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The Continuing Unacceptable Marketing of Alka-Seltzer® Containing Aspirin for Stomach-Related Disorders

Aspirin (acetylsalicylic acid) is one of the most successful drugs in the history of medicine. Its benefits are unquestionable, in particular when used at low doses (75–150 mg/day) for the secondary prevention of cardiovascular and cerebrovascular disorders. Although declining in some countries, its use at higher doses for pain, inflammation and fever is still highly prevalent, with more than 4 billion 500 mg tablets sold worldwide in 2006.[1] Aspirin is also an ingredient of multiple over-the-counter fixed-dose combination products. One of the most popular of these is the group of medicines included under the trade name Alka-Seltzer®, whose advertising has been celebrated as one of the most successful and influential of all time.[2]

The original Alka-Seltzer® was introduced back in the 1930s as a remedy for pain-related disorders (headache, flu) and stomach-related complaints (indigestion, stomach upset, heartburn),[2] and soon became very popular for the treatment of hangover and over-indulgence. The basic original ingredients of Alka-Seltzer® are aspirin (325 mg), sodium bicarbonate (1.9 g) and citric acid (1 g). The alleged role of sodium bicarbonate is 3-fold: (i) to neutralize the stomach acid (the 'Alka' component); (ii) to facilitate the dissolution of aspirin, thereby increasing its absorption speed; and (iii) to react with citric sodium in order to produce carbon dioxide gas (the 'Seltzer' component). The usual dose is two tablets at a time (650 mg of aspirin), with a maximum daily dose of eight tablets (2600 mg of aspirin) for adults and four tablets (1300 mg of aspirin) if aged ≥60 years.[2] The product is marketed in 68 countries, and in at least 36 countries, including the US, the UK, Ireland, Canada, Australia and all but one Latin-American country. It is authorized for stomach-related indications such as acid indigestion, sour stomach, upset stomach, heartburn, over-indulgence and hyperacidity.[1] In the US, there is also an extra-strength formulation containing aspirin 500 mg per tablet, with the recommendation to take two tablets at a time; this product is advertised as "a powerful relief for sour stomach and pain".[2] On the contrary, only five (Italy, Austria, Romania, Hungary and Malta) of 22 continental EU countries where Alka-Seltzer® containing aspirin is marketed have gastric indications.[1] In 2004 the Spanish Agency for Medicines and Medical Devices, after a negative report from its Committee on Safety of Medicines, requested the withdrawal of the aspirin component, leaving it as an antacid drug only. One year later, France withdrew any reference to stomach conditions.

Aspirin is well known to increase the risk of upper gastrointestinal complication (UGIC; bleeding or perforation) with a steep dose-dependent gradient. At low dosages (≤325 mg/day), the risk increases by a factor of around 2,[3] while the relative risk can get as high as 8–21 at daily doses ≥500 mg.[4,5] Being conservative, we may estimate an average incidence rate of 4.8 per 1000 person-years associated with these high doses, assuming a relative risk of 8 and a baseline incidence of 0.6 in 1000 person-years (0.4 in females and 0.8 in males),[6] which would result in an excess risk of 4.2 per 1000 person-years. This excess risk of UGIC may increase further in patients >60 years of age or with antecedents of UGICs (table I). Importantly, several studies have shown that the risk is not reduced with the use of enteric coated or buffered formulations (with antacids such as sodium bicarbonate).[3]

Although the magnitude of this risk may be considered acceptable for mild to moderate pain relief or fever in a population without gastrointestinal risk factors, it blatantly lacks scientific evidence and is unacceptable as a treatment for gastric-related disorders, for two main

Table I. Excess risk of upper gastrointestinal complications (UGIC) attributed to a daily dose of aspirin 650 mg (two tablets of Alka-Seltzer®) and the number of person-days of exposure needed to have one UGIC case attributed to aspirin (number needed to harm [NNH]), depending on the presence of different risk factors[a]

Risk factors	Unexposed (per 1000 person-years)	Exposed (per 1000 person-years)	Excess risk (per 1000 person-years)	NNH in person-days (figures rounded)
No gastrointestinal risk factor	0.6	4.8	4.2	87 000
≥60 years	1.8	14.4	12.6	29 000
History of dyspepsia	1.2	9.6	8.4	43 000
History of peptic ulcer	3.6	28.8	25.2	14 000
History of UGIC	6.0	48.0	42.0	9 000
≥60 years plus history of dyspepsia	3.6	28.8	25.2	14 000
≥60 years plus peptic ulcer history	10.8	86.4	75.6	5 000
≥60 years plus history of UGIC	18.0	144	126.0	3 000

a Assumptions: (a) A baseline incidence rate of UGIC of 0.6 per 1000 person-years (0.8 for males and 0.4 for females); (b) RR of UGIC in people exposed to aspirin 650 mg = 8; (c) RR of UGIC in people aged ≥60 years vs <60 years = 3; (c) RR of past history of dyspepsia vs no antecedents = 2; (d) RR of past history of peptic ulcer vs no antecedents = 6; (e) RR of past history of UGIC vs no antecedents = 10 (data from Hernández-Díaz and García-Rodríguez[6]).

RR = relative risk.

reasons: (i) the aspirin component has never been shown to contribute to the alleviation of any gastric symptom (indigestion, heartburn, stomach pain); and (ii) the aspirin component may actually exacerbate the gastric symptoms and, in the worst case scenario, may induce serious gastrointestinal complications, in particular in patients with gastroduodenal disorders stemming from an underlying peptic ulcer. One may also question the role of sodium bicarbonate as an antacid because of its short-term action, its high content in sodium, and the associated belching and distension that may actually cause acid reflux.

In 2006, worldwide sales of Alka-Seltzer® containing aspirin and sodium bicarbonate exceeded 1 billion tablets (excluding presentations containing other ingredients, such as those for common cold).[1] Assuming that only 25% of this exposure (250 million tablets) occurred in people who took two tablets a day for a stomach-related problem (e.g. dyspepsia) and that 15% of these people were >60 years of age, the number of UGIC cases expected to be caused by these products worldwide, using the data provided in table I, would reach 3800 per year, with 190–380 resulting in death (case-fatality rate 5–10%). Nonetheless, this estimation is conservative because some of these people may actually have an active peptic ulcer, in whom the UGIC risk would be much higher. In 2003, the cost of a gastrointestinal bleeding event was estimated at €2786.[7] Thus, the damage caused by this product would cost €11 million a year, which would add to the cost of the drug itself (€3–5 for a packet of 20 tablets).

Ten years ago, a popular Spanish journalist died when he was diving in the Mediterranean Sea. The autopsy revealed that the cause of death was an upper gastrointestinal bleeding which provoked haematemesis and aspiration. He had a history of gastric problems and that morning he took Alka-Seltzer® for a stomach upset.[8] Unfortunately, the regulatory action that forced the withdrawal of the aspirin-component in Spain, came too late. He was 43 years of age. This paper should serve as a tribute to him and many others who may have suffered unnecessarily from gastrointestinal complications because of misguided use resulting from an irrational labelling indication for this combination product. After 78 years of marketing and promotion of Alka-Seltzer® products containing aspirin for stomach-related problems, it is time to act and stop this gratuitous damage to the public, or provide a convincing reason not to do so.

Francisco J. de Abajo[1] and *Luis A. García Rodríguez*[2]

1 Division of Pharmacoepidemiology and Pharmacovigilance, Spanish Agency for Medicines and Medical Devices, Madrid, Spain

2 Spanish Centre for Pharmacoepidemiological Research, Madrid, Spain

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