

Vacancy 010115 PhD student medical biology

Proton pump inhibitors (PPIs) are the most widely used drugs for acid related gastrointestinal disorders. Although PPIs are considered to have an excellent safety profile, we have shown that long-term use is associated with pneumonia. In addition, several case reports have reported PPI-induced hypomagnesemia causing symptoms varying from muscle weakness to neurological disturbances, but the responsible molecular mechanism is unclear. The identification of several inherited hypomagnesemic syndromes has led to the identification of new Mg²⁺ transporters such as the epithelial magnesium (Mg²⁺) channel TRPM6. The serendipitous finding of PPI-induced hypomagnesemia opens up new avenues to study. The principal aim of this proposal is to gain understanding in the scope of the clinical problem and molecular basis of PPI-induced hypomagnesemia. To this end, the following key objectives will be studied:

1) *Incidence of PPI-induced hypomagnesemia*

We will evaluate the incidence of hypomagnesemia in a large cohort of PPI users using a cross sectional approach. We target a significant group of outpatients that visit the department of Gastroenterology & Hepatology annually. An estimated 35% of these patients use any PPI. Mg²⁺ will be measured in residual plasma. In addition, blood, urine and duodenal biopsies will be obtained for electrolyte, mRNA, protein and single nucleotide polymorphisms (SNP) analysis.

2) *Molecular mechanism of PPI-induced hypomagnesemia*

Humans and mice models will be exposed to PPIs and characterized in detail. Subsequently, in intestinal epithelial cells the effect on possible targets of the PPI's including TRPM6 and the H,K-ATPase will be studied. Potential causative SNPs in TRPM6 of PPI users will be functionally characterized.

3) *Treatment of PPI-induced hypomagnesemia*

Protective therapies will be developed to prevent hypomagnesemia during PPI-treatment. To this end, dietary rescue therapies will be evaluated in various mice models of PPI-induced hypomagnesemia. Our approach integrates specific complementary areas of investigation including human, animal and cell physiological studies, and is also ideally positioned to make research breakthroughs in the area of Mg²⁺ pathophysiology.