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Original Article

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Influence of drugs and comorbidity on serum potassium in 15 000 consecutive hospital admissions

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Abstract

Background. Drug trials often exclude subjects with relevant comorbidity or comedication. Nevertheless, after approval, these drugs will be prescribed to a much broader collective. Our goal was to quantify the impact of drugs and comorbidity on serum potassium in unselected patients admitted to the hospital.

Methods. This was a retrospective pharmacoepidemiologic study in 15 000 consecutive patients admitted to the medical department of the Kantonsspital St. Gallen, a 700-bed tertiary hospital in eastern Switzerland. Patients with 'haemolytic' plasma and patients on dialysis or with an estimated glomerular filtration rate (GFR) <10 mL/min/1.73 m^2 were excluded. For the remaining 14 146 patients, drug history on admission, age, sex, body weight, physical findings, comorbidity (ICD-10 diagnoses) and laboratory information (potassium and creatinine) were extracted from electronic sources.

Results. Estimated GFR was the strongest predictor of serum potassium ($P < 0.0001$). Angiotensin-converting enzyme inhibitors, cyclosporine, loop diuretics and potassium-sparing diuretics all showed a significant effect modification with decreasing GFR ($P < 0.001$). Similarly, in patients with liver cirrhosis a significantly stronger effect on potassium was found for angiotensin receptor blockers, betablockers and loop diuretics ($P < 0.01$). Several significant drug–drug interactions were identified. Diabetes, male sex, older age, lower blood pressure and higher body weight were all independently associated with higher serum potassium levels ($P < 0.001$). The model explained 14% of the variation of serum potassium.

Conclusions. The effects of various drugs on serum potassium are highly influenced by comorbidity and comedication. Although the presented model cannot be used to predict potassium in individual patients, we demonstrate that clinical databases could evolve as a powerful tool for industry-independent analysis of postmarketing drug safety.

Keywords: adverse drug effects; hyperkalaemia; hypokalaemia; pharmacoepidemiology; potassium

Introduction

Potassium is the most abundant cation in the body. The vast majority (98%) of total body potassium (4000 mmol) is stored in the intracellular fluid compartment, whereas only about 60 mmol are in the extracellular fluid [1,2]. Total body potassium contents are balanced by food intake and urinary and faecal losses. The two main regulators of renal potassium excretion are mineralocorticoid activity and the availability of sodium in the distal nephron [3]. In healthy people, serum potassium is further maintained in a narrow range by key hormones (insulin, β-adrenergic agonists), promoting its entry into the cells via Na^+/K^+-ATPase [2]. Both hypokalaemia and hyperkalaemia are associated with increased mortality, mainly due to a higher risk of potentially fatal arrhythmia [2,4,5].

Several clinical conditions are associated with either increased (e.g. renal dysfunction, hypoaldosteronism) or decreased (e.g. diarrhoea, hyperaldosteronism) serum potassium concentration [5,6]. Many frequently prescribed drugs influence the serum potassium concentration by either modulating renal potassium excretion (e.g. diuretics) or by transcellular shifting (e.g. insulin and β-mimetics) [1,6]. The magnitude of these drug-induced changes and the effect modification by disease is often unknown, since patients with relevant comorbidity tend to be excluded from drug trials. We therefore aimed to determine the relative contributions of drugs and comorbidities on serum potassium in a large, unselected cohort of patients admitted to a representative tertiary referral centre.

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Methods

Patients

The Kantonsspital St. Gallen is the main tertiary referral centre in eastern Switzerland. Fifteen thousand consecutive patients admitted to the Department of Internal Medicine between January 2002 and July 2004 were included in this study. Patients on dialysis and those with an estimated glomerular filtration rate (GFR) <10 mL/min were excluded. If the first blood sample was 'haemolytic', the patient was also excluded, unless a non-haemolytic sample was available within 24 h of admission. Complete drug history on admission, age, sex, body weight, blood pressure and comorbidities (ICD-10-diagnoses: congestive heart failure, liver cirrhosis, diabetes, diarrhoea, vomiting and malabsorption) were derived from the electronic patient record (Phoenix©, Parametrix, Lachen, Switzerland).

Drug history and defined daily doses

Seventeen drugs or groups of drugs with either a potassium-lowering or a potassium-increasing potential were recorded: angiotensin-converting enzyme inhibitors (ACEIs; 12 different generic substances), angiotensin receptor blockers (ARBs; 4), betablockers (14), β2-mimetics (5), carboanhydrase inhibitors (1), corticosteroids (5), calcineurin inhibitors (2), digitalis (1), L-Dopa or dopamine agonists (4), high- and low-molecular-weight heparin (4), laxatives (>10), loop diuretics (2), nonsteroidal antiinflammatory drugs (NSAID; 18), K-sparing diuretics (3), theophylline (1), potassium supplements, as well as thiazides (6). Insulin and other antidiabetics were not included in the analysis because they were considered substitutes for an endogenous hormone deficiency and at the same time highly collinear with the variable diabetes, which was included in the analysis. To standardise doses of different drugs within a class, the daily dose of a given substance was expressed as multiples of a defined daily dose (DDD) according to the world health organization (WHO) [7].

Laboratory analysis

Creatinine and potassium values were extracted from the laboratory database. GFR was estimated according the modification of diet in renal disease (MDRD)-short formula ($186 \times (\text{SCr})^{-1.154} \times (\text{age})^{-0.203} \times 0.742$ (if the subject is female) [8]. Correction for African background was not done because this information was not available and <1% of the local population is black. GFR was tested as a linear predictor and after log transformation. Log-transformed GFR proved to be the stronger predictor. For the graphical display of the results patients were stratified according to the National Kidney Foundation (NKF) classification: (i) GFR ≥90 mL/min, (ii) GFR 60–89 mL/min, (iii) GFR 30–59 mL/min, (iv) GFR 15–29 mL/min and (v) GFR <15 mL/min [8].

Statistical analysis

Statistical analysis was performed using SAS release 8.2 (SAS institute Inc., Cary, NC, USA). Continuous variables are presented as means and standard deviations (SD), or as medians and interquartile range (IQR), and categorical variables as percentages (%) and rates. Missing values for body weight were imputed using a regression model with the variables gender and age. If the strength of the drug or the exact dosing schedule was not reported or ambiguous, the daily intake of 1 DDD was assumed. If the drug was taken 'on demand' the daily intake of half DDD was assumed.

A mixed-effects regression model, controlled for clustering by repeated admission of individual patients was developed. All variables were included in the model, irrespective of their statistical significance. Predefined interactions were identified using backward elimination techniques and they were only included in the final model if their *P*-value was <0.05. Predictors of low (<3.0 mmol/L) and high (>5.0 mmol/L) potassium were identified using logistic regression and backward elimination techniques. These models were not adjusted for clustering.

Results

From the original cohort of 15 000 admissions, 283 were excluded due to dialysis or GFR <10 mL/min, and 571 were excluded due to 'haemolytic' plasma. The present analysis is based on the data of 14 146 admissions in 10 320 patients, 4440 (43%) were females and 5880 (57%) males. The mean (SD) age was 63.1 (16.1) years, and the weight was 70.0 (15.6) kg. GFR was overall 77 (30) mL/min/1.73 m^2 and serum potassium (K) 3.96 (0.53) mmol/L. Potassium increased from an average of 3.8 (0.4) mmol/L in stage I (normal) kidney function to 4.6 (1.0) mmol/Lin patients with stage V kidney dysfunction.

The reasons for hospital admission and the prevalence of comorbidities are summarized in Table 1. If kidney dysfunction is omitted, overall 2829 (20%) had at least one comorbidity with alleged influence on serum potassium. The most prevalent condition was diabetes (13.4%), followed by congestive heart failure (CHF; 10.7%). The intake of drug classes is presented in Table 2. At least one drug with the potential to modify potassium was taken by 8909 (63%). Betablockers were taken by almost 30%; the second largest group were inhibitors of the renin–angiotensin–aldosterone (RAA) system, followed by various diuretics.

Predictors of excessively low or high potassium levels

In 210 patients (1.5%) K was <3.0 mmol/L, and in 520 patients (3.7%) K was >5.0 mmol/L. Diarrhoea was the strongest predictor of K <3.0 mmol/L, followed by anorexia/malabsorption. The potential of thiazide diuretics to induce hypokalaemia [Odds ratio (OR) 2.1, $P < 0.0001$] was much higher than that of loop diuretics (OR 1.05, $P = 0.2$). But also liver cirrhosis, *lower* weight and, surprisingly, female gender were independent predictors of hypokalaemia (Table 3).

Table 1. Principal diagnoses and comorbidity at admission

	N	%
Principal diagnoses		
Cardiovascular diseases	5248	37.1
Oncological diseases	3296	23.3
Gastrointestinal diseases	1062	7.5
Respiratory diseases	849	6.0
Neurologic/psychiatric	721	5.1
Various disorders	2970	21.0
Comorbidity		
GFR $\leq$ 15 mL/min/1.73 m^2	179	1.3
GFR 15–29 mL/min/1.73 m^2	545	3.9
GFR 30–59 mL/min/1.73 m^2	3203	22.6
GFR 60–89 mL/min/1.73 m^2	6105	43.2
GFR $\geq$ 90 mL/min/1.73 m^2	4114	29.1
Diabetes	1891	13.4
Congestive heart failure	1511	10.7
Diarrhoea	544	3.9
Gastrointestinal bleeding	381	2.7
Liver cirrhosis	269	1.9
Anorexia or malabsorption	60	0.4

GFR: glomerular filtration rate estimated according to the abbreviated Modification in Diet in Renal Disease (MDRD) study formula.

Table 2. Drug use at admission

Drugs	*N*	%	Daily dose (median; IQR)
ACE-inhibitors	2538	17.9	1.0 (1.0–2.0)
Angiotensin receptor blockers	974	6.9	1.0 (1.0–2.0)
Potassium-sparing diuretics	1000	7.1	0.5 (0.3–0.7)
Loop diuretics	2291	16.2	1.0 (0.5–1.3)
Thiazide diuretics	1168	8.3	0.5 (0.5–1.0)
Carboanhydrase inhibitors	35	0.3	0.3 (0.3–0.7)
Betablockers	4210	29.8	0.5 (0.3–0.7)
Betaadrenergic stimulants	852	6.0	0.8 (0.8–1.1)
Dopaminergic drugs	160	1.1	0.6 (0.3–1.0)
Theophylline	62	0.4	1.0 (0.8–1.0)
Corticosteroids	922	6.5	1.0 (0.5–2.5)
Heparinoids	925	6.5	2.0 (1.5–3.0)
Cyclosporine	167	1.0	0.8 (0.4–1.1)
Nonsteroidal anti-inflammatory drugs	796	5.6	0.5 (0.3–1.3)
Digitalis	445	3.2	0.5 (0.5–1.0)
Laxatives	944	6.7	2.0 (1.0–4.0)
Potassium supplements	134	1.0	1.0 (0.7–2.0)

N: number of persons affected; Daily dose: cumulative daily dose expressed as multiples of defined daily dose (DDD) according to WHO; IQR: interquartile range; ACE: angiotensin-converting enzyme.

The strongest predictor of K >5.0 mmol/L was the combination of ACE inhibitors with K-sparing diuretics (OR 4.0; $P < 0.0001$). K-sparing diuretics alone, cyclosporine, ACE inhibitors and ARBs were also associated with hyperkalaemia. ARBs had an identical OR of 1.2 per DDD as ACE inhibitors, but due to a smaller sample size (only 974 patients took ARBs as opposed to 2538 patients taking ACE inhibitors) the former association was not statistically significant ($P = 0.11$). Among non-pharmaceutical influences, impaired kidney function, diabetes and *higher* body weight were all significantly associated with hyperkalaemia (Table 3).

Table 3. Predictors of extreme potassium values

Potassium <3.0 mmol/L	OR	95% CI	*P* value
Diarrhoea	4.0	2.9–5.5	<0.0001
Malabsorption or anorexia	3.6	1.6–8.3	<0.01
Thiazide diuretics	3.5	2.6–4.7	<0.0001
Cirrhosis	2.7	1.5–5.0	0.0008
Female gender	1.6	1.3–2.0	<0.0001
Weight (per 10 kg *lower*)	1.2	0.7–0.9	<0.0001
Loop diuretics	1.1	1.0–1.2	0.06
Potassium >5.0 mmol/L			
ACE inhibitors in combination with potassium-sparing diuretics	4.0	2.7–5.9	<0.01
GFR (per 10 mL/min/1.73 m^2 lower)	2.0	1.9–2.1	<0.0001
Potassium sparing diuretics	1.9	1.4–2.7	<0.0001
Diabetes	1.7	1.3–2.2	<0.0001
Cyclosporine	1.4	1.1–1.7	<0.001
Weight (per 10 kg *higher*)	1.3	1.2–1.4	<0.0001
ACE inhibitors	1.2	1.02–1.4	0.02
AT2-receptor blockers	1.2	0.9–1.5	0.1

Adjusted for risk factors and drugs with alleged influence on potassium. OR: odds ratio per one defined daily dose (DDD); 95% CI: lower and upper 95% confidence intervals; ACE: angiotensin-converting enzyme; AT2-receptor: angiotensin receptor 2 blocker.

Regression model

Renal function evolved as the strongest predictor of serum potassium ($P < 0.0001$). Log GFR proved to be a better predictor than GFR. Older persons with similar GFR had slightly higher potassium values than younger persons ($\pm$0.01 mmol/L per decade; $P < 0.001$). Male sex was associated with higher serum potassium ($\pm$0.16 mmol/L; $P < 0.0001$). A negative association between blood pressure and potassium was further evident ($P < 0.001$).

Diabetes was associated with significantly higher potassium even after adjustment for body weight ($P < 0.0001$). A mild elevation of potassium in the presence of CHF or liver cirrhosis in the univariate analysis was no longer present after multivariate adjustment; however, a strong potassium-lowering effect could be attributed to vomiting and diarrhoea ($P < 0.0001$) (Figure 1). The effect of ACE inhibitors, and K-sparing diuretics on serum potassium was amplified with decreasing renal function ($P < 0.001$), whereas the potassium-lowering effect of loop-diuretics decreased with lower estimated GFR ($P < 0.0001$). Similarly, liver cirrhosis significantly enhanced the effect of ARBs and loop diuretics on serum potassium ($P < 0.01$). Likewise, the potassium-lowering effect of thiazide diuretics was diminished in CHF (Figure 2).

For ACE inhibitors ($P < 0.0001$), cyclosporine ($P < 0.0001$), K-sparing diuretics ($P < 0.0001$) and surprisingly also inhalative beta stimulants ($P = 0.04$) and laxatives ($P < 0.0001$) a significant association with higher serum potassium was found, whereas the intake of loop diuretics ($P < 0.01$) and thiazides ($P < 0.0001$) was associated with lower values. For several drugs no significant association between dose and serum potassium could be proven in this multivariate analysis (ARBs, betablockers, carboanhydrase inhibitors, digitalis, heparin, NSAIDs, corticosteroids and theophylline). We believe that—despite the relatively large sample size—this is mainly due to limited power. In the case of heparin, the exposure to the drug may have been

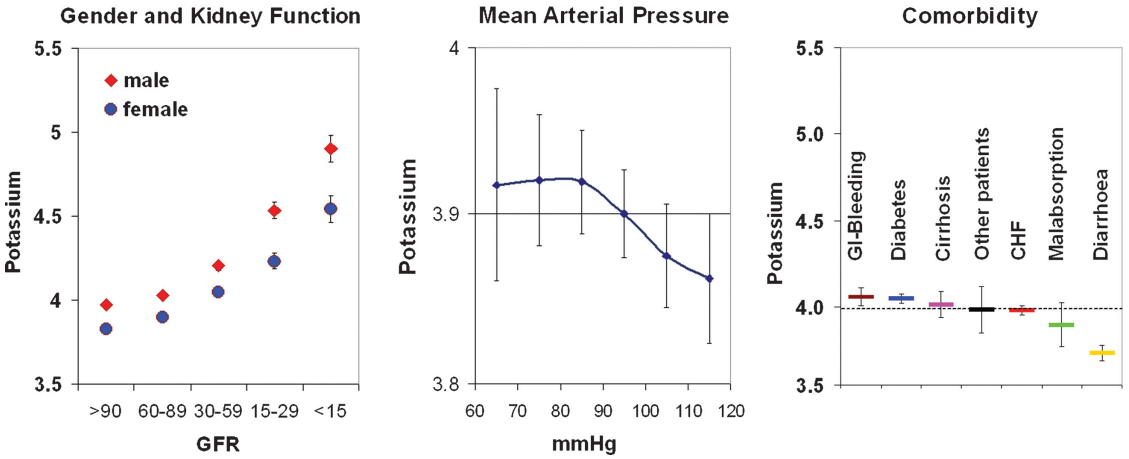

Fig. 1. Effect of patient characteristics and comorbidity on serum potassium. Vertical axis: serum potassium concentration in mmol/l. CHF denotes congestive heart failure. Error bars: 95% confidence limits.

too short, since most persons with heparin were transferred from regional hospitals due to acute coronary syndromes. Nevertheless, the model undoubtedly has to be adjusted for the well-known effects of these compounds. Moreover, many of the latter drugs had significant interactions with other drugs or comorbidity.

Significant additive drug–drug interactions were found for ACE inhibitors with K-sparing diuretics and for betablockers with NSAIDs, whereas the potassium-lowering effect of thiazide diuretics was significantly reduced by ACE inhibitors, NSAIDs and K-sparing diuretics. Similarly ARBs attenuated the potassium-lowering effect of loop diuretics. The R^2, i.e. the explained variance of serum potassium by the regression model, amounted to 0.14.

Discussion

We have shown that in an unselected population admitted to a representative tertiary referral centre, several drugs as well as comorbidities and demographic factors have a significant impact on serum potassium. In addition, the present analysis demonstrates that the potassium-modifying effects of several classes of drugs are altered by renal or hepatic dysfunction. The majority of the identified relationships are in line with the knowledge about pharmacokinetics and pharmacodynamics of the tested drugs, whereas some of them are unexpected, warrant further explanation, or highlight some limitations of our study.

Renal function

As anticipated, we identified a strong inverse relation between GFR and serum potassium. Several mechanisms impair the excretion of potassium with decreasing renal function: (i) decreased delivery of sodium to the distal nephron, (ii) aldosterone deficiency and (iii) abnormal function of the cortical collecting ducts [3]. In addition, hyporeninaemic hypoaldosteronism and metabolic acidosis may contribute to hyperkalaemia. Renal dysfunction additionally enhanced the potassium-retaining effect of cyclosporine and of some inhibitors of the RAA system (see below).

