Are medicines an additional source of phosphate to be considered in patients with chronic kidney disease?

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Several observational studies suggest that hyperphosphatemia increases the risk of cardiovascular morbidity and mortality in CKD patients [1], [2]. Diet (i.e., protein) is the main source of intake of phosphate and low-protein diet has been demonstrated to delay the progression of CKD. The aim of this study was to explore the use of phosphate-containing drugs in a cohort of CKD patients from a general population of Southern Italy.

As data source, we used the general practice 'Arianna' database, containing data from 158,510 patients living in Caserta and registered with 123 general practitioners (GPs). Incident CKD patients were identified in the database by searching for: 1) ICD-9 coded CKD as cause of hospitalisation; 2) CKD-relevant procedures undergone in hospital (e.g., dialysis); 3) drug prescriptions issued for a CKD-related indication. Using prescription data, we retrieved all the individual medicines which were prescribed to the CKD patients by GPs or specialists during the years 2006-2011. We then identified all of the medicines containing phosphate, based on the review of drug summary of product characteristics (SPC), PubChem, Micromedex and literature review. Specifically, we distinguished drugs containing phosphorus (P) either in the active ingredient or in the excipients. We considered only drugs for systemic administration (e.g., enteral and parenteral routes). We finally analysed the frequency of drugs containing phosphate by first and fifth ATC level and estimated the total and mean duration of exposure to these drugs in CKD patients.

Out of 3,779 medicines identified from prescriptions to CKD patients, 317 (8.4 %) for systemic use contained phosphorus. Looking at single compounds (ATC V level), overall 741 individual ingredients were received by CKD patients, and 96 (12.9 %) of them contained phosphorus. Considering different system/organs (ATC I level), the highest number of P-containing drugs was reported for the alimentary tract and metabolism (n=21; 20.8%) and cardiovascular drugs (n=17; 14.7%). On average, CKD patients received 14.3 P-containing drug prescriptions during the study period (mean follow-up=2.6 years), with this number being much larger than what observed in the general population (7.8). The greatest number of prescriptions for P-containing drugs was issued for cardiovascular drugs (ATC I level: C; n=12,219; 9.8% of all cardiovascular drugs) and drugs for the alimentary tract and metabolism (n=9,965; 17.7%). For each CKD patient, on average, we calculated a cumulative exposure of 538 days for cardiovascular drugs and 420 days for drugs targeting the alimentary tract and metabolism, which contain phosphorus.

The work carried out so far in this study demonstrates that there is high use of drugs containing phosphorus in CKD patients for prolonged periods. This was particularly the case for cardiovascular drugs which are associated with chronic use and therefore higher cumulative doses. Further evaluation is needed to determine the exact additional intake of phosphorus through the use of these chronic medications and the possible effects of the exposure to P-containing drugs on the cardiovascular risk in CKD patients.

1. Gutierrez, O.M., et al., *Fibroblast growth factor 23 and mortality among patients undergoing hemodialysis.* N Engl J Med, 2008. **359**(6): p. 584-92.

2. Ganesh, S.K., et al., *Association of elevated serum PO(4), Ca x PO(4) product, and parathyroid hormone with cardiac mortality risk in chronic hemodialysis patients.* J Am Soc Nephrol, 2001. **12**(10): p. 2131-8.