### 18th Expert Committee on the Selection and Use of Essential Medicines

Reviewer No. 2 checklist for:

Application for the removal of "Antacids" from the WHO Model List of Essential Medicines

<table>
<thead>
<tr>
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<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Have all important studies that you are aware of been included?</td>
<td>X</td>
<td></td>
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<tr>
<td>2</td>
<td>Is there adequate evidence for the proposed deletion?</td>
<td>X</td>
<td></td>
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<tr>
<td>3</td>
<td>Is there evidence of efficacy in diverse settings and/or populations?</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>4</td>
<td>Are there adverse effects of concern?</td>
<td></td>
<td>X</td>
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<tr>
<td>5</td>
<td>Are there special requirements or training needed for safe/effective use?</td>
<td></td>
<td>X</td>
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<tr>
<td>6</td>
<td>Is this product needed to meet the majority health needs of the population?</td>
<td></td>
<td>X</td>
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<tr>
<td>7</td>
<td>Is the proposed dosage form registered by a stringent regulatory authority?</td>
<td>X</td>
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</tbody>
</table>
(8) What action do you propose for the Committee to take?

In agreement with Dr. Cheraghali’s application, I propose the removal of antacids (aluminium hydroxide and magnesium hydroxide) from the WHO Model List of Essential Medicines, due to its lesser symptomatic efficacy in the management of acid peptic disorders, gastroesophageal reflux disease (GERD) and non-ulcer dyspepsia (NUD) in comparison to histamine H2 receptor antagonists and proton-pump inhibitors (PPIs), given to adults and children.\(^1\) Additionally, in NUD, antacids were not statistically significantly superior to placebo, contrasting with prokinetics, H2 receptor antagonists and PPIs.

In symptomatic GERD, a meta-analysis (10 trials)\(^2\) showed benefit increase with alginate/antacid combinations (60%), histamine H2 receptor antagonists (41%) and antacids (11%) when compared to placebo.

Besides, antacids show prescription difficulties, such as palatability in liquid formulation and multiple daily administrations, with unfavourable consequences on adherence.

Finally, the current formulations/preparations on the list are not the most adequate, since the combination of aluminium and magnesium salts has the advantage of maintaining normal intestinal function (constipation action counterbalancing laxative action, respectively – that is, the corrective effect) and liquid form would be preferred.

References:


(9) Additional comment, if any.

Concerning Dr. Manikandan’s comments, I focus this short review in the management of heartburn or oesophagitis associated to GERD during pregnancy.

Heartburn is a normal consequence of pregnancy. Serious reflux complications during pregnancy are rare. Heartburn affects 30% to 50% of all pregnant women and tends to worsen as pregnancy advances. Upper abdominal pain, regurgitation, and heartburn, as GERD symptoms during pregnancy should be managed with a step-up algorithm beginning with lifestyle modifications and dietary changes. If these measures fail, antacids are considered as first-line therapy. If symptoms persist, any of the histamine-receptor antagonists can be used. Proton pump inhibitors (PPIs) are reserved for women with intractable symptoms or complicated reflux disease. All but omeprazole are FDA category B drugs during pregnancy.\(^1\) Omeprazole is classified as risk factor C. Based on data collected by the Teratogen
Information System (TERIS), it was concluded that therapeutic doses used during pregnancy would be unlike to pose a substantial teratogenic risk.2

More than one decade ago, the evidence of foetal and neonatal safety was scarce. Even though, one case-control study (178 exposed pregnant women) found no increase in major malformations following first-trimester exposure to H2 receptor antagonists.3 In 1997, Motherisk Program initiated a prospective cohort study whose preliminary results showed no significant difference in the incidence of major malformations in infants of exposed mothers to PPIs during pregnancy.4 In 1999, two cohorts of pregnant women, one in the United Kingdom (n=1,179) and the other in Italy (n=1,057), were performed to assess the incidence of malformations following first trimester exposure to cimetidine, omeprazole, or ranitidine. Compared with nonexposed women, a major excess risk of malformations was not found in any of these three exposed groups. The overall malformation rate was 4.4%. The relative risks for nongenetic congenital malformations associated with the use of cimetidine, omeprazole, and ranitidine were 1.2 (CI95%: 0.6-2.3; 0.9 (CI95%: 0.3-2.2); and 1.4 (CI95%: 0.8-2.4), respectively, compared with the nonexposed. These findings suggest that the use of acid-suppressing medicines during the first trimester of pregnancy is not associated with a major teratogenic risk.5

More recently, a study evaluated data from the European Network of Teratology Information Services (ENTIS). Data on the outcome of 553 pregnancies with exposure to an H2-blocker (ranitidine n=335; cimetidine n=113, famotidine n=75; nizatidine n=15, roxatidine n=15), most of them exposed in the first trimester, showed a higher incidence of premature deliveries in the exposed group compared to the control group (exposed to non-teratogenic substances). There was no increase in the incidence of major malformations. Two pregnancies with maternal use of famotidine in early pregnancy were terminated after the prenatal diagnosis of a neural tube defect.6

In 2009, another meta-analysis7 evaluated the fetal safety of H2 blockers during pregnancy. With data from 2,398 exposed and 119,892 nonexposed to H2 blockers, overall odds ratio was 1.14 (CI95%: 0.89-1.45). Further analysis revealed no increased risks for spontaneous abortions, preterm delivery, and small for gestational age with odds ratios of 0.62 (CI95%: 0.36-1.05), 1.17 (0.94-1.147), and 0.28 (0.06-1.22), respectively.

In 2010, a study analysed computerized databases of medicines dispensed from 1998 to 2007 and maternal and infant hospitalization records from a district hospital in Israel. A total of 84, 823 infants were born during the study period, whose mothers were registered at a health maintenance organization; 1,148 of them were exposed to H(2)-blockers during the first trimester of pregnancy. This exposure was not associated with an increased risk for congenital malformations (adjusted odds ratio [OR] = 1.03; 95%CI:
0.80-1.32); also, no such association was found when therapeutic pregnancy terminations were included in the analysis (adjusted OR = 1.17; 95% CI: 0.93-1.46). Exposure to H(2)-blockers was not associated with perinatal mortality, premature delivery, low birth weight, or low Apgar scores. 

A meta-analysis of five cohort studies assessed the risks of congenital fetal malformations in women using PPIs in the first trimester of pregnancy. A total of 593 infants were exposed to PPIs, most (534) received omeprazole. The relative risk for all major malformations among any PPI exposure was 1.18 (95% CI: 0.72–1.94), a non-significant relative risk \( (P = 0.7) \). For the four studies where data for only omeprazole could be extracted, the relative risk was 1.05 (95% CI: 0.59–1.85), also indicating a non-significant relative risk for malformations.

A more recent meta-analysis of seven studies \( (n=134,940 \text{ patients}) \) identified 1,530 exposed and 133,410 not exposed to PPIs. The overall odds ratio (OR) for major malformations was 1.12 (95% CI: 0.86-1.45). Further analysis revealed no increased risk for spontaneous abortions \( (OR=1.29, 95\% \text{ CI: } 0.84-1.97) \); similarly, there was no increased risk for preterm delivery \( (OR=1.13, 95\% \text{ CI: } 0.96-1.33) \). In the secondary analysis of 1,341 exposed and 120,137 not exposed to omeprazole alone, the OR for major malformations was 1.17 \( (\text{CI95\%: } 0.90-1.53) \).

In conclusion, both H2 receptor antagonists and PPIs, including omeprazole, could be used in symptomatic pregnant women that do not respond to lifestyle modifications and dietary changes. Consequently, the suggested antacids deletion would not be detrimental to pregnant women, since those can be switched by the other acid-suppressing agents.

References: