Eur J Clin Pharmacol (2014) 70:215–223
DOI 10.1007/s00228-013-1597-2

PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Patient- and physician-related risk factors for hyperkalaemia in potassium-increasing drug–drug interactions

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Received: 2 August 2013 / Accepted: 30 September 2013 / Published online: 23 October 2013

Abstract
Purpose Hyperkalaemia due to potassium-increasing drug–drug interactions (DDIs) is a clinically important adverse drug event. The purpose of this study was to identify patient- and physician-related risk factors for the development of hyperkalaemia.
Methods The risk for adult patients hospitalised in the University Hospital Zurich between 1 December 2009 and 31 December 2011 of developing hyperkalaemia was correlated with patient characteristics, number, type and duration of potassium-increasing DDIs and frequency of serum potassium monitoring.
Results The 76,467 patients included in this study were prescribed 8,413 potentially severe potassium-increasing DDIs. Patient-related characteristics associated with the development of hyperkalaemia were pulmonary allograft [relative risk (RR) 5.1; $p<0.0001$), impaired renal function (RR 2.7; $p<0.0001$), diabetes mellitus (RR 1.6; $p=0.002$) and female gender (RR 1.5; $p=0.007$). Risk factors associated with medication were number of concurrently administered potassium-increasing drugs (RR 3.3 per additional drug; $p<0.0001$) and longer duration of the DDI (RR 4.9 for duration ≥6 days; $p<0.0001$). Physician-related factors associated with the development of hyperkalaemia were undetermined or elevated serum potassium level before treatment initiation (RR 2.2; $p<0.001$) and infrequent monitoring of serum potassium during a DDI (interval >48 h: RR 1.6; $p<0.01$).
Conclusion Strategies for reducing the risk of hyperkalaemia during potassium-increasing DDIs should consider both patient- and physician-related risk factors.

Keywords Drug–drug interactions · Hyperkalaemia · Monitoring · Potassium · Risk factors

Introduction

Although drug–drug interactions (DDIs) are often preventable, they constitute an important cause of adverse drug events leading to increased morbidity and mortality [1–3]. Potassium-increasing DDIs are among the most common DDIs, occurring in up to 10 % of hospitalised patients [4, 5]. Such DDIs may induce hyperkalaemia and life-threatening cardiac arrhythmias [6].

It is a challenge for physicians to identify potentially harmful potassium-increasing DDIs due to polypharmacy and the increasing number of therapeutic agents. Computerized physician order entry (CPOE) technology in combination with clinical decision support systems (CDSS) may help the prescribing physician(s) to detect DDIs and alerts them to a potential problem. However, these systems are often based on DDI knowledge databases which do not take patient characteristics into account, resulting in a low specificity of

Electronic supplementary material The online version of this article (doi:10.1007/s00228-013-1597-2) contains supplementary material, which is available to authorized users.

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alerts, overalerting and alert fatigue [7–10]. In order to avoid alert fatigue the University Hospital Zurich has implemented on-demand DDI checks into the electronic health record [11].

Several published studies have analysed the risk factors for developing hyperkalaemia during potassium-increasing DDIs, with a focus on patient-related risk factors, such as demographic parameters and comorbidities, and on medication, such as number and types of drugs involved [12–18]. One study considered the effect of potassium monitoring during potassium-increasing DDIs in outpatients [19]. To our knowledge, no study has as yet investigated the effect of physician-related risk factors, such as missing serum potassium measurement at the start of therapy and periodicity of serum potassium monitoring during drug therapy in hospitalised patients.

The purpose of this study was to identify patient- and physician-related risk factors for the development of hyperkalaemia. Such information may provide a foundation for the implementation of strategies for reducing the risk of hyperkalaemia during potassium-increasing DDIs without overalerting.

Methods

Setting

The University Hospital Zurich is a publicly owned, tertiary care academic medical centre with 850 beds and 35,000 hospital admissions per year. We included all in-patients from 1 December 2009 to 31 December 2011 except for patients on dialysis and those hospitalized exclusively in intensive care units.