Liver cirrhosis, CHF and blood pressure

Both liver cirrhosis and CHF are commonly associated with secondary hyperaldosteronism [9]. Nevertheless, neither in cirrhosis nor in CHF was a significant reduction of serum potassium found in our adjusted model. This may be attributed to renal sodium sparing. Effective kaliuresis in hyperaldosteronism is only possible if sufficient sodium reaches the distal renal tubule. Intravascular volume depletion (in cirrhosis) with consecutive hyponatraemia due to non-osmotic vasopressin secretion may limit natriuresis and thereby kaliuresis. Indeed, serum sodium concentration was on average 4 mmol/L lower ($P < 0.0001$) in patients with liver cirrhosis than in other patients. Cirrhosis further resulted in a significant amplification of the potassium-modifying effects of ARBs and loop diuretics. This may be explained by potent natriuresis in the case of loop diuretics [10] or an antagonism of hyperaldosteronism (ARBs).

The potassium-lowering effect of thiazide diuretics was mitigated in patients with CHF. This may be attributed to the fact that hypotension reduces the glomerular filtration of sodium and thus kaliuresis [11]. This concept of pressure natriuresis is supported by a significant inverse relationship between blood pressure and serum potassium in our data. However, also an inverse causal association may be true: low potassium intake (with a consecutive deficit of potassium in the body) has been accused of causing hypertension [12].

Inhibitors of the renin–angiotensin–aldosterone system

In patients with CHF, clinical trials have shown a survival benefit for ACE inhibitors and ARBs either alone [13,14] or in combination [15,16]. Interestingly, the rate of hyperkalaemia was very low in these major trials, whereas in unselected outpatients 10% develop hyperkalaemia during 1 year of therapy [17]. We found a strong dose–effect relationship between therapy with ACEIs and serum potassium. Due to an interaction with kidney function, this effect was most pronounced in patients with lower GFR. The effect of ARBs seemed to be much milder and no interaction with

