PHARMACY

Evaluation of the acid-neutralizing capacity and other properties of antacids marketed in Morocco

Mohamed Yafout, Hicham Elhorr, Ibrahim Sbai El Otmani, Youssef Khayati

Laboratory of Drug Sciences, Biomedical Research and Biotechnology, Faculty of Medicine and Pharmacy Casablanca, Hassan II University, Casablanca, Morocco.

Abstract

Aim. The aim of this study was to evaluate the acid-neutralizing capacity (ANC) and other properties of antacid drugs marketed in Morocco.

Methods. Samples of 12 antacids were collected from pharmacies and were subjected to the test described in the US Pharmacopoeia in order to measure their ANC. Other properties such as price and sodium content were also studied.

Results. All the tested brands met the minimal requirement of 5 mEq. However, Aluminum hydroxide/Magnesium hydroxide combinations showed a superior acid-neutralizing capacity over other products and oral suspensions showed better results compared to other pharmaceutical forms. Regarding the cost of antacids, Aluminum hydroxide/Magnesium hydroxide combinations and calcium carbonate/magnesium carbonate combinations showed the most favorable ANC/price ratio. Some of the antacids studied contain a high amount of sodium.

Conclusion. All the antacids marketed in Morocco meet the USP requirement regarding their ANC. However, the ANC value should be included in the antacids' labels so that both patients and physicians can choose the most appropriate product. The ANC value should be evaluated according to the dose of the active substance instead of the minimum labeled dosage in order to allow a better result interpretation.

Keywords: antacids, acid-neutralization capacity, gastroesophageal reflux, peptic ulcer, united states pharmacopoeia

Background and aims

The stomach is an organ of the digestive tract, specialized in processing food and preparing it for intestinal absorption. One of its main functions is undoubtedly the secretion of gastric juice which is produced at a rate of 1.2 to 1.5 liters per day. Among the constituents of gastric juice, hydrochloric acid plays an essential role in the digestion process. It also prevents the proliferation of pathogens and converts pepsinogen into pepsin, an essential enzyme for the digestion of proteins [1,2]. The gastric juice is strongly acid as its pH can drop to around 1.7 in fasted state [3]. Normally, a balance exists between aggressive acid secretion and gastric mucosal defense. Peptic ulcer can occur when this equilibrium is disrupted. Hyperacidity is among the factors that were shown to cause peptic ulcer [4-6]. Many studies have demonstrated that the prevalence in western countries of gastroesophageal reflux disease (GERD)-related symptoms like heartburn or acid reflux ranges from 10% to 48% [7,8]. GERD therapy costs more than US$15 billion annually only in the United States [9,10]. Other studies concluded that the world prevalence of peptic ulcer disease ranges from 0.1% to 4.7%, with an annual incidence range of 0.3% to 0.19% [11].

Antacids are known to be effective in gastric and duodenal ulcer and GERD for several decades. Although they have not been proven to directly act on the erosive lesions, they are able to neutralize the excess of HCl in the gastric juice and therefore, reduce the activity of pepsin, enhance the healing process, and offer rapid relief of heartburn and acid reflux [12-15]. Antacids are alkaline drugs that neutralize gastric acidity and exert a buffering effect to stabilize the pH of the gastric juice.

DOI: 10.15386/mpr-2082

Manuscript received: 21.02.2021
Received in revised form: 24.03.2021
Accepted: 15.04.2021

Address for correspondence:
yafoutm@yahoo.fr

They are divided into 2 categories: absorbable compounds such as sodium bicarbonate, calcium carbonate ($CaCO_3$), and magnesium carbonate ($MgCO_3$), and non-absorbable compounds such as aluminum phosphate ($AlPO_4$), aluminum hydroxide ($Al(OH)_3$), and magnesium hydroxide ($Mg(OH)_2$). They are usually marketed as a combination of 2 or 3 compounds [16,17]. As most people use low doses, antacids are generally well tolerated by individuals with normal renal function. Aluminum-containing and calcium-containing products are known to cause constipation, while magnesium-containing products can cause diarrhea. Sodium bicarbonate-based antacids should be used carefully as they can lead to sodium overload [18].

Since antacids are mainly over-the-counter drugs (OTC), they are widely used in self-medication around the world. A survey carried out in Finland found that 88% of persons buying antacids, alginates or sucralfate in pharmacies, self-medicated for heartburn [19]. Another study of self-medication practices among a sample of medical students showed that antacids were the second most commonly used drugs with a frequency of use of 55% [20]. Antacids' global market size was estimated at US$ 5.83 billion in 2017 and annual sales of antacids in France reached € 59 million in 2000 [21,22].