The local research ethics committee approved the analyses, and patient consent was waived.

Drug–drug interactions and potassium-increasing drugs

Drug–drug interactions were identified using the knowledge base galdat/hospINDEX (distributed by e-mediat AG, Berne, Switzerland—derived from ABDATA Pharma-Daten Service, Werbe- und Vertriebsgesellschaft Deutscher Apotheker, Eschborn, Germany), which tiers DDIs by severity (severity level 1: recommended activity 'contraindicated'; 2: 'contraindicated as precaution',3: 'monitoring or adaptation required', 4: 'monitoring or adaption in case of risk factors', 5: 'monitoring as a precaution', 6: 'no activity required') [20]. DDIs with severity levels 1 to 3 were considered to be severe.

Potassium-increasing drugs (PIDs) were defined as drugs involved in severe potassium-increasing DDIs according to the knowledge base galdat/hospINDEX. Thus, PIDs included angiotensin-converting enzyme inhibitors (ACE inhibitors), angiotensin antagonists (angiotensin-receptor blockers), direct renin inhibitors, immunosuppressive agents (calcineurin inhibitors), potassium-sparing diuretics (aldosterone-receptor antagonists and epithelial sodium channel blockers), potassium supplements and trimethoprim (ingredient of cotrimoxazole), irrespective of whether these drugs were ordered as a monotherapy or participated in a DDI.

Serum potassium measurements

Serum potassium levels were categorized into four groups: (1) hypokalaemia: serum potassium ≤3.2 mEq/l [21]; (2) reference range: ≥3.3 mEq/l to ≤4.5 mEq/l [22]; (3) moderately increased: ≥4.6 mEq/l to ≤5.4 mEq/l; (4) hyperkalaemia: ≥5.5 mEq/l [12].

The following parameters, explored for their association with hyperkalaemia, need to be defined:

(1) Estimated glomerular filtration rate (GFR) was calculated using the Cockcroft–Gault equation [23] with the first serum creatinine level measured during DDI± 1 day. The kidney dysfunction categories 'normal', 'mild' and 'moderate to severe' were assigned to a GFR of ≥90 ml/min, 60 ml/min ≤ GFR < 90 ml/min and GFR <60 ml/min, respectively [24].
(2) Blood transfusions were identified by ICD-9 (International Classification of Diseases, World Health Organization, Geneva, Switzerland) treatment code 99.0.
(3) Comorbidities were identified using ICD-10 discharge diagnosis codes E10, E11, E12, E13, and E14 for diabetes mellitus, code I10 for arterial hypertension, code I50 for heart failure, codes I50.11 and I50.12 for NYHA class I/II, codes I50.13 and I50.14 for NYHA class III/IV and code Z94.2 for pulmonary allograft.

Statistical analyses

Data analyses and statistical tests were performed using the R language and environment for statistical computing, version 2.15.1 (R Foundation for Statistical Computing, Vienna, Austria). p levels of ≤0.05 were considered to be statistically significant. The two-tailed chi-square test was used to analyse categorical data of 2×2 contingency tables. p levels for multiple comparisons were adjusted using the Holm correction [25]. Binomial confidence intervals were calculated using the Clopper–Pearson method [26].

Results

We analysed data of 76,467 inpatients. Mean duration of hospitalisation for all patients and for patients with potassium-increasing DDIs was 6.9 and 13.5 days, respectively. Patients'

characteristics are listed in the Electronic Supplementary Material (ESM) 1.

A total of 1,543,578 drugs were prescribed, resulting in 20.1 drugs per patient on average. PIDs accounted for 5.0 % of all drug prescriptions. Potassium supplements were the most frequently ordered PIDs (30 % of all PID prescriptions), followed by immunosuppressive agents (21 %), ACE inhibitors (20 %), angiotensin antagonists (14 %), trimethoprim (9 %), potassium-sparing diuretics (6 %) and direct renin inhibitors (0.3 %).

Drug–drug interactions

We identified 197,351 potential DDIs (2.6 per patient) in the included patients, of which 90,811 were classified as severe (1.2 per patient). The 8,413 potassium-increasing DDIs constituted the largest part of level-1 DDIs (972 of 1,402 DDIs) and also played an important role in level-3 DDIs (7,441 of 84,093 DDIs).

In 17 % of the potassium-increasing DDIs, treatment had been started in the absence of a serum potassium measurement within the preceding 48 h. Moreover, 60 potassium-increasing DDIs (0.7 %) were initiated despite the presence of hyperkalaemia. The histogram of the last serum potassium levels measured within 48 h prior to a potassium-increasing DDI shows a bimodal distribution (Fig. 1), with one peak in the hypokalaemic range and another one in the reference range. Most of the therapies that were started with the patient in the hypokalaemic range included a potassium supplement, suggesting that these therapies were purposely prescribed to correct the low potassium level.

The frequency of daily serum potassium level measurements decreased from 72 % on the day before the DDI to 59 % on the first day of the DDI and remained between 46 and 53 % during the next 2 weeks (the frequencies per day are shown in ESM 2).

The intervals between serum level measurements during potassium-increasing DDIs showed a wide range (median interval 24 h) with 84.8 % of the serum level measurements embedded in intervals of ≤48 h. Thus, 15.2 % of the monitoring intervals exceeded 48 h (the frequency distribution of serum potassium monitoring intervals is presented in ESM 3). Similar monitoring frequencies were observed in surgical and non-surgical specialties, with the median monitoring period in both groups being 1.0 days. In surgical specialties the monitoring intervals exceeded 48 and 96 h in 14.3 and 2.3 % of DDIs, respectively; in non-surgical specialties the respective numbers were 15.6 and 2.5 %.

Hyperkalaemia

The occurrences of hyperkalaemia were analysed after the exclusion of DDIs started in the presence of hyperkalaemia (60 DDIs in 28 patients), leaving 8,353 potassium-increasing DDIs in 5,609 patients for further analysis. Hyperkalaemia was observed during 161 DDIs involving 78 patients. A further increased serum potassium level of >6.0 mEq/l occurred during 31 DDIs observed in 15 patients.

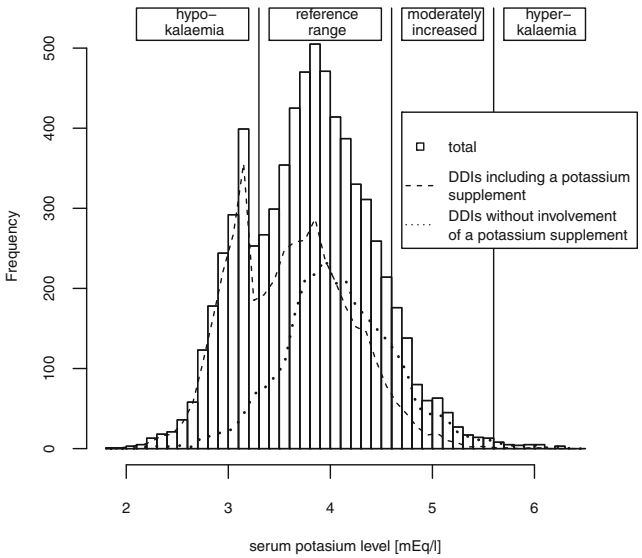

Fig. 1 Last serum potassium level measured within 48 h prior to initiation of potassium-increasing drug–drug interactions (*DDIs*) with and without potassium supplements

Two physician-related risk factors for hyperkalaemia were the consideration of the initial serum potassium level and the serum potassium monitoring frequency. First, the initiation of a potassium-increasing DDI with either an undetermined or an elevated (>4.5 mEq/l) serum potassium level (2,252 DDIs, 71 with hyperkalaemia during DDI) was associated with an increased relative risk (RR) of 2.2 of developing hyperkalaemia, compared to starting a DDI at normokalaemic or hypokalaemic levels (6,101 DDIs, 90 with hyperkalaemia during DDI; chi-square test $p<0.001$). Second, monitoring intervals exceeding 48 h during the interaction period were associated with a higher risk of hyperkalaemia: a new hyperkalaemia event was detected in 1.00 % (36 out of 3,635) of the serum potassium levels measured more than 48 h after the preceding measurement, compared to 0.61 % (122 out of 20,092) when levels were measured within 48 h (chi-square test: $p<0.01$). Three medication factors were associated with the development of hyperkalaemia:

(1) The higher the number of PIDs concurrently administered, the higher the risk for hyperkalaemia (Table 1). Starting with a RR of 1 for patients without PIDs, the RR increased to 3.9 for PID monotherapies (chi-square test: $p<0.001$) and 5.7 for therapies with two concurrent PIDs ($p=0.040$), peaking at 18.1 for three or more concurrent PIDs ($p<0.001$). The triple PID combination of immunosuppressive agents + trimethoprim + ACE inhibitor achieved the

highest RR of 29. Nevertheless, the absolute risk was low, with hyperkalaemia occurrences of 0.7, 1.0 and 3.3 % for patients treated with one, two or more than two PIDs, respectively.

(2) The duration of potassium-increasing DDIs was significantly associated with hyperkalaemia (Table 2).

(3) A high number of concurrently administered potassium-decreasing drugs were associated with a higher risk of hyperkalaemia (Table 2). Blood transfusions showed a non-significant trend towards an increased risk of hyperkalaemia.

Five out of seven electronically available patient-related characteristics predicted the development of hyperkalaemia in a univariate analysis (Table 2): (1) female gender, (2) renal impairment, (3) diabetes mellitus, (4) pulmonary allograft and (5) serum potassium level exceeding the normokalaemic range before onset of potassium-increasing DDI.

The effect of renal impairment on the risk of hyperkalaemia was analysed in greater detail as a function of the number of concurrently administered PIDs (Fig. 2). The risk significantly increased for patients with moderate to severe kidney impairment compared to patients with mild kidney impairment. Hyperkalaemia observed during potassium-increasing DDIs was associated with a significantly increased risk of transfer to the intensive care unit (ICU) or death (Table 3). The risk of death within 2 days after detecting hyperkalaemia was 5.3-fold higher than that for non-hyperkalaemic patients also treated with concurrent PIDs. The likelihood of being transferred to the ICU was 1.9-fold higher for hyperkalaemic patients than for non-hyperkalaemic ones. Furthermore, the length of hospitalisation increased significantly for patients with hyperkalaemia during potassium-increasing DDIs.

Table 1 Occurrences of hyperkalaemia as a function of concurrent administration of potassium-increasing drugs

Therapy		Hyperkalaemia	
No. of concurrent PID administrations and PIDs involved in concurrent administrations	Total no. of patients[a]	No. of patients	Per total
No PID administration	30,723	56	0.2 %
PID monotherapy[b]	17,010	122	0.7 %
Concurrent administration of 2 PIDs	4,221[e]	44	1.0 %
ACE inhibitor or angiotensin antagonist + potassium supplement	2,311	24	1.0 %
ACE inhibitor or angiotensin antagonist + potassium-sparing diuretic	824	9	1.1 %
Trimethoprim[c] + PIDs	418	3	0.7 %
Potassium-sparing diuretic + potassium supplement	380	6	1.6 %
Immunosuppressive agent + PID	353	2	0.6 %
Concurrent administration of 3 or more PIDs[d]	1,028	34	3.3 %
ACE inhibitor or angiotensin antagonist + potassium-sparing diuretic + potassium supplement	380	10	2.6 %
Immunosuppressive agent + trimethoprim[c] plus PID	359	19	5.3 %
ACE inhibitor or angiotensin antagonist + potassium supplement + trimethoprim[c]	245	2	0.8 %

PIDs, Potassium-increasing drugs; ACE, angiotensin converting enzyme

[a] Patients with at least one serum potassium level measurement within 48 h prior to onset of therapy, with the last value not being hyperkalaemic (no time restriction for patients with no PID administration)