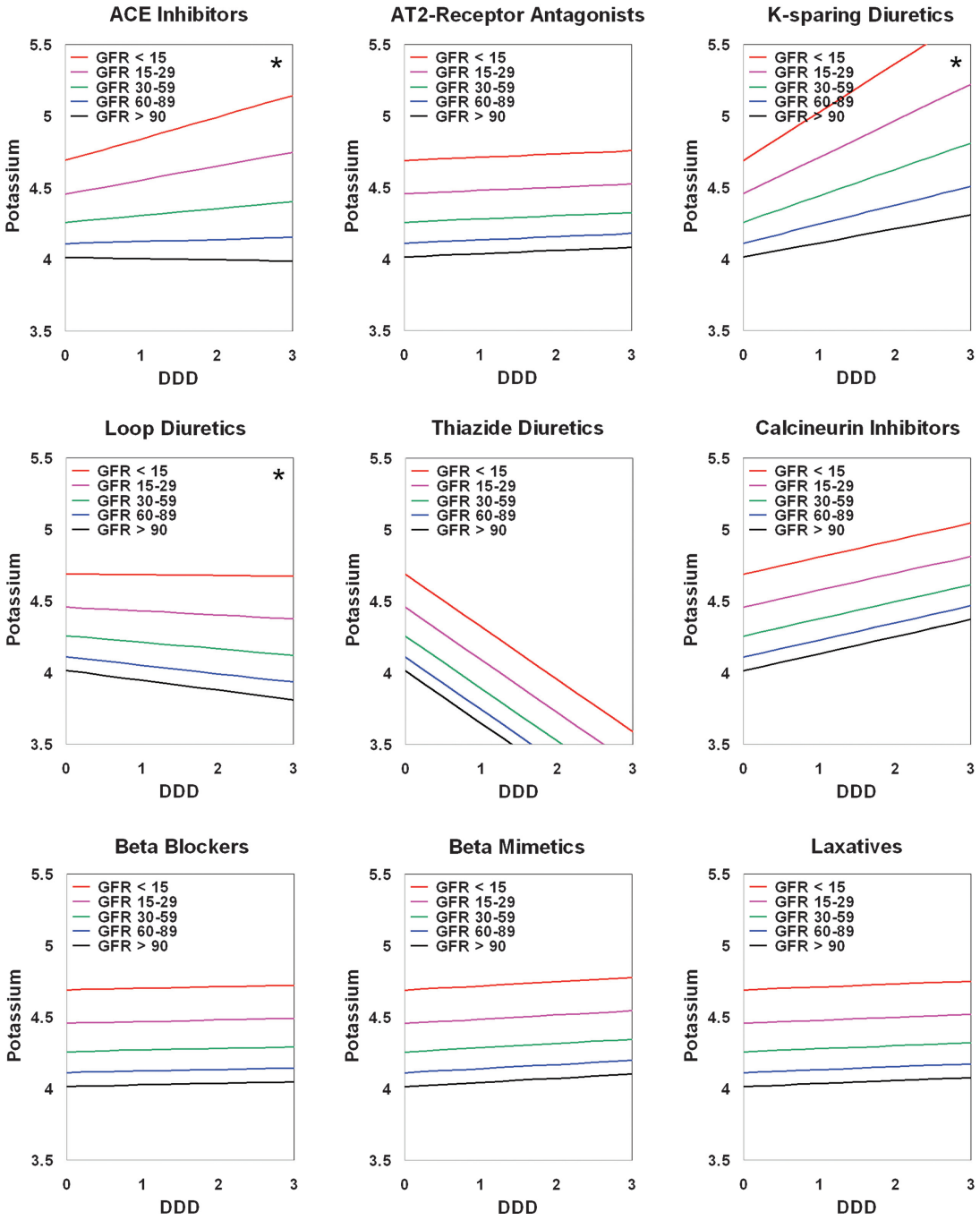

Fig. 2. Effect of drugs on serum potassium. Vertical axis: serum potassium concentration in mmol/l. Horizontal axis: DDD (defined daily dose of a drug class according to WHO definitions). All drug effects are normalized for a 50-year-old male patient with a GFR of 50 ml/min/1.73 m^2 and a body weight of 75 kg. GFR stands for estimated glomerular filtration rate. *A significant interaction between drug and estimated GFR.

kidney function was found for ARBs, which is consistent with earlier trials [18–20]. One explanation for this difference may be that many ACE inhibitors accumulate in renal failure, whereas ARBs are usually eliminated by the liver.

Potassium-sparing diuretics

The intake of K-sparing diuretics was strongly predictive of higher serum potassium, and the magnitude of this effect increased with declining renal function. Spironolactone has been shown to provide additional cardiovascular protection in patients with CHF, maximal therapy and NYHA classes III–IV [21]. The rate of hyperkalaemia in the key study [21] was extremely low (1%), probably due to careful selection [average serum creatinine level was 1.2 mg/dL (106 μmol/L)] and rigorous monitoring of the participating patients. However, there is substantial evidence that the incidence of hyperkalaemia is much higher,

if patients with more advanced renal failure, comorbidities and less intense monitoring undergo the same treatment [22,23]. This holds especially true if several drugs with an influence on the RAA system are combined [24]. Indeed, we found an OR of four for the development of hyperkalaemia if ACEIs were combined with K-sparing diuretics.

Calcineurin inhibitors

Immunosuppressive therapy with calcineurin inhibitors was strongly predictive of elevated potassium levels even after adjustment for hyperkalaemia due to impaired kidney function. Our results are in accordance with previous studies, which found hyperkalaemia in up to 73% of transplant recipients treated with cyclosporine or tacrolimus [25]. The mechanisms of cyclosporine-induced hyperkalaemia seem to include renal tubular dysfunction and secondary hypoaldosteronism [26,27].

Non-steroidal anti-inflammatory drugs

NSAIDs reduce prostaglandin-dependent renin-release and vasodilatation of the renal afferent arteriole. This predisposes to impaired kidney function and hyperkalaemia [11]. In our data, a strong tendency towards higher serum potassium in patients taking NSAIDs was no longer significant after adjustment for renal dysfunction. Therefore, the potential of NSAIDs to increase potassium *beyond* a drug-mediated worsening of kidney function may be rather small. Our analysis, however, suggests a significant potassium-retaining interaction between NSAIDs and beta-blockers as well as thiazide diuretics.

β_2*-mimetics*

In contrast to our expectations we found significantly higher potassium concentrations in patients with a drug history of inhalative β_2-mimetics. These drugs induce a short-term potassium shift into the cell, which has also been documented in several studies for their inhalative forms [28,29]. One explanation for our seemingly paradox findings may be a partial β_2-antagonistic effect of salbutamol. In a state of increased adrenergic tone this effect has been shown to lead to an increase of serum potassium similarly to the effect of beta-blocking agents [30].

Laxatives

The most unexpected finding in our study was a significantly higher serum potassium level in patients taking laxatives. Although hypokalaemia can be observed in laxative abuse, no changes of serum electrolytes is usually found if newer laxatives are taken at the recommended doses [31]. However, the use of laxatives indicates the presence of constipation and patients usually do not overcorrect constipation to the point of inducing diarrhoea. Stool volumes and the consecutive electrolyte losses may thus be smaller in constipated persons even if they report the intake of laxatives. Furthermore constipated persons are often recommended to eat fibre-rich foods. These foods typically contain abundant potassium, which could also explain our seemingly paradox findings.

Hospital databases as sources of pharmacoepidemiologic data

Our study demonstrates that hospital databases can be used to study the effect of drugs in severely ill patients. Many of the patients in this analysis would have been excluded from drug studies due to comorbidity. In recent years, several drugs had to be withdrawn from the market or their indication had to be restricted only after thousands of patients had been exposed to them. Many tragic deaths could have been prevented if the information of hospital databases would systematically be analysed. Unfortunately, this information is often little structured. We therefore propose to define standards for the electronic documentation of medical diagnoses, laboratory data and drug exposure and that the regulatory authorities should have access to the safety signals derived from the analysis of aggregated data in a timely manner [32,33].

Limitations of the study

Our study is retrospective and the analysis is based on the assumption that a steady state is present for all of the included drugs and conditions at hospital admission. This assumption has to be challenged because acute derangements leading to admission, as dehydration or fever, may influence serum electrolytes. Patients might further report to take a prescribed drug although they were incompliant. This leads to an underestimation of the true effect of this drug. On the other hand some drugs may not have been reported, because patients did not consider them to be drugs. Many drugs not only influence the excretion of potassium, but they can also impair kidney function (e.g. cyclosporine). If the effect of the drug is statistically adjusted for the degree of kidney dysfunction, which was also caused by this drug, the true effect of the drug on potassium is again underestimated. Finally, our model only explains 14% of the variation of serum potassium. The residual variation may primarily be caused by large interindividual variations of potassium intake with food. However, it could also be the consequence of genetic differences in the handling of potassium, drug metabolism and differences at the molecular site of drug action, which have yet to be elucidated.

Conclusions

Despite these limitations several conclusions can be drawn from the present analysis. Renal function is the strongest single predictor of serum potassium at hospital admission. The effects of various drugs are significantly influenced by comedication and comorbidity. As the studied drugs and diseases are common, our analysis adds to the understanding of disturbances of serum potassium in patients with several comorbidities and who are treated with a large number of different drugs. Finally, our analysis demonstrates that

hospital databases could provide cheap and reliant information for the analysis of post-marketing drug safety.

Conflict of interest statement. This study was in part supported by educational grants of AstraZeneca and Pfizer. These companies had neither a role in the study design nor in the analysis of data or the writing process. The investigators were completely independent of the funding source. All authors state that they have no potential conflicts of interest to declare.

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