The acid-neutralizing capacity (ANC) is the amount of acid that can be neutralized by an antacid. The United States Pharmacopoeia (USP) describes the ANC test as a back-titration method using sodium hydroxide (0.5N solution) to a set endpoint of pH 3.5 to determine the number of milliequivalents of acid (hydrochloric acid 1N solution) neutralized by the minimum labeled dosage (MLD) of an antacid [23].

In Morocco, a large number of antacid drugs are officially registered. They mainly come in the form of chewable tablets and oral suspensions. Most of them contain combinations of aluminum hydroxide and magnesium hydroxide [24]. Since these antacids are non-prescription drugs authorized for publicity to the general public [25], pharmaceutical companies promote their products by praising certain characteristics such as the flavor or the rapidity of symptoms relief. This encourages patients to use antacids for self-medication.

The aim of this study is to perform the ANC test as described in the USP, to evaluate the neutralizing capacity of antacids marketed in Morocco. As all these drugs already have marketing authorizations obtained in accordance with regulatory and quality requirements, the final objective is not to question the quality or the effectiveness of each antacid but to discuss the difference in neutralization capacity depending on the composition, the strength, the pharmaceutical form, the price, and other properties and characteristics, and to give an objective and balanced result interpretation.

Methods

Sampling method and samples

First, we consulted the Moroccan Ministry of Health registered drugs database [24] in search of antacids belonging to ATC class A02A, and other drugs for peptic ulcer and GERD belonging to ATC class A02BX13 (alginates in combination with antacids). This research identified 18 brands. The different packaging sizes, bottle capacities, and flavors of the same brand were considered as a single drug. The samples of 12 drugs were then purchased from pharmacies in Rabat and Casablanca (Morocco) and transported to the laboratory of analytical chemistry of the Faculty of Medicine and Pharmacy of Casablanca (Morocco) and were labeled AC1 to AC12. Six out of the 18 initially identified brands were not available in the pharmacies of Rabat and Casablanca during the period from October 5, 2020 to October 11, 2020.

Test preparation and procedure

The preparation and standardization of reagents, the test preparation, and the test procedure were conducted as described in the United States Pharmacopoeia.

1. Preparation of reagents

1 N hydrochloric acid (HCl) was prepared by diluting 85 ml of concentrated HCl (37%) with distilled water to 1000 ml.

0.5 N sodium hydroxide (NaOH) was prepared by diluting 500 ml of 1 N NaOH with carbon dioxide-free (CO_2-free) water to 1000 ml. 1 N NaOH was prepared by dissolving 162 g of sodium hydroxide in 150 ml of CO_2-free water. After being cooled to room temperature and filtered through a hardened filter paper, 54.5 ml of the clear filtrate was diluted with CO_2-free water to 1000 ml.

The standardization of 1 N HCl was performed by titrating a solution of tromethamine (5 g dried at 105° for 3 hours and dissolved in 50 ml of distilled water) using 2 drops of bromocresol green as an indicator to a pale-yellow endpoint. The normality of HCl is then calculated using the following formula: N_{HCL} = mg of tromethamine / (121.14 x ml HCl).

The standardization of 0.5 N NaOH was performed by titrating a solution of benzoic-acid (200 mg in 15 ml of CO_2-free water) using 2 drops of phenolphthalein as an indicator until a permanent pale-pink color is produced. The normality of NaOH is then calculated using the following formula: N_{NaOH} = mg of benzoic-acid / (122.1 x ml NaOH).

2. Test preparation

Oral suspensions: After shaking the bottle and measuring the density, the minimum labeled dosage was accurately weighed and transferred to a 250-ml beaker. Distilled water was then added to a total volume of 70 ml and the preparation was mixed on the magnetic stirrer for 1 minute.

Chewable tablets: Twenty tablets were weighed and the average tablet weight was determined. After grinding the tablets to a fine powder, a weight equivalent to the minimum labeled dosage was accurately weighed and transferred to a 250-ml beaker. 70 ml of distilled water was then added and the preparation was mixed on the magnetic stirrer for 1 minute.

Effervescent tablets: A quantity equivalent to the minimum labeled dosage was transferred to a 250-ml beaker. 10 ml of distilled water was added and the beaker was slowly swirled while the effervescence reaction took place. Another 10 ml of distilled water was added and the beaker was slowly swirled again. Finally, the walls of the beaker were washed with 50 ml of distilled water and the preparation was mixed on the magnetic stirrer for 1 minute.

