Pharmacokinetics and pharmacodynamics

PKP-014 Proton pump inhibitor induced malabsorption of transition metals with co-factor function: simulation of the impact of raising gastrointestinal ph

H Jenzer, M Krummenacher, M Beyeler, L Sadeghi

Author affiliations +

Abstract

Background Proton pump inhibitors (PPI) raise gastric fasting pH from 2.2 (men) or 2.5 (women) to >4.0 for up to 16 hours/day. Suppressed gastric function may lead to malabsorption of 3d block ions. As metal aqua complexes are weak acids, their absorption kinetics and bioavailability are likely to be modified by a pH shift.

Purpose The objective of this contribution was to assess the relevance of changing gastric pH on absorption of 3d block ions with co-factor function.

Material and methods Amounts corresponding to the daily allowances of a selection of co-factor relevant oligo-elements were assayed using an in vitro simulated digestive system (modified from Kopf-Bolanz 2012). The elements were tested visually and by turbidimetric UV/Vis absorption spectrometry.

Results Oligo-elements were mainly actively absorbed from the upper duodenal part of the GI tube. There, the luminal pH gradient sharply rises within 10 cm at the duodenojejunal junction. Acidity passes at this site from pH=2 to pH=5 (fasting state) and from pH=1.7 to pH=4.3 (postprandial). Ferric, cupric and cuprous, but neither ferrous, cobalt, manganese nor zinc aqua complexes precipitated at pH<6. $[Fe(H_2O)_6]^{3+}$ formed amorphous red–brown $[Fe(H_2O)_3(OH)_3]^0$ due to pK_a=2.2, 3.5 and 6.0. $[Cu(H_2O)_6]^{2+}$ formed uncharged $[Cu(H_2O)_4(OH)_2]^0$ due to pK_a=6.3 and 8.5. $[Cu(H_2O)_6]^+$ formed uncharged $[Cu(H_2O)_5(OH)]^0$ in one step due to pK_a=3.9.

Deprotonations of $[Fe(H_2O)_6]^{2+}$ occurred due to pK_a=6.74 and 9.5, $[Co(H_2O)_6]^{2+}$ due to pK_a=8.8 and 12.4, $[Mn(H_2O)_6]^{2+}$ due to pK_a=10.7 and 12.0, and $[Zn(H_2O)_6]^{2+}$ due to pK_a=10.1. Neither one of these aqua complexes has pK_a <6 and neither one was relevant for malabsorption.

Conclusion Apart from iron (III), copper is also likely to be significantly malabsorbed by pH shifts in the GI tube. Neither ferrous, cobalt, manganese nor zinc aqua complexes were relevant for malabsorption due to PPI treatment. A different absorption behaviour at altered pH conditions must also be anticipated for weak acids with functional groups, such as carboxylic acids, vinylogous carboxylic acids, acid halides, –l-mono- or disubstituted phenols, or sulfonic acids (eg, many non-steroidal anti-inflammatory drugs and ascorbic acid). On the other hand, weak bases may be more bioavailable as a result of a higher fraction of the diffusible undissociated molecules.

References and/or acknowledgements Kopf-Bolanz KA. J Nutr2012;142:245–50.

No conflict of interest

http://dx.doi.org/10.1136/ejhpharm-2017-000640.442