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Risk Factors Associated with a High Velocity of the Development of Hyperkalaemia in Hospitalised Patients

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Abstract

Background/objective: Drugs have been recognised as a primary or contributing cause of hyperkalaemia, especially when administered to patients with underlying risk factors. The objective of this study was to analyse the influence of the known risk factors for hyperkalaemia on the velocity of the development of hyperkalaemia.

Study design/methods: Clinical characteristics, laboratory data and medication profiles of patients developing hyperkalaemia (serum potassium ≥5.0 mmol/L) hospitalised between 2000 and 2004 in the University Hospital Basel, Switzerland, were recorded. Factors associated with a high velocity of the development of hyperkalaemia were detected using a multiple logistic regression model. Subsequently, the velocity during a defined observation period was compared between patients with one risk factor and patients with two or more risk factors. Finally, the dose effects of drugs identified as risk factors for a high velocity of the development of hyperkalaemia were analysed using two sample comparisons.

Results: A random sample of 551 hospitalised patients was analysed. Compared with the drug treatment at entry, significantly more patients during the hospitalisation were treated with drugs associated with hyperkalaemia, such as heparins ($p < 0.001$), ACE inhibitors or angiotensin receptor blockers (ARBs) [$p = 0.002$], potassium supplements ($p < 0.001$), potassium-sparing diuretics ($p < 0.001$) and/or NSAIDs or selective cyclo-oxygenase (COX)-2 inhibitors ($p < 0.001$). Risk factors associated with a high velocity of the development of hyperkalaemia were use of potassium supplements (adjusted odds ratio [OR] 3.386; 95% CI 2.251, 5.091), severe renal impairment (OR 3.119; 95% CI 2.007, 4.850), use of ACE inhibitors or ARBs (OR 2.642; 95% CI 1.742, 4.006), use of potassium-sparing diuretics (OR 2.065; 95% CI 1.310, 3.254), and diabetes mellitus (OR 1.525; 95% CI 1.005, 2.313). The velocity of the development of hyperkalaemia significantly increased in patients with two or more risk factors. Dose effects could be found for potassium supplements ($p = 0.006$) and potassium-sparing diuretics ($p = 0.007$), but not for ACE inhibitors or ARBs ($p = 0.289$). In contrast, the use of kaliuretics (loop diuretics or thiazides) was associated with a decreased velocity of the

development of hyperkalaemia in patients with serious renal impairment (p = 0.016) and in patients treated with two or more drug classes associated with a high velocity of the development of hyperkalaemia (p = 0.001).
Conclusions: Risk factors associated with a high velocity of the development of hyperkalaemia are use of potassium supplements > severe renal impairment > use of ACE inhibitors or ARBs > use of potassium-sparing diuretics > diabetes mellitus. The presence of two or more of these risk factors is associated with an even faster development of hyperkalaemia. Clinicians should be aware of these risk factors in order to avoid a rapid development of potentially life-threatening hyperkalaemia.

Background

Potassium disorders belong to the most frequent electrolyte abnormalities in clinical practice. Hyperkalaemia is less common than hypokalaemia but potentially more serious, especially if potassium levels are rising rapidly.[1] In hospital settings, drugs have been recognised as a major cause of hyperkalaemia in up to 75% patients presenting with this electrolyte abnormality.[2] Reported incidences of hyperkalaemia vary from 1.1% to 10%, depending on the threshold used for hyperkalaemia, which ranges from 5.0 to 6.0 mmol/L.[2,3]

