tablet. It was not possible to carry out this study in a weak acidic environment. The overall conclusion reached for the Maalox suspension products in terms of onset of action showed that the Maalox Plus Oral Suspension had a faster rate of neutralization compared to Maalox Oral Suspension in a strong acidic environment in both a fasted and a full stomach. It was not possible to carry out this study in a weak acidic environment (Table 5).

The overall conclusion reached in terms of duration of action using the modified Rossett and Rice method and observing a drop below pH 2 for Maalox Tablets in a strong acidic environment in both a full stomach and a fasted stomach showed that Maalox Tablets were superior to Maalox Plus Tablets. The same conclusion was observed in a weak acidic environment. The overall conclusion reached for the Maalox suspension products in terms of duration of action showed that in a fasted stomach in a strong acidic environment Maalox Oral Suspension was superior to Maalox Plus Oral Suspension however this was reversed in the full stomach and Maalox Plus Oral Suspension was the superior product. In the weakly acidic environment Maalox Plus Oral Suspension was superior in both the fasted and the full stomach (Table 6).

Table 4: Table of placebo-controlled trials in which antacid was the primary investigational product.

Duration	2 weeks	4 weeks (+1 week additional run-in)	6 weeks
Arms	2	2	3
Crossover / Parallel	Crossover	Parallel	Crossover
Antacid Brand	Link	Maalox Therapeutic Concentration	Novaluzid
	(1100 mg)		
Antacid Formulation	1100 mg aluminium hydroxide and magnesium carbonate co-dried gel	1800 mg aluminium hydroxide	Aluminium hydroxide
	per tablet	900 mg magnesium hydroxide	Magnesium hydroxide
		Per 15 ml dose	Magnesium carbonate
			Per 10 ml
Antacid Dose	1 chewable tablet	15 ml	10 ml
	4 x daily	7 x daily	7 x daily
Comparator	Matched sorbitol tablets with no ANC	Matching placebo suspension	1) ranitidine 150mg twice daily + antacid placebo
		10% sorbitol, 10% lactose, 0.5% guar gum, 0.5% titanium dioxide	2) double placebo
Number Subjects	50 recruited	32 recruited	57 recruited
	47 completed	21 remain after run-in	37 completed
		(to exclude placebo responders)	
		10 received antacid	
		11 received placebo	
Population	Endoscopically confirmed esophagitis	Symptomatic GER	Endoscopically confirmed esophagitis
	Chronic or recurrent reflux symptoms	Positive Bernstein test	Symptoms of GER
		Positive esophagealpHmetry	
Outcome:	Global symptom score	none	Heartburn score
Antacid significantly superior to placebo	(-16.9 mm, -6.3 mm; p<0.05)		(1.1, 0.7; p<0.005)
	% patients with reduced global symptom score		
(antacid effect, placebo effect; p=)	(78.7%, 55.3%; p<0.05)		
	% patients with improvement in regurgitation		
	(86.1%, 61.1%, p<0.05)		
	Number of days with heartburn		
	(6.2, 8.0; P<0.01))		
	Number of nights with heartburn		
	(3.1, 4.2; p<0.05)		

Outcome:	% patients with improvement in heartburn	Heartburn frequency	Regurgitation
Antacid not significantly different to placebo	(80.4%, 60.9%; p=0.07)	Heartburn severity	(0.1, 0.2; p>0.10)
	% patients with improvement in dysphagia	Endoscopic score of oesophagitis	Dysphagia
(antacid effect, placebo effect; p =)	(64.3%, 50.0%; p=0.7)	Bernstein acid perfusion test	(0.0, 0.0; p>0.10)
		(p>0.05)	Histological appearance of esophageal mucosa
			(1.8, 2.0; p>0.10)
			Endoscopic appearance
			(2.2, 2.4; p>0.10)
Author	Weberg&Berstad[56]	Graham & Patterson[62]	Grove et al[64]
Year	1989	1983	1985

Table 5: The onset of action (neutralization) for Maalox Tablet and suspension products in seconds (s)

Environment	Tablets		Suspension	
	Maalox Plus (s)	Maalox (s)	Maalox Plus Oral (s)	Maalox Oral (s)
Strong acidic, fasted stomach	40-50	50-60	60-70	80-90
Strong acidic, full stomach	70-80	120-130	120-130	130-140
Weak acidic, fasted stomach	N/A	N/A	N/A	N/A
Weak acidic, full stomach	N/A	N/A	N/A	N/A

Table 6: The duration of action (neutralization) for Maalox Tablet and suspension products in seconds (s).

Environment	Tablets		Suspension	
	Maalox Plus (s)	Maalox (s)	Maalox Plus Oral (s)	Maalox Oral (s)
Strong acidic, fasted stomach	1920-1980	3270-3330	1620-1680	1740-1800
Strong acidic, full stomach	1840-1900	2340-2370	600-660	540-600
Weak acidic, fasted stomach	3420-3480	3720-3780	2040-2100	1980-2040
Weak acidic, full stomach	2520-2580	4260-4320	2160-2220	2040-2100

Conclusions

Antacids are not glorified placebos but real medicines that must be taken seriously. They are designed for short term use (2 weeks maximum). In addition, care must be taken if other drugs are prescribed and an appropriate cost/benefit analysis should be performed because drug interactions are commonplace with antacid use. Antacids are quick acting to control symptoms, but the effect is relatively short lived (less than 2 hours). There is little evidence to suggest that long-term antacid use provides any additional benefit in terms of symptom control or healing of esophagitis. Antacid use should be symptom driven and used at full therapeutic doses for short periods until symptoms are controlled.

In terms of Maalox products evaluated the tablet product demonstrating the fastest onset of action in a strong acidic environment was the Maalox Plus Tablet (Mean speed of onset of action 45 seconds) and the tablet product demonstrating the greatest duration of action was the Maalox Tablet (Mean duration of neutralization 71 minutes and 30 seconds). For the suspension products the difference between products was not as clear with Maalox Plus Oral Suspension having a faster onset of action in the fasted stomach and just faster in the full stomach but both Maalox Oral Suspension and Maalox Plus Oral Suspension had a similar duration of action in

the fasted and full stomachs in strong and weak acidic conditions.

Declarations

Ethics approval and consent to participate

No healthy control subjects or patients were recruited to this review other than those described in the literature and in the public domain.

Consent for publication

All the materials used in this review and study were either peer reviewed literature-based studies or from studies conducted in the author's own laboratories and available for publication.

Availability of data and material

All the data and materials used in this review were either obtained from the literature or from studies conducted and kept on file in the author's own laboratories.

Competing interests

The authors declare that they have no conflicts or competing interests.

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Authors contributions

PWD and VS designed the study and wrote the review, ADW and JF carried out all the laboratory procedures and analysed the data and are accountable for all aspects of the work, PWD and JF prepared the document. All authors read and approved the final manuscript.

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