[b] Involved the PIDs (in decreasing order of monotherapy leading to hyperkalaemia): potassium supplements, trimethoprim, immunosuppressive agents (calcineurin inhibitors), ACE inhibitors, angiotensin antagonists, potassium-sparing diuretics and direct renin inhibitors

[c] Trimethoprim is part of the combination antibiotic cotrimoxazole (sulfomethoxazole and trimethoprim) used as therapy or prophylaxis for certain infections

[d] Concurrent DDIs with <100 patients exposed were not considered

[e] Total of patients exposed – sum of patients exposed, as the same patient might have been considered for two different potassium-increasing DDI groups if they were not overlapping

Discussion

A number of patient- and physician-related factors have been analysed to identify characteristics associated with the development of hyperkalaemia during potassium-increasing DDIs.

The results of this study demonstrate that physician-related factors affect the risk for developing hyperkalaemia in hospitalised patients. First, less frequent monitoring of serum potassium during DDI was associated with an increased risk of hyperkalaemia, likely because the rapid development of hyperkalaemia may be missed with longer monitoring intervals [27] and subsequent therapy adjustments may be delayed. Among our patient cohort, the frequency of serum potassium level measurements decreased after the first day of DDI (as shown in ESM 2), despite the finding that the risk of hyperkalaemia increased with a longer DDI duration (Table 2). Secondly, the lack of serum level monitoring at onset of potassium-increasing DDIs correlated with an increased risk for developing hyperkalaemia (Table 2). This association has been reported in a previous study on outpatients [19].

Medication also affected the risk for hyperkalaemia. As expected, the risk for hyperkalaemia increased with the number of concurrently administered PIDs. Surprisingly, the risk of hyperkalaemia also rose with a growing number of concurrent potassium-decreasing drugs. A possible explanation for this finding might be that potassium-decreasing drugs were used to correct higher serum potassium

Table 2 Development of hyperkalaemia during potassium-increasing DDIs as a function of selected parameters

Group	Characteristic	Property	Total no. of potassium-increasing DDIs	No. of potassium-increasing DDIs with hyperkalaemia	Percentage of DDIs with hyperkalaemia	Relative risk (95 % CI)	Chi-square test
Overall			8,353	161	1.9		
Demographics	Age (years) (in rounded-off quartiles)	<57	2,147	54	2.5	1.00	0.0984
		≥57, <66	2,076	32	1.5	0.62 (0.40–0.95)	
		≥66, <75	1,983	39	2.0	0.79 (0.52–1.19)	
		≥75	2,147	36	1.7	0.67 (0.44–1.02)	
	Gender	Male	5,041	80	1.6	1.00	0.0067*
		Female	3,312	81	2.5	1.53 (1.13–2.07)	
Therapy	Severity level of potassium-increasing DDI[a]	1	968	20	2.1	1.00	0.8341
		3	7,385	141	1.9	0.92 (0.58–1.47)	
	Duration of potassium-increasing DDI (days) (in rounded-off quartiles)	<1	1,938	14	0.7	1.00	<0.0001*
		≥1, <3	2,506	29	1.2	1.60 (0.85–3.01)	
		≥3, <6	1,856	46	2.5	3.37 (1.86–6.11)	
		≥6	2,053	72	3.5	4.72 (2.67–8.35)	
	Number of concurrent potassium-decreasing drugs[b]	0	2,092	38	1.8	1.00	0.0027*
		1	4,150	64	1.5	0.85 (0.57–1.27)	
		≥2	2,111	59	2.8	1.52 (1.02–2.28)	
	Recent blood transfusion[c]	No	8,000	148	1.9	1.00	0.0243
		Yes	353	13	3.7	1.96 (1.12–3.41)	
Comorbidities	Renal function (estimated GFR) (in ml/min)	≥90	2,429	29	1.2	1.00	<0.0001*
		≥60 to<0	2,313	38	1.6	1.37 (0.85–2.21)	
		<60	2,727	87	3.2	2.62 (1.73-3.98)	
		Unknown[d]	884	7	0.8	0.67 (0.29–1.51)	
	Diabetes mellitus	No	6,231	103	1.7	1.00	0.0024*
		Yes	2,122	58	2.7	1.64 (1.19–2.25)	
	Primary arterial hypertension	No	3,855	71	1.8	1.00	0.6545
		Yes	4,498	90	2.0		

Table 2 (continued)

Group	Characteristic	Property	Total no. of potassium-increasing DDIs	No. of potassium-increasing DDIs with hyperkalaemia	Percentage of DDIs with hyperkalaemia	Relative risk (95 % CI)	Chi-square test
						1.08 (0.80–1.48)	
	lung transplant	No	7,757	116	1.5	1.00	<0.0001*
		Yes	596	45	7.6	4.76 (3.41–6.66)	
Progression parameters	Last serum potassium before onset of DDI[e]	Hypokalaemic	1,390	21	1.5	1.03 (0.63–1.67)	<0.0001*
		Normokalaemic	4,711	69	1.5	1.00	
		>4.5 mEq/l	815	36	4.4	2.93 (1.97–4.36)	
		Unknown[d]	1,437	35	2.4	1.65 (1.10–2.46)	
Department		Surgical specialties	3,408	63	1.8	1.00	0.7232
		Non-surgical specialties	4,945	98	2.0	1.07 (0.78–1.46)	

*Significant using the Holm correction for multiple testing (with $\alpha=0.05$, $n=12$)

DDI, Drug–drug interaction; GFR, glomerular filtration rate; CI, confidence interval

[a] Co-administration of potassium-sparing diuretics + potassium supplements is the only severity level 1 ("contraindicated") potassium-increasing DDI listed in the used knowledge database. All other potassium-increasing DDIs included in this study are classified as severity level 3 DDIs ("monitoring or adaptation required")

[b] Prescriptions of kaliuretic diuretics coexisting at onset of potassium-increasing DDIs

[c] Administered between the day prior to the DDI and the end of DDI

[d] Not considered in chi-square test

[e] Maximum of 48 h before onset of DDI

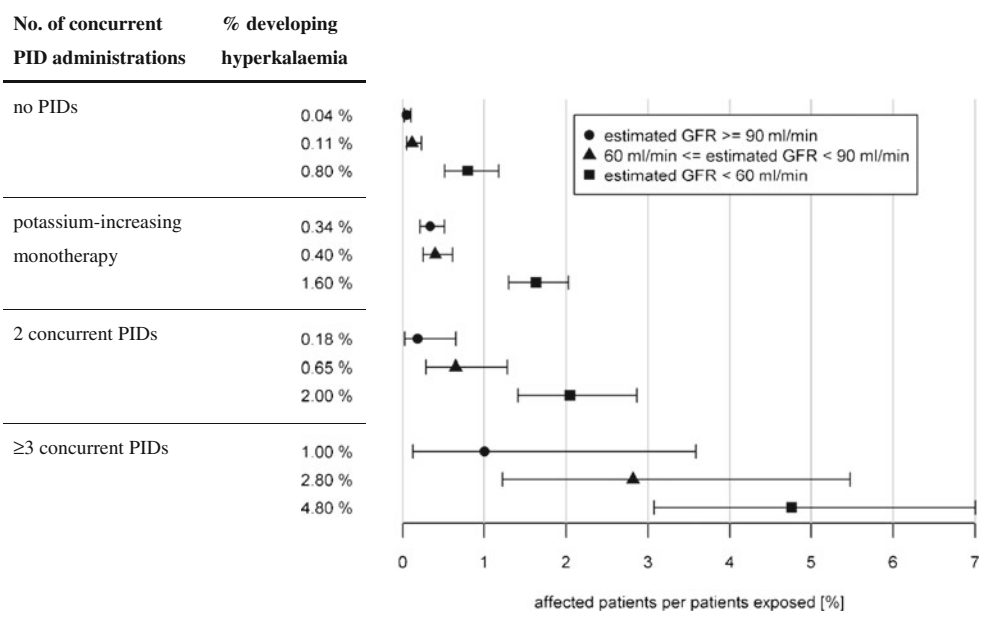

Fig. 2 Occurrences of hyperkalaemia as a function of the number of concurrently administered potassium-increasing drugs (*PIDs*) categorized by the estimated glomerular filtration rate (*GFR*); inclusion and exclusion criteria based on those of Table 1, whereby only patients for whom an GFR estimation was available were considered. */Symbols* Mean, *Lines* encompass a 95 % confidence interval

levels. Thirdly, the level of severity of the involved DDIs was not predictive for the likelihood of developing hyperkalaemia. This might be due to the frequent usage of the contraindicated level-1 potassium-increasing DDI (i.e. the combination of potassium-sparing diuretics with potassium supplements) to correct a hypokalaemia (Fig. 1) [10] including a high degree of physician awareness [28]. The agreement on whether these DDIs should indeed be labelled contraindicated is low [29, 30].

Finally, the results of our study confirmed that specific patient-related characteristics are associated with the development of hyperkalaemia. These include moderately or severely impaired renal function (Fig. 2), diabetes mellitus [6, 31], pulmonary allograft (which was associated with the highest risk mainly due to PID combinations of immunosuppressive agents, trimethoprim and ACE inhibitor) [32, 33], female gender (confirming another analysis of gender as a predictor of drug-induced hyperkalaemia [34]) and elevated serum potassium level (>4.5 mEq/l) at onset of the DDI.

In contrast to other studies, we were unable to establish an association between hyperkalaemia during potassium-increasing DDIs and age or hospitalisation in surgical versus non-surgical specialties [12].

There are limitations to our analysis. Dosing of PID prescriptions was not considered. Only DDIs between two specific drugs were explored. PIDs not listed in the DDI knowledge base, such as nonsteroidal anti-inflammatory drugs or heparin, were not taken into account.

The association between the presence of hyperkalaemia during potassium-increasing DDIs and transfer to the ICU or death within 2 days was considered to be statistically significant. However, the positive correlation does not imply causation, since the relationship is influenced by comorbidities and therapies. Overall, the risk of developing hyperkalaemia was low, occurring only in one of 50 potassium-increasing DDIs in our study. This is in line with other reports [28].

Despite infrequent occurrences, hyperkalaemias must be detected in order to avoid severe complications. Clinical decision support systems may help the prescribing physicians to adjust the therapy early. However, unspecific alerts will lead to alert fatigue [7–9]. The results of our study improve our understanding of factors associated with hyperkalaemia [12] and add physician-related factors, which may help to design more specific alerts.

Table 3 Correlation of death, transfer to intensive care unit and length of stay with the presence and absence of hyperkalaemia during potassium-increasing drug–drug interactions

Effect	Patients with hyperkalaemia during potassium-increasing DDIs	Patients without hyperkalaemia during potassium-increasing DDIs
Death*	5/103 (4.9 %)[a]	50/5,506 (0.9 %)[b]
Transfer to ICU*	9/103 (8.7 %)[a]	245/5,506 (4.5 %)[b]
Length of hospitalisation (days)**	26.8±26.5[c]	12.2±13.8[c]

*Significant increase at $p < 0.05$ (chi-square test); **significant increase at $p < 0.001$ (Mann–Whitney test)

[a] Death or transfer to ICU within 2 days of occurrence of hyperkalaemia

[b] Death or transfer to ICU during or <2 days after potassium-increasing DDI

[c] Mean ± standard deviation

Conclusions

Strategies for the prevention of hyperkalaemia during treatment with potassium-increasing drugs should consider both patient- and physician-related characteristics. Patient-related factors include impaired renal function, diabetes mellitus and pulmonary allograft. Risk factors associated with medication include a higher number of concurrently administered PIDs and a longer DDI duration. Physician-related factors include undetermined or elevated serum potassium levels before the initiation of treatment and inadequate frequency of potassium monitoring during DDIs. Therefore, the systematic measuring of serum potassium levels before therapies involving potassium-increasing DDIs are prescribed and periodic monitoring are essential for reducing the risk of hyperkalaemia.

Disclosure of conflict of interests None.

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