3. Test procedure

The experiment was carried out at a temperature of 37 °C ± 3 and three determinations were performed for every brand.

A volume of 30 ml of 1 N HCl accurately measured was added to the preparation and the stirring was continued for 15 min accurately timed at a rate of 300 rpm. At the end of the 15 min, the excess HCl was titrated in less than 5 minutes with a 0.5 N solution of NaOH to attain a stable pH of 3.5. When the pH obtained at the end of the 15 min before beginning the titration was superior to 3.5, the procedure was started all over again using 60 ml of HCl instead of 30 ml and the appropriate modification was made in the formula. The number of milliequivalents (mEq) of acid consumed was calculated by the formula:

$$ANC\ (mEq) = (30 \times N_{HCl}) - (V_{NaOH} \times N_{NaOH})$$

Where N_{HCl} and N_{NaOH} are, respectively, the normalities of HCl and NaOH and V_{NaOH} is the volume of NaOH added to obtain a stable pH of 3.5.

Equipment and reagents

We used hydrochloric acid 37% for analysis from Carlo Erba, sodium hydroxide powder for analysis from Solvachim, tromethamine primary standard from Sigma-Aldrich, and benzoic acid reference material for titrimetry from Supelco. pH measurements were performed using a HACH sensION+ MM374 pH-meter coupled to a HACH 50-14-T pH electrode with a temperature sensor. pH-meter was calibrated using standardizing buffer solutions from HACH. Weighing operations were carried out using a RADWAG AS 220/C/2 analytical balance. Stirring and heating were carried out using a VELP SCIENTIFICA heating magnetic stirrer. All the operations were performed in A-class glassware.

Results

Sampling

Before being tested, the 12 sampled antacids underwent a pre-study whose objective was to collect all the pharmaceutical and pharmacological information appearing on the packaging and patient leaflet. Seven of the sampled brands were oral suspensions, 4 were chewable tablets, and one was effervescent tablets. From the 7 oral suspensions, 4 were 250 ml glass bottles, one was 150 ml glass bottle, one was 4.3 ml sachets, and one was 20 g sachets. Nine brands are locally manufactured and 3 are imported (two from the United Kingdom and one from France). All the tablets (except the effervescent tablets AC5) are mint-flavored. Oral suspensions are mint-flavored (AC6, AC9, AC11, and AC12), mint/anise-flavored (AC7), orange-flavored (AC10), and lemon-flavored (AC8). Six out of the 12 brands have aluminum hydroxide and magnesium hydroxide as active ingredients. Minimum labeled dosages for these 6 drugs ranged from 400 mg to 900 mg for $AlOH_3$ and from 400 mg to 800 mg for $MgOH_2$. Three brands have sodium alginate at a minimum labeled dosage of 500 mg, in combination with antacids (sodium bicarbonate, potassium bicarbonate, and calcium carbonate). One brand has aluminum phosphate as the active ingredient at a minimal labeled dosage of 2476 mg and another brand is a combination of 680 mg/80 mg of calcium carbonate/magnesium carbonate. One brand is an effervescent tablet containing sodium sulfate, sodium bicarbonate, and sodium hydrogenophosphate (285 mg/170 mg/195 mg). It should be noted that brands AC2, AC5, and AC7 contain sodium at the respective rates of 117.5 mg, 53 mg, and 411 mg per minimum labeled dose as indicated in their patient leaflets. Brands AC1, AC4, and AC8 contain sugar in their composition. The cost of the MLD ranged from $ 0.04 to $ 0.63. All the collected information is summarized in table I and table II.

Table I. Packaging size, volume, origin, price, batch numbers, and expiry date of sampled antacids.

