Proton Pump Inhibitor-induced Hypomagnesemia, the tip of the iceberg?

Clinical relevance
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, several case reports have reported that long-term use of PPI’s can lead to hypomagnesemia causing symptoms varying from muscle weakness to neurological disturbances.

Background
The molecular mechanisms underlying PPI-induced hypomagnesemia remain unclear. The identification of several inherited hypomagnesemic syndromes has led to the identification of new Mg$^{2+}$ transporters such as the epithelial Mg$^{2+}$-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:

Goals

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 5000 outpatients that visit the department of Gastroenterology & Hepatology annually. An estimated 35% of these patients use any PPI. Mg$^{2+}$ 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 Mg$^{2+}$ pathophysiology.

We offer:
The possibility to perform and present high-quality clinically-oriented research in a professional, multicultural and highly-motivating working environment with about 35 colleagues in a well-equipped department. The student will learn how to perform basic molecular biology techniques including cloning, quantitative real-time PCR analysis, immunohistochemistry, confocal laser scanning microscopy and various biochemical assays including blood ion determinations.

Contact:
Department: Physiology
Supervisor: Mark Hess
Contact person: Tim Schreuder
Telephone number: 0243614222
Email address: tim.schreuder@radboudumc.nl
Website: www.physiomics.eu