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Medication is an additional source of phosphate intake in chronic kidney disease patients

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Abstract *Background and aims:* Hyperphosphatemia increases the risk of cardiovascular morbidity but the use of medicines as a source of phosphate has not been investigated yet. This study aims to explore the use of absorbable phosphate-containing drugs in CKD patients.
Methods and results: Incident CKD patients were identified within the Arianna database (containing data from 158,510 persons in Caserta (Southern Italy) registered with 123 general practitioners) from 2005 to 2011. Drugs prescribed to these patients were classified as phosphate-containing based on the summary of product characteristics (SPC), PubChem and Micromedex. The number and duration of prescriptions for these drugs as well as the overall intake of phosphate were estimated.

Out of 1989 CKD patients, 1381 (70%) were prescribed 266 medicinal products containing absorbable phosphate over a median follow-up of 6 years (interquartile range (IQR) = 5.2 −6.0). Most patients were prescribed ATC A (650; 47.1%) and C (660; 47.8%) phosphate-containing drug products targeting the gastrointestinal and cardiovascular system for a median of 232 (IQR: 56–656) and 224 (IQR: 56–784) days respectively.
Conclusions: Several medications, especially chronically prescribed ones, contain absorbable phosphate. This study's findings confirm the relevance of medicines as a phosphate source for the first time.

Introduction

Phosphate is the most abundant intracellular anion and second most common mineral in the body. It has several roles in the body, including intracellular signalling, pH buffering, biosynthesis of ATP and as a main component of nucleic acids, phospholipids and bone, where it is primarily located [1]. Elevated phosphate levels are of particular relevance in chronic kidney disease (CKD) patients since their impaired renal function reduces the kidney's ability to eliminate phosphate, potentially

Abbreviations: 1,25-OH-D, 1,25 dihydroxy vitamin D; API, active pharmaceutical ingredient; ATC, anatomic therapeutic class; ATP, adenosine triphosphate; CKD, chronic kidney disease; DDD, defined daily dose; FGF-23, fibroblast growth factor 23; GFR, glomerular filtration rate; GP, general practitioners; ICD-9 CM, 9th edition international classification of disease, clinical modification; IQR, interquartile range; NSAID, non-steroidal anti-inflammatory drug; OTC, over-the-counter; SPC, summary of product characteristics.

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resulting in hyperphosphatemia, for which phosphate-binding drugs are prescribed.

Dietary protein is the main source of phosphate intake and a low-protein diet has been demonstrated to delay the start of dialysis [2], highlighting the importance of phosphatemia reduction in CKD. Food additives such as polyphosphates and beverages containing elevated quantities of phosphate were also demonstrated to pose a real and insidious cardiovascular risk for renal patients [1,3].

However, it is possible that other clinically relevant sources of phosphate intake are being overlooked. Therapeutic medicinal products may also contain phosphate that is present in the active pharmaceutical ingredient (API) such as bisphosphonates, in the drug counter-ion (e.g., betamethasone sodium phosphate) or in the excipient (e.g., anhydrous calcium hydrogen phosphate). Nevertheless, the use of phosphate-containing medicinal products in CKD patients has never been investigated. The aim of this population-based study was therefore to explore the use of phosphate-containing drugs in a cohort of CKD patients from a general population of Southern Italy.

Methods

Data source

Data was extracted from the Arianna database from the years 2005–2011. This database was set up by the Caserta Local Health Agency in Southern Italy in the year 2000 and currently contains information on a population of almost 400,000 inhabitants registered in the list of approximately 300 general practitioners (GPs). Participating GPs record data during their daily clinical practice using dedicated software and send complete and anonymous clinical data to the Arianna Database on a monthly basis. The Arianna database can be linked to a hospital discharge registry as well as other administrative registries through a unique and anonymous patient identifier. If the quality or completeness of submitted data was outside the defined range of acceptability, the data was investigated and back-submitted to each participating GP in order to receive an immediate feedback and correct the issue. GPs failing to meet these standard quality criteria were excluded from epidemiologic studies. Of all the GPs in Caserta, 123 GPs covering a population of 158,510 inhabitants met these standard quality criteria for the period under consideration and had at least one year of database history.

Information on patient demographics, prescriptions for drugs reimbursed by National Health Service (coded according to the Anatomical Therapeutic Chemical (ATC) classification system) and their indications for use, and hospital admissions and procedures (coded by the ninth edition of International Classification of Diseases, Clinical Modification (ICD-9 CM)) was collected. So far, the Arianna database has been shown to provide accurate and reliable information for pharmacoepidemiology research, as documented elsewhere [4–6].

Study population

All patients with an incident diagnosis of CKD during the study period 2006–2011 (2005 was considered as run-in period) and with at least one year of database history prior to study entry were included in the study. The index date was defined as the date of first CKD diagnosis during the study period. CKD patients were identified as those with at least one of the specific codes among either primary/secondary causes of hospital admission, procedures or indication of use associated to the prescribed drugs (Appendix 1), as documented elsewhere [7].

Exposure

All drug prescriptions issued to CKD patients during the study period were retrieved from the Arianna database. Using PubChem, Micromedex, the summary of product characteristic (SPC) from the Italian Drug Agency website and drug monographs made available freely by pharmaceutical companies, all the prescribed medicinal products containing phosphate were identified by two pharmacists (YI, JS), while distinguishing between drugs containing phosphate either in the active drug moiety, in the drug counter-ion or in the excipient. The full list of these phosphate-containing drugs (Appendix 2) was independently screened by an expert in pharmaceutical sciences (UMM), who classified the medicinal products containing phosphate as having absorbable or non-absorbable phosphate content based on the source of phosphate, the pharmaceutical dosage form and the route of administration (Appendix 3). In case of disagreement among different evaluators, consensus was sought via discussion. For each of the medicinal products containing phosphate, the quantity of phosphate is known if it is present in the active drug moiety or as drug counter-ion; it was estimated, according to pharmaceutical considerations reported in Appendix 3 if the phosphate was present in the excipients. Only drugs for systemic administration (e.g., enteral and parenteral routes) were considered when estimating the quantity of absorbable phosphate.

Data analysis

A descriptive analysis of the use of all the phosphate-containing medications among CKD patients was carried out. In particular, the number of medicinal products and APIs containing theoretically absorbable phosphate was measured. APIs were defined as single drug substances (for example, meformin etc). Medicinal products were defined as APIs having a different dose, formulation, pharmaceutical manufacturer or brand etc. (for example, metformin 500 mg, metformin 1000 mg etc.)

The number of patients with prescriptions for at least one phosphate-containing medicinal product, the number of prescriptions in the cohort and the median duration of these prescriptions (along with the interquartile range) was estimated by first level ATC. ATC first level categories represent the following anatomically-related drug