Product ID	Package	Flavor	Country of origin	Minimum labeled dosage price ($)	Batch number	Expiry date
Tablets						
AC1	20 or 40 tablets	Mint	Morocco	0.04	10421	Feb. 2023
AC2	20 tablets	Mint	United Kingdom	0.46	005001	Feb. 2022
AC3	20 or 40 tablets	Mint	Morocco	0.13	02044-1	May. 2023
AC4	36 or 72 tablets	Mint	Morocco	0.04	CB00373	Jun. 2023
Effervescent tablets						
AC5	20 effervescent tablets	-	Morocco	0.63	06087-1	May. 2024
Oral suspensions						
AC6	250 ml bottle of oral suspension	Mint	Morocco	0.13	10630	Jun. 2023
AC7	150 ml bottle of oral suspension	Mint or anise	United Kingdom	0.17	009481	Apr. 2022
AC8	20 sachets of 4.3 ml oral suspension	Lemon	France	0.17	XI008	Nov. 2022
AC9	250 ml bottle of oral suspension	Mint	Morocco	0.25	03037-2	Jul. 2023
AC10	20 sachets of 20 g	Orange	Morocco	0.19	J1745	Jun. 2023
AC11	250 ml bottle of oral suspension	Mint	Morocco	0.14	10804	Jul. 2023
AC12	250 ml bottle of oral suspension	Mint	Morocco	0.20	180223	Feb. 2021

Table II. Pharmacological class, active ingredients, indications, strength, and dosage of sampled antacids.

Product ID	Pharmacological class	Active Pharmaceutical Ingredients	Labeled therapeutic indications	Minimum labeled dosage	Strength of minimal labeled dosage (mg)
Tablets					
AC1	Antacids ATC code: A02AD01	- Aluminum Hydroxide - Magnesium Hydroxide	Heartburn - Acid reflux - Dyspepsia - Gastric intolerance to certain drugs	1 tablet	400 400
AC2	Alginic acid in combination with antacids ATC code: A02BX13	- Sodium Alginate - Sodium Bicarbonate - Calcium Carbonate	Acid regurgitation - Heartburn - Indigestion	2 tablets	500 267 160
AC3	Antacids ATC code: A02AD01	- Aluminum Hydroxide - Magnesium Hydroxide	Heartburn - Acid reflux - Dyspepsia - Gastric and duodenal ulcer	2 tablets	800 800
AC4	Antacids ATC code: A02AX	- Calcium Carbonate - Magnesium Carbonate	Heartburn	1 tablet	680 80
Effervescent tablets					
AC5	Antacids ATC code: A02AH	- Anhydrous Sodium Sulfate - Sodium Bicarbonate - Anhydrous Sodium Hydrogenophosphate	Heartburn - Stomach or esophagus pain	1 effervescent tablet	285 170 195
Oral suspensions					
AC6	Antacids ATC code: A02AD01	- Aluminum Hydroxide - Magnesium Hydroxide	Heartburn - Acid reflux - Dyspepsia - Gastric intolerance to certain drugs	1 tbsp. (15ml)	525 600
AC7	Alginic acid in combination with antacids ATC code: A02BX13	- Sodium Alginate - Potassium Bicarbonate - Calcium Carbonate	Acid regurgitation - Heartburn - Indigestion	5 ml	500 100 100
AC8	Antacids ATC code: A02AD01	- Aluminum Hydroxide - Magnesium Hydroxide	Heartburn - Acid reflux	1 sachet (4.3 ml)	460 400
AC9	Antacids ATC code: A02AD01	- Aluminum Hydroxide - Magnesium Hydroxide	Heartburn - Acid reflux - Dyspepsia - Gastric and duodenal ulcer	1 tbsp. (15 ml)	633 780
AC10	Antacids ATC code: A02AB03	- Colloidal Aluminum Phosphate (20 % gel)	Mucous membranes protection, antacid, antipeptic - Esophageal, gastric and intestinal disorders - Ulcerative esophagitis, dyspepsia, hyperchlorhydria - Colopathies, colitis, sigmoiditis, proctitis	1 sachet (17 ml)	2476
AC11	Alginic acid in combination with antacids ATC code: A02BX13	- Sodium Alginate - Sodium Bicarbonate	Acid reflux - Heartburn	2 tsp. (10 ml)	500 267
AC12	Antacids ATC code: A02AD01	- Aluminum Hydroxide - Magnesium Hydroxide	Antacid - Mucous membranes protection - Gastric and duodenal ulcer	2 tsp. (10 ml)	900 600