Several drugs have been identified as a primary or contributing cause of hyperkalaemia.[2,4,5] Especially when administered to patients with underlying disturbances in potassium homeostasis, hyperkalaemia induced by these drugs can occasionally become life-threatening.[2] Pitt et al.[6] and Juurlink et al.[7] recognised increasing rates of hyperkalaemia due to the widespread use of spironolactone after the publication of the RALES (Randomised Aldactone Evaluation Study). Use in patients with pre-existing risk factors for hyperkalaemia, inappropriately high doses of spironolactone, additional medications contributing to hyperkalaemia, inadequate clinical or laboratory monitoring and no clear indication for critical drugs were considered to be major causes for the increasing occurrence of hyperkalaemia.[8,9] However, the reality is that spironolactone is often prescribed to patients with additional drug and non-drug-related risk factors for hyperkalaemia.[9] Most patients found to develop life-threatening hyperkalaemia while being treated with ACE inhibitors or angiotensin receptor blockers (ARBs) and spironolactone had additional risk factors including renal failure, diabetes mellitus and/or treatment with NSAIDs.[10,11]

Combinations of potassium-sparing diuretics, potassium supplements and ACE inhibitors or ARBs interact with each other because of their additive pharmacodynamic effects.[12] In a study performed at the University Hospital of Basel, Switzerland, potential drug interactions between potassium-sparing diuretics, potassium supplements and ACE inhibitors were most prevalent compared with other potentially severe drug interactions in patients at discharge.[13] Furthermore, besides drug interactions with HMG-CoA reductase inhibitors (statins), the combination of ACE inhibitors and potassium-sparing diuretics was the most prevalent potentially severe drug interaction in ambulatory dyslipidaemic patients.[14] Additional drugs, for instance NSAIDs, selective cyclo-oxygenase (COX)-2 inhibitors, non-selective β-adrenoceptor antagonists, ciclosporin, digoxin, drospirenone, heparins, lithium, pentamidine, suxamethonium chloride, tacrolimus, trimethoprim and drugs administered as a potassium salt as well as potassium-containing salt substitutes have been reported to be associated with hyperkalaemia.[2,4,12] Furthermore, case-control studies with multivariate analyses have revealed that diabetes mellitus, renal impairment and the use of spironolactone or the use of ACE inhibitors are independent risk factors for hyperkalaemia in hospitalised patients with congestive heart failure.[15,16]

Although the velocity of the increase in serum potassium levels appears to be a risk factor for the development of adverse effects associated with hyperkalaemia,[1] the risk factors associated with a high speed for the development of hyperkalaemia have so far not been investigated. The objective of

this study was therefore to analyse the influence of single and multiple drug and non-drug-related risk factors on the velocity of the development of hyperkalaemia in hospitalised patients.

Methods

Study Design, Patients and Data Collection

A random sample of patients developing hyperkalaemia (serum potassium levels ≥5.0 mmol/L[5]) during their hospitalisation between January 2000 and March 2004 in four general medical wards of the University Hospital of Basel was retrospectively identified using electronic clinical laboratory records. The University Hospital Basel is a medical-surgical teaching institution covering an urban area of approximately 300 000 inhabitants in the Northwest of Switzerland.

Laboratory data, drug and non-drug-related risk factors for hyperkalaemia (identified as described below) were assessed for a minimum period of 2 days and maximum period of 10 days, beginning at the date when the patient's serum potassium level began to rise until the date when the maximal value was measured (observation period). Information on drugs, demographic characteristics (age, sex, size and weight), major diagnoses and treatments were retrieved from the patient records. Since it was assumed that the risk factors associated with a high velocity of the development of hyperkalaemia were among the risk factors associated with hyperkalaemia itself, such risk factors were identified in recent publications. Non-drug-related risk factors were obtained from the review of Evans and Greenberg,[5] and drugs potentially interfering with potassium homeostasis were retrieved from the recent reviews of Perazella,[2] Palmer[4] and Evans and Greenberg.[5] In addition, all drugs stopped or added within 2 days prior to the observation period were also included in the analysis.

Patients receiving long-term haemodialysis, surgical patients and patients with hyperkalaemia on hospital admission were not included in the study. The minimal increase in serum potassium levels had to be 0.5 mmol/L, and at least two serum potassium levels (in addition to the level obtained at entrance) had to be measured during one admission. Patients with serum potassium levels >4.5 mmol/L at the beginning of the observation period were also not included in the study. Pseudohyperkalaemic patients were recognised based on comments of the chemical laboratory mentioning haemolysed samples and could therefore be excluded from the analysis. Creatinine clearance (CrCl) was estimated by the Cockroft-Gault formula.[17] Severe renal impairment was defined as CrCl <30 mL/min. The velocity of the development of hyperkalaemia was calculated as the mean daily increase in serum potassium over the observation period in mmol/L per day and is given as (equation 1):

$$\frac{\text{max serum } K^+ \text{ level} - \text{min serum } K^+ \text{ level}}{\text{number of days between these two measurements}} \quad \text{(Eq. 1)}$$

For the majority of patients, more than two potassium serum levels were obtained during the observation period. To analyse the influence of the daily dose of drugs associated with a higher velocity of the development of hyperkalaemia, high and low daily doses were defined for each drug. These definitions were based on the defined daily dose (DDD) by the WHO Collaborating Centre for Drug Statistics Methodology. A 'high dose' was defined as a daily dose >DDD. For spironolactone daily doses >25mg were considered to be a 'high dose'.[4] The study protocol was approved and accepted by the regional ethics committee.

Statistical Analysis

Results are expressed as proportions and as medians with the corresponding interquartile range (IQR). Numerical variables were tested for normal distribution using the Kolmogorov-Smirnov test. The non-parametric Mann-Whitney U test was used for unpaired two-sample comparisons. Statistical significance was defined as a p-value <0.05. Statistical analyses were performed using SPSS for Windows version 13.0 (SPSS Inc., Chicago, USA). To test for a correlation between the velocity of the development of hyperkalaemia and the extent of hyperkalaemia, patients were grouped into quartiles according to velocity. The mean maximal serum potassium levels of these groups were then compared among each other using analysis of variance followed by Tukey-HSD *post hoc* analysis. To com-

Table I. Demographic and clinical characteristics of the patients (n = 551)

Characteristic	Median value (IQR)
Age (years)	72.2 (63.5–80.3)
Male sex	270 (49)[a]
Length of hospital stay (days)	18 (11–30)
Observation period (days)	5 (3–6)
No. of diagnoses per patient	7 (6–9)
No. of drugs per patient	10 (7–12)
No. of new drugs per patient added 2 days before or during observation period	3 (2–5)
No. of drugs per patient stopped 2 days before or during observation period	2 (0–3)
Maximal serum potassium level (mmol/L)	5.4 (5.1–5.8)
Serum potassium level at the beginning of the observation period (mmol/L)	3.8 (3.4–4.1)
Daily increase in serum potassium (mmol/L)	0.38 (0.26–0.57)
Creatinine clearance[b] (mL/min)	43.3 (28.9–63.6)
Creatinine clearance[b] at the beginning of the observation period (mL/min)	46.9 (31.9–67.9)

a No. of patients (%).

b Creatinine clearance estimated by the Cockroft-Gault formula.[17]

IQR = interquartile range.

pare risk factors that changed during the observation period, McNemar's Chi-squared test was used. For the analysis of potential risk factors for hyperkalaemia, continuous variables were dichotomised. Known risk factors from the literature were included in a multiple logistic regression model to analyse the independent association of these risk factors with a higher velocity of the development of hyperkalaemia. The median was used as cut-off point to dichotomise the velocity of the development of hyperkalaemia. Variables independently associated with a higher velocity in this multiple logistic regression analysis were defined as 'major risk factors'. Comparison of patients with no, one and multiple risk factors were performed using Tukey-HSD post-hoc test.

Results

Patients Characteristics

A random sample of 600 patients hospitalised in the University Hospital of Basel developing hyperkalaemic serum potassium levels (≥5.0 mmol/L) between January 2000 and January 2004 was extracted from the electronic laboratory database, taking into account the inclusion and exclusion criteria described above. Of these 600 patients, 49 (8.1%) had to be excluded from the analysis because of pseudohyperkalaemia. Demographic and clinical characteristics of the remaining study sample containing 551 patients are summarised in table I.

At the beginning of the observation period, 144 (26.1%) patients were hypokalaemic (serum potassium <3.5mmol/L). These patients showed a significantly higher median velocity of the development of hyperkalaemia (0.42 vs 0.35 mmol/L/day; $p < 0.001$) than initially normokalaemic patients, but the median of their serum potassium level at the end of the observation period was not significantly different compared with patients who were normokalaemic at the beginning of the observation period (5.37 vs 5.41 mmol/L/day; $p = 0.405$). The number of patients with severe renal impairment (CrCl <30 mL/min) significantly increased from 121 (22.0%) at the beginning to 152 (27.5%) at the end of the observation period ($p = 0.031$). Importantly, the velocity of the development of hyperkalaemia was positively correlated with the extent of hyperkalaemia (figure 1).

None of the 81 deaths (14.7%) were directly attributable to hyperkalaemia. However, patients who died reached a significantly higher median of serum potassium level at the end of the observation period compared with the surviving patients (5.38 vs 5.53 mmol/L; $p = 0.025$). Of 30 (5.4%) patients developing severe hyperkalaemia (serum potassium levels >6.5 mmol/L), eight died. Heart failure

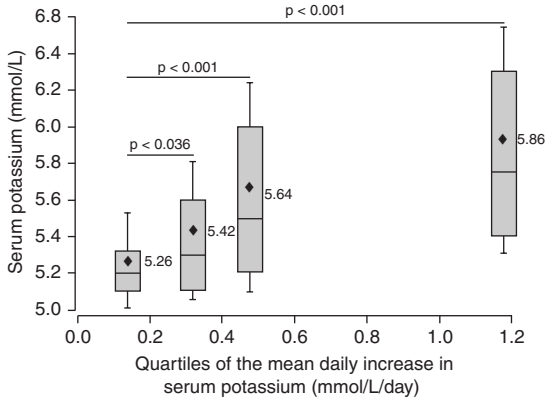

Fig. 1. Correlation of the velocity of the development of hyperkalaemia (mean daily increase in serum potassium) with the extent of hyperkalaemia. Patients were grouped into quartiles regarding velocity. A high velocity of the development of hyperkalaemia was associated with high maximal serum potassium levels (analysis of variance followed by Tukey-HSD *post hoc* analysis). Boxes represent interquartile range (25–75%) [with mean (♦) and median (–)] ± standard deviation.

(37%), pneumonia (13.5%) and myocardial infarction (11.1%) were the most frequent causes of death.

Risk Factors for a High Velocity of the Development of Hyperkalaemia

Known potential non-drug-related risk factors for hyperkalaemia were obtained from the literature and are listed in table II. The most prevalent risk factors in our patients were advanced age, diabetes mellitus and congestive heart failure. During the observation period, the mean drug use significantly increased from 8 (IQR 5–10) to 10 (IQR 7–12) different drugs per patient ($p < 0.001$). Exposure to drugs associated with hyperkalaemia before and during hospitalisation is shown in table III. As could be expected, the drugs associated with hyperkalaemia used most often in our patients were heparin, ACE inhibitors/ARBs, potassium supplements, potassium-sparing diuretics and NSAIDs. For all of these drug classes, the exposure of patients increased during hospitalisation compared with entry. Accordingly, the number of patients treated with drugs potentially causing hyperkalaemia increased from 351 (63.7%) to 508 (92.1%) [$p < 0.001$]. Of the 144 patients that were hypokalaemic (serum potassium <3.5 mmol/L) at the beginning of the observation period, 133 (92.4%) were treated with potassium supplements. The number of patients with more than one drug potentially causing hyperkalaemia significantly increased ($p < 0.001$) from 226 (40.7%) to 315 (63.2%) during the observation period. Of the 160 patients with a diagnosis of congestive heart failure, 138 (86.3%) were treated with an ACE inhibitors or an ARB, and a potassium-sparing diuretic or a potassium supplement.

In the multiple logistic regression model, drug-related risk factors (table III) and non-drug-related risk factors (table II) for the development of hyperkalaemia were included and tested for their influence on the velocity of the development of hyperkalaemia. Risk factors independently associated with a high velocity are listed in table IV. The identified risk factors increased the velocity in the following order: use of potassium supplements > severe renal impairment > use of ACE inhibitors or ARBs > use of potassium-sparing diuretics > diabetes mellitus. Figure 2 shows that the velocity increased with a rising number of risk factors. Pair wise comparison by Tukey-HSD *post hoc* analysis showed that the velocity of the development of hyperkalaemia is significantly higher for patients with two or more risk factors than patients with one or zero risk factors (figure 2).

Dose of Drugs Identified as Risk Factors (Risk Drugs)

In an additional analysis, we focussed on the daily dose of risk drugs as a risk factor for the velocity of the development of hyperkalaemia. Patients treated with 'high-dose' (daily doses >3000mg potassium chloride) potassium supplements showed a significantly higher median velocity of the daily increase in serum potassium levels ($n = 99$) than patients ($n = 101$) treated with 'low-dose' potassium supplements (0.48 vs 0.40 mmol/L/day; $p = 0.006$). The median velocity of the daily increase in serum potassium levels was significantly higher in patients ($n = 63$) treated with 'high-dose' potassium-sparing diuretics (daily doses of amiloride >10mg or spironolactone >25 mg) compared with those ($n = 74$) treated with 'low-dose' potassium sparing diuretics (0.52 vs 0.40 mmol/L/day; $p = 0.007$). On the other hand, there was no significant

Table II. Prevalence of non-drug-related risk factors for hyperkalaemia

Non-drug-related risk factor[a]	No. of patients (%)
Advanced age (≥65 years)	388 (70.4)
Diabetes mellitus	166 (30.1)
Congestive heart failure	160 (29.0)
Severe renal impairment[b]	152 (27.5)
Blood transfusions	41 (7.4)
Acute kidney failure	36 (6.5)
Chronic kidney disease	31 (5.6)
Tubulointerstitial nephritis	14 (2.5)
Renal sclerosis	5 (0.9)
Obstructive uropathy	4 (0.7)
Volume depletion	3 (0.5)
Primary adrenal insufficiency	2 (0.4)
Metabolic acidosis	2 (0.4)
Haemolysis	1 (0.2)
Hyperglycaemia	1 (0.2)
Acute tumour lysis, amyloidosis, congenital adrenal hyperplasia, fluoride poisoning, gastrointestinal bleeding, Gordon syndrome, hyperkalaemic periodic paralysis, hyporeninemic hypoaldosteronism (type IV renal tubular acidosis), papillary necrosis, post kidney transplantation, primary hyporeninism, rhabdomyolysis, systemic lupus erythematosus, sickle-cell disease, surgery, tissue trauma	0
Catabolic states, geophagia, vigorous exercise	NA

a Risk factors to develop hyperkalaemia according to Palmer,[4] and Evans and Greenberg.[5]

b Creatinine clearance (<30 mL/min) estimated by the Cockroft-Gault formula.[17]

NA = not available.

difference in the median velocity of the daily increase of serum potassium levels between patients treated with 'high-dose' (n = 129) ACE inhibitors or ARBs (daily doses >DDD) versus those treated with 'low-dose' (n = 139) ACE inhibitors or ARBs (0.47 vs 0.43 mmol/L/day; p = 0.289). Fifty-seven (53.8%) of the 106 patients treated with spironolactone were treated with daily doses >25mg.

Combinations of Risk Drugs

In another analysis, we focused on combinations among the drugs associated with a high risk of developing rapid hyperkalaemia (potassium supplements, potassium-sparing diuretics and ACE inhibitors or ARBs). At the end of the observation period, 410 (74.4%) patients obtained at least one of these drugs. Of them, 138 were treated with a double and 28 with a triple combination. Patients with double or triple combinations were compared with patients with only single drug use.

The median velocity of the development of hyperkalaemia was significantly lower in patients treated with an ACE inhibitor or ARB (n = 120) versus patients treated with an ACE inhibitor or ARB combined with potassium sparing diuretics (n = 60) [0.39 vs 0.53 mmol/L/day; p = 0.002]. Furthermore, a significantly lower median velocity was found in patients treated with an ACE inhibitor or ARB versus patients treated with the combination of ACE inhibitor or ARB and potassium supplements (n = 60) [0.39 vs 0.52 mmol/L/day; p = 0.002].

On the other hand, in patients treated with potassium supplements or potassium-sparing diuretics, the median velocity was not lower than in patients treated with potassium supplements or potassium-sparing diuretics combined with an ACE inhibitor or ARB. The velocity of the development of hyperkalaemia in patients with triple combinations (potassium supplements, ACE inhibitors or ARBs and potassium-sparing diuretics (n = 28) equaled 0.50 (IQR 0.37–0.94) mmol/L/day. This velocity is significantly higher ($p < 0.05$) compared with patients using only one of these drug classes, but not significantly different compared with patients with double combinations.

Table III. Number of patients exposed to drugs associated with risk for hyperkalaemia in the study population (n = 551) before, and at the end of, the observation period[a]

Drug	Before observation period [n (%)]	End of observation period [n (%)]	p-Value
Heparin	174 (31.6)	320 (58.1)	<0.001
ACE inhibitors/ARBs	217 (39.4)	268 (48.6)	0.002
Potassium supplements	139 (25.2)	200 (36.3)	<0.001
Potassium-sparing diuretics	80 (14.5)	137 (24.9)	<0.001
spironolactone	65 (11.8)	106 (19.2)	<0.001
amiloride	15 (2.7)	31 (5.6)	0.016
NSAID/selective COX-2 inhibitors	32 (5.8)	76 (13.8)	<0.001
Digoxin	38 (6.9)	44 (8.0)	0.491
Trimethoprim	14 (2.5)	25 (4.5)	0.073
Calcineurin-antagonists	15 (2.7)	16 (2.9)	0.855
ciclosporin	12 (2.3)	13 (2.4)	0.840
tacrolimus	3 (0.5)	3 (0.5)	1.000
Antineoplastic drugs	3 (0.5)	12 (2.2)	0.019
Nonselective β-adrenoceptor antagonists	5 (0.9)	8 (1.5)	0.403
Intravenous amino acids (arginine, lysine, aminocaproic acid)	4 (0.7)	4 (0.7)	1.000
Lithium	2 (0.4)	2 (0.4)	1.000
Drospirenone, mannitol, metyrapone, benzylpenicillin potassium, pentamidine, post-kidney transplantation, somatostatin, suxamethonium	0	0	
Herbal medications, high potassium-containing food	NA		

a McNemar's Chi-squared test was performed to compare exposure to risk drugs for hyperkalaemia before and at the end of observation period.

ARBs = angiotensin receptor blockers; **COX-2** = cyclo-oxygenase type 2; **NA** = not available.

Kaliuretics

At the end of the observation period, significantly ($p < 0.001$) more patients were treated with a kaliuretic (thiazide or loop diuretic) than before the observation period (288 [52.3%] vs 178 patients [32.1%]). Patients with severe renal impairment (CrCl ≤30 mL/min) treated with kaliuretics (n = 85) showed a significantly lower velocity of the increase in serum potassium than patients with severe renal impairment without kaliuretics (n = 67) [0.44 vs. 0.52 mmol/L/day; $p = 0.016$]. Of 167 patients treated with at least two of the three drug classes identified as risk drugs associated with a higher velocity,

Table IV. Independent risk factors significantly associated with a high velocity of the development of hyperkalaemia[a]

Major risk factors	B	OR	95% CI	p-Value
Use of potassium supplements	1.220	3.386	2.251, 5.091	<0.001
Severe renal impairment[b]	1.138	3.119	2.007, 4.850	<0.001
Use of ACE inhibitors or ARBs	0.971	2.642	1.742, 4.006	<0.001
Use of potassium-sparing diuretics	0.725	2.065	1.310, 3.254	0.002
Diabetes mellitus	0.442	1.525	1.005, 2.313	0.047

a In a multiple logistic regression analysis, all drugs associated with hyperkalaemia (table III) and non-drug-related risk factors for hyperkalaemia (table II) were included to identify independent risk factors significantly associated with a high velocity of the development of hyperkalaemia.

b Creatinine clearance (<30 mL/min) estimated by the Cockroft-Gault formula.[17]

ARBs = angiotensin receptor blockers; **B** = regression coefficient; **OR** = adjusted odds ratio.

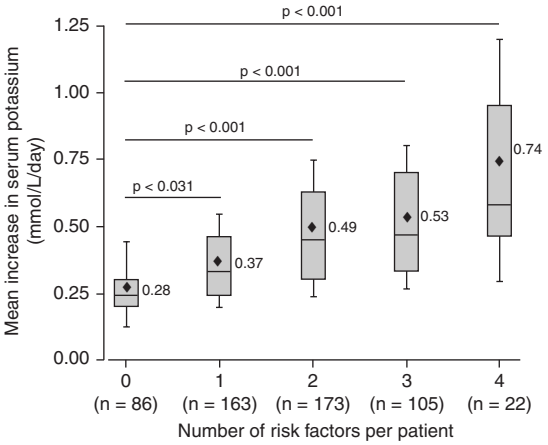

Fig. 2. The velocity of the development of hyperkalaemia (mean daily increase in serum potassium) according to the number of risk factors. The risk factors included for the calculation were severe renal impairment, diabetes mellitus and treatment with potassium-sparing diuretics, ACE inhibitors, angiotensin receptor blockers or potassium supplements. The velocity of the development of hyperkalaemia is higher with an increasing number of these risk factors. In comparison to patients without such risk factors, patients with one or more risk factors show a significantly higher velocity of the development of hyperkalaemia ($p > 0.05$) (analysis of variance followed by Tukey-HSD *post hoc* analysis). Boxes represent interquartile range (25–75%) [with mean (♦) and median (–)] ± standard deviation.

138 (82.6%) were treated with a kaliuretic. These 138 patients showed a significantly lower median velocity of the development of hyperkalaemia compared with the remaining 29 patients of this group without kaliuretics (0.45 vs 0.63 mmol/L/day; $p = 0.001$).

Discussion

Hyperkalaemia is a life-threatening electrolyte disturbance associated with different drug or non-drug-related risk factors. The current study reveals that several risk factors can contribute to a fast development of hyperkalaemia. By multivariate analysis, the risk factors significantly associated with a high velocity of the development of hyperkalaemia were identified in the following order: use of potassium supplements > severe renal impairment > use of ACE inhibitors or ARBs > use of potassium-sparing diuretics > diabetes mellitus (table IV). Importantly, the velocity correlated with the extent of hyperkalaemia that was reached and was higher in the presence of more than one of these risk factors.

Except for the use of potassium supplements, the order of the risk factors (as expressed by the adjusted odds ratios) is comparable with the corresponding odds ratios for the development of hyperkalaemia identified in a recent case-control study in hospitalised patients with congestive heart failure.[15] In our study, potassium supplements contribute most strongly to the velocity of the development of hyperkalaemia in the multivariate model. This may be explained by the facts that in our study 144 (26.4%) of the patients were hypokalaemic at the beginning of the observation period and that most of these patients were treated quite aggressively with potassium supplements. These patients showed a significantly ($p = 0.001$) higher velocity of the daily increase of serum potassium levels. However, in a study of 4921 outpatients treated with potassium supplements, only 3.6% developed hyperkalaemia.[2,18] In comparison, hospitalised patients treated with potassium supplements appear to have a higher risk for hyperkalaemia, since hyperkalaemia was found in 15–40% of these patients.[2] This difference in the frequency of hyperkalaemia between hospