Risks of proton-pump inhibitors: what every doctor should know
Francisco J Fernández-Fernández, Gonzalo Pía and Pascual Sesma

TO THE EDITOR: We read with interest Talley’s excellent and informative editorial about the risks associated with proton-pump inhibitors (PPIs).1 Other possible serious side effects of PPIs that need to be taken into account are potential drug interactions with aspirin and clopidogrel.

Aspirin is a weak acid that crosses the mucosa in its lipid state. The suppression of acid production reduces the lipophilic nature of this drug and, theoretically, might reduce its absorption and bioavailability.2 On the other hand, clopidogrel is a prodrug that is converted in the liver to an active metabolite. This bioactivation is mediated by hepatic cytochrome P450 isoenzymes,3 with cytochrome P450 2C19 (CYP2C19) playing a particularly important role. There is evidence suggesting that some PPIs (omeprazole, lansoprazole and rabeprazole) can inhibit CYP2C19, which would alter the effectiveness of clopidogrel and potentially lead to an increased risk of adverse cardiovascular outcomes.

In a recent Canadian case–control study among patients prescribed clopidogrel after acute myocardial infarction, current use of PPIs was associated with an increased risk of reinfarction (adjusted odds ratio, 1.27; 95% CI, 1.03–1.57).4 The risk was limited to patients currently taking a PPI (the authors did not find any association with more distant exposure to PPIs), and did not extend to pantoprazole, a drug that does not
interfere with the conversion of clopidogrel to its active form.

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TO THE EDITOR:


Talley discusses a range of risks of proton-pump inhibitors (PPIs). Another rare but serious side effect of PPIs of which every doctor should be aware is hyponatraemia. Eleven cases of hyponatraemia caused by PPIs have been published. Consistent features were the rapid onset of hyponatraemia within days of commencement of the PPI therapy, the severity of hyponatraemia often being associated with confusion or delirium, and rapid recovery after cessation of the PPI medication. Test results in each case were consistent with inappropriate release of antidiuretic hormone. One case occurred 5 days after a patient changed from lansoprazole to esomeprazole. Hyponatraemia needs to be considered whenever there is clinical deterioration, even after brief exposure to a PPI.

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IN REPLY:

Proton-pump inhibitors (PPIs) are often prescribed for patients taking aspirin and clopidogrel to reduce gastrointestinal bleeding. There are emerging data that omeprazole diminishes the therapeutic effect of clopidogrel because the active enzyme in the liver, cytochrome P450 2C19 (CYP2C19), metabolises omeprazole and activates clopidogrel.1,2 In a large cohort study of 8205 patients with acute coronary syndrome and taking clopidogrel, 64% were also taking a PPI (60% omeprazole), 21% of those who were taking clopidogrel but no PPI died or were rehospitalised for acute coronary syndrome, versus 30% of those taking clopidogrel as well as a PPI.3 Notably, not all the PPIs have the same metabolic pathway. For example, omeprazole and esomeprazole are principally metabolised by CYP2C19 in contrast to lansoprazole, which is metabolised by cytochrome P450 3A4 (CYP3A4), and pantoprazole, which is metabolised by CYP2C19 O-demethylation then rapid sulfate conjugation. Thus, the negative interaction with clopidogrel may not apply to all PPIs (and pantoprazole may be the drug of choice if a PPI is required, as cytochrome P450 interactions are least likely).1 However, until more data are accumulated, all PPIs should probably be avoided where possible in patients who have been prescribed clopidogrel, unless there is no alternative.

It is correct that hyponatraemia has, rarely, been reported in patients taking PPIs. However, this knowledge is based solely on case report data, and therefore the level of evidence for cause and effect is relatively weak.

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2 Siller-Matula JM, Spiel AO, Lang JM, et al. Effects of pantoprazole and esomeprazole on platelet inhibi-