Acid-neutralizing capacity test

Twelve antacids drugs and alginate/antacid combination drugs marketed in Morocco were tested for their acid-neutralizing capacity according to the method described in the USP. The results are summarized in table III. Brand AC12, an oral suspension based on $Al(OH)_3$/$Mg(OH)_2$ combination showed the highest ANC of MLD (49.85±0.97), and brand AC7, an oral suspension containing sodium alginate combined with potassium bicarbonate and calcium carbonate showed the lowest ANC of the MLD (6.50±0.52). Among tablets, AC3 ($Al(OH)_3$/$Mg(OH)_2$ combination-based) showed the highest ANC of MLD (27.70±0.79) and AC2 (sodium alginate combined with sodium bicarbonate and calcium carbonate) showed the lowest ANC of the MLD (12.30±0.18). Brand AC1, a tablet containing $Al(OH)_3$/$Mg(OH)_2$ combination, showed the highest ANC per gram of substance tested (19.2) while AC10 which is an $AlPO_4$-based oral suspension showed the lowest ANC per gram of substance tested (0.51). It is worth noting that the density of oral suspensions ranged from 1.09 to 1.36. The 2 suspensions containing sodium alginate combined with antacids (AC7 and AC11) have the same density while $Al(OH)_3$/$Mg(OH)_2$ combination-based suspensions have different densities.

Table III. ANC per minimum labeled dosage (MLD) of tested samples.

Product ID	Density (Suspensions)	Average labeled dosage weight (g) (Tablets)	ANC (mEq) of MLD (Det. 1)	ANC (mEq) of MLD (Det. 2)	ANC (mEq) of MLD (Det. 3)	ANC (mEq) of MLD (Mean ± SD)	ANC (mEq) per gram of substance tested
Tablets							
AC1		1.23	24.10	24.40	23.95	24.15 ± 0.23	19.60
AC2		1.63	12.15	12.25	12.50	12.30 ± 0.18	7.57
AC3		3.04	26.80	28.05	28.25	27.70 ± 0.79	9.12
AC4		1.31	14.05	14.10	14.60	14.25 ± 0.30	10.84
Effervescent tablets							
AC5		1.99	8.25	8.15	7.60	8.00 ± 0.35	4.01
Oral suspensions							
AC6	1.09		45.70	48.00	46.25	46.65 ± 1.20	2.85
AC7	1.16		5.90	6.85	6.75	6.50 ± 0.52	1.12
AC8	1.36		26.60	25.85	24.80	25.75 ± 0.90	4.41
AC9	1.29		38.10	39.05	39.70	38.95 ± 0.80	2.02
AC10	1.12		10.05	9.45	9.60	9.70 ± 0.31	0.51
AC11	1.16		11.20	10.65	11.00	10.95 ± 0.28	0.94
AC12	1.23		48.80	50.05	50.70	49.85 ± 0.97	4.06

Discussion

In this study, the acid-neutralizing capacity of twelve antacids and alginates combined with antacids was studied along with other characteristics and properties. Eight out of 12 brands are mint-flavored and one is either mint-flavored or anise-flavored. This shows that mint could be a flavor appreciated by patients using antacids. This observation should be confirmed by a palpability study. Except for brands AC2, AC7, and AC8, all the antacids tested are locally manufactured. This proves that the increasing patients' demand for antacids is followed and satisfied by the Moroccan pharmaceutical companies.

In terms of ANC, all the tested brands meet the minimum value of 5 mEq required by the United States Food and Drug Administration (FDA) [26]. Brands containing $Al(OH)_3/Mg(OH)_2$ combination as active ingredients have the highest ANC values ranging from 25.75±0.90 to 49.85±0.97 per MLD. Moreover, there seems to be a certain correlation between ANC and strength of minimal labeled dosage in $Al(OH)_3/Mg(OH)_2$ combinations as the most potent product AC12 have the highest strength (900mg/600mg) and the least potent product AC1 have the lowest strength (400mg/400mg). $CaCO_3/MgCO_3$-based combination AC4 showed an ANC of 14.25±0.30, followed by aluminum phosphate AC10 (9.70±0.31), and sodium sulfate/sodium bicarbonate/sodium hydrogenophosphate combination AC5 (8.00±0.35). Sodium alginate/antacid combinations showed an ANC ranging from 6.50±0.52 to 12.30±0.18. Since the main pharmacological action of alginate/antacid combinations is to form a raft that floats on the stomach content and given that the neutralization of the gastric acidity is only an adjuvant action [27], the low ANC of these combinations makes perfect sense. However, the oral suspension AC11 has a higher ANC than the oral suspension AC7. This is probably due to the higher active ingredient content per MLD of AC11. When it comes to pharmaceutical forms, oral suspensions are clearly more potent than tablets as the top 3 ANCs of MLD belong to oral suspensions AC6, AC9, and AC12. This is certainly due to the fact that oral suspensions are in a favorable state of dispersion which allows them to act faster and more effectively.

It is proven that high sodium-containing drugs are associated with cardiovascular risk [28]. The sodium content of MLD of drugs AC2, AC7, and AC5 is respectively 117.5 mg, 53 mg, and 411 mg as indicated in the patient leaflet. Based on the labeled daily recommended intake of each drug, these contents correspond to a daily sodium intake of respectively 470 mg, 212 mg, and 1233 mg. Therefore, sodium content must be taken into consideration when choosing an antacid. Brands with low ANC/sodium content ratio such as AC5 should not be recommended for patients with high blood pressure, cardiovascular illnesses, or sodium-restricted diet.

Many other studies evaluated the acid-neutralizing capacity of antacids marketed in several countries, and have also shown great variability in terms of pharmaceutical form, composition, strength, ANC, and salt content of the different brands [29-33]. As with our study, the findings of these studies showed that aluminum hydroxide/magnesium hydroxide combinations have the highest ANC values, that oral suspensions are the most used dosage forms, and that sodium content is a very important concern linked to the use of antacids.

Table IV. Price of the minimum labeled dosage and ANC/Price of minimum labeled ratio of tested samples.

Product ID	Active Pharmaceutical Ingredients	Pharmaceutical form	PMLD ($)	ANC/PMLD ratio
Tablets				
AC1	Aluminum Hydroxide Magnesium Hydroxide	Tablet	**0.04**	**584.02**
AC2	Sodium Alginate Sodium Bicarbonate Calcium Carbonate	Tablet	**0.46**	**26.46**
AC3	Aluminum Hydroxide Magnesium Hydroxide	Tablet	**0.13**	**210.02**
AC4	Calcium Carbonate Magnesium Carbonate	Tablet	**0.04**	**329.53**
Effervescent tablets				
AC5	Anhydrous Sodium Sulfate Sodium Bicarbonate Anhydrous Sodium Hydrogenophosphate	Effervescent tablet	**0.63**	**12.67**
Oral suspensions				
AC6	Aluminum Hydroxide Magnesium Hydroxide	Oral suspension (Bottle)	**0.13**	**352.54**
AC7	Sodium Alginate Potassium Bicarbonate Calcium Carbonate	Oral suspension (Bottle)	**0.17**	**37.27**
AC8	Aluminum Hydroxide Magnesium Hydroxide	Oral suspension (Sachets)	**0.17**	**148.87**
AC9	Aluminum Hydroxide Magnesium Hydroxide	Oral suspension (Bottle)	**0.25**	**155.97**
AC10	Colloidal Aluminum Phosphate	Oral suspension (Sachets)	**0.19**	**52.01**
AC11	Sodium Alginate Sodium Bicarbonate	Oral suspension (Bottle)	**0.14**	**80.39**
AC12	Aluminum Hydroxide Magnesium Hydroxide	Oral suspension (Bottle)	**0.20**	**245.27**

The cost of antacids is a factor that should be taken into consideration when choosing a product. In the present study, the price of the minimum labeled dosage (PMLD) ranges from $0.04 for brand AC1 to $0.63 for brand AC5. Combinations of $Al(OH)_3$ and $Mg(OH)_2$ have a PMLD ranging from $0.04 to $0.25 where oral suspensions showed a higher price than tablets. Sodium alginate-based brands showed a PMLD ranging from $0.14 to $0.46 where tablets are more costly than suspension. $CaCO_3$/$MgCO_3$-based combination AC4 and AlPO4-based suspension AC10 showed respective PMLD of $0.04 and $0.19. We compared these PMLD with ANC of each brand by calculating the ANC/PMLD ratio (Table IV). The best ANC/PMLD ratio belongs to brand AC1 (582.02) and the least favorable ratio belongs to AC5 (12.67). After analyzing these ratios, it appears clearly that products containing $Al(OH)_3$/$Mg(OH)_2$ combination and $CaCO_3$/$MgCO_3$ combination (particularly tablets) offer the economically most favorable choice for the patient. The low ANC/price ratio of sodium alginate-based brands (26.46 to 80.39) is understandable since they are not pure antacids. It is to note that the brand AC5 has the highest PMLD, the highest sodium content, the second-lowest ANC, and the lowest ANC/PMLD ratio. In our opinion, the use of this product as an antacid is not relevant and offers no benefits to the patient. These findings are consistent with many other studies that have also shown great variability in terms of the cost/effectiveness ratio of antacids and recommended the economic factor to be taken into account when choosing the most suitable product [34-36].

The USP requires the ANC to be evaluated for the MLD of each product. If we focus on $Al(OH)_3$/$Mg(OH)_2$ combinations, we find that the strengths of the active ingredients in the MLD of the studied antacids are not equal (Table II). Thus, in our opinion, comparing different products based on different active ingredient strengths makes no sense. Moreover, two tablet formulations containing $Al(OH)_3$/$Mg(OH)_2$ combination (AC1 and AC3) have the same strength per tablet (400mg/400mg) but different MLD (respectively 1 tablet and 2 tablets per dose). These MLDs correspond respectively to 400mg/400mg per dose for AC1 and 800mg/800mg per dose for AC3. Therefore, it appears clear that the requirement to evaluate the ANC on the MLD is a bias that constitutes a limitation

for the ANC test as described in the USP. In our opinion, the strength of the active ingredients in the MLD should be taken into account when evaluating the ANC of an antacid. Furthermore, expressing the result in terms of mEq per gram of the substance tested as specified by the USP is more suitable for active pharmaceutical ingredients since the weight of finished pharmaceutical products MLD depends on several factors such as the excipients used in the formulation, the tablet's size, the suspension's density, the molecular weight of the active ingredient, etc.

Conclusion

The evaluation of the acid-neutralizing capacity of the antacids available in Morocco showed that all the marketed brands meet the minimal requirement. However, aluminum hydroxide/magnesium hydroxide combinations showed superiority over other products. Therefore, since the majority of patients choose their antacids based on non-objective criteria such as flavor, we recommend that the ANC value be included in the label of antacids to help both patients and physicians choose the most suitable product. The choice of the appropriate antacid should also take into account other properties such as the sodium content and the ANC/price ratio. We also believe that the ANC test as described in the USP should be revised so that it is based on active ingredients content instead of minimum labeled dosage.

References

1. Wolfe MM, Soll AH. The physiology of gastric acid secretion. N Engl J Med. 1988;319:1707-1715.
2. Keeton WT. Human digestive system. Encyclopædia Britannica. Available from: https://www.britannica.com/science/human-digestive-system.
3. Dressman JB, Berardi RR, Dermentzoglou LC, Russell TL, Schmaltz SP, Barnett JL, et al. Upper gastrointestinal (GI) pH in young, healthy men and women. Pharm Res. 1990;7:756-761.
4. Holle GE. Pathophysiology of ulcer disease. Langenbecks Arch Chir. 1985;366:81-87.
5. Brooks FP. The pathophysiology of peptic ulcer disease. Dig Dis Sci. 1985;30(11 Suppl):15S-29S.
6. Carlson BM. Chapter 12: The Digestive System. In: The Human Body. Academic Press, 2019, p. 321-355.
7. Heading RC. Prevalence of upper gastrointestinal symptoms in the general population: a systematic review. Scand J Gastroenterol Suppl. 1999;231:3-8.
8. Manterola C, Grande L, Bustos L, Otzen T. Prevalence of gastroesophageal reflux disease: a population-based cross-sectional study in southern Chile. Gastroenterol Rep (Oxf). 2020;8:286–292.
9. Cappell MS. Clinical presentation, diagnosis, and management of gastroesophageal reflux disease. Med Clin North Am. 2005;89:243-291.
10. Shaheen NJ, Hansen RA, Morgan DR, Gangarosa LM, Ringel Y, Thiny MT, et al. The burden of gastrointestinal and liver diseases, 2006. Am J Gastroenterol. 2006;101:2128-2138.
11. Sung JJ, Kuipers EJ, El-Serag HB. Systematic review: the global incidence and prevalence of peptic ulcer disease. Aliment Pharmacol Ther. 2009;29:938-946.
12. Peterson WL, Sturdevant RA, Frankl HD, Richardson CT, Isenberg JI, Elashoff JD, et al. Healing of duodenal ulcer with an antacid regimen. N Engl J Med. 1977;297:341-345.
13. Garrigues-Gil V. Antacids in the treatment of peptic ulcer disease. Methods Find Exp Clin Pharmacol. 1989;11 Suppl 1:73-77.
14. Patrick L. Gastroesophageal reflux disease (GERD): a review of conventional and alternative treatments. Altern Med Rev. 2011;16:116-133.
15. Tytgat GN. Review article: treatment of mild and severe cases of GERD. Aliment Pharmacol Ther. 2002;16 Suppl 4:73-78.
16. Tomina OE, Yabluchansky MI, Bychkova OY, Ivleva OO. Antacids clinical pharmacology. Journal of V. N. Karazin Kharkiv National University. 2015;(28):52-57. Available from: https://periodicals.karazin.ua/medicine/article/view/2875
17. Waller DG, Sampson AP; Chapter 33: Dyspepsia and peptic ulcer disease. In: Medical Pharmacology and Therapeutics (Fifth Edition). Elsevier, 2018, p. 401-410.
18. Maton PN, Burton ME. Antacids revisited: a review of their clinical pharmacology and recommended therapeutic use. Drugs. 1999;57:855-870.
19. Sihvo S, Hemminki E. Self-medication of dyspepsia: how appropriate is it? Scand J Gastroenterol. 1997;32:855-861.
20. Kasulkar AA, Gupta M. Self Medication Practices among Medical Students of a Private Institute. Indian J Pharm Sci. 2015;77:178-182.
21. Antacids market size, share & trends analysis report by dosage form (Tablet, Liquid), By Distribution Channel (Retail, Hospital, Online Pharmacy), By Region (APAC, Europe, North America), And Segment Forecasts, 2019-2025. Grandview Research. Available from: https://www.grandviewresearch.com/industry-analysis/antacids-market.
22. Balsan D, Chambaretaud S. Discussion Paper: Elements of analysis on the antacids and anti-ulcer drugs market. N°23, March 2002. French Ministry of Employment and Solidarity (Directorate of research, studies, evaluation and statistics). [French]
23. United States Pharmacopeia and National Formulary (USP 41-NF 36). Chemical Tests: (301) Acid-neutralizing capacity. Rockville, MD: United States Pharmacopeial Convention; 2016.
24. Information on drug. Moroccan Ministry of Health, Directorate of Medicines and Pharmacy. Available from: http://dmp.sante.gov.ma/recherche-medicaments.
25. Article 41 of Law 17-04 on the Drug and Pharmacy Code (Official Bulletin of the Kingdom of Morocco n° 5480 of Thursday, December 7, 2006).

26. United States Food and Drug Administration. Code of Federal Regulations. Title 21, Volume 5. Revised as of April 1, 2019.
27. Mandel KG, Daggy BP, Brodie DA, Jacoby HI. Review article: alginate-raft formulations in the treatment of heartburn and acid reflux. Aliment Pharmacol Ther. 2000;14:669-690.
28. Perrin G, Korb-Savoldelli V, Karras A, Danchin N, Durieux P, Sabatier B. Cardiovascular risk associated with high sodium-containing drugs: A systematic review. PLoS One. 2017;12:e0180634.
29. MacCara ME, Nugent FJ, Garner JB. Acid neutralization capacity of Canadian antacid formulations. Can Med Assoc J. 1985;132:523-527.
30. Duffy TD, Fawzy SZ, Ireland DS, Rubinstein MH. A comparative evaluation of liquid antacids commercially available in the United Kingdom. J Clin Hosp Pharm. 1982;7:53-58.
31. Katakam P, Tantosh NM, Al Eshy AM, Rajab LJ, Elfituri AA. A comparative study of the acid neutralising capacity of various commercially available antacid formulations in Libya. Libyan Journal of Medical Research. 2010;7:41–49.
32. Ayensu I, Bekoe SO, Adu JK, Amponsaa Brobbey A, Appiah E. Evaluation of acid neutralizing and buffering capacities of selected antacids in Ghana. Scientific African 2020;8:e00347.
33. Rao SV, Chamundeswari B, Padmalatha K. Acid neutralization capacity and cost effectiveness of antacid suspensions sold across various retail pharmacies in Vijayawada. Int J Pharm Sci & Res. 2018;9:1963-1968.
34. Mahmood D, Alnaseer S, Muhammad BY, Khalilullah H, Abdulghani MA, Anwar MJ, et al. Acid-neutralising capacity and pharmacoeconomic studies of commercially available antacids in the Qassim Region of Saudi Arabia. Hamdan Med J. 2020;13:150-155.
35. Vedavathi H, Tejasvi TS, Revankar SP. Evaluation of cost effectiveness and efficacy of commonly used different antacid gel preparations. Int J Basic Clin Pharmacol 2013;2:788-791.
36. Jacob S, Shirwaikar A, Anoop S, Khaled R, Imtiaz M, Nair A. Acid neutralization capacity and cost-effectiveness of antacids sold in various retail pharmacies in the United Arab Emirates. Hamdan Med J. 2016;9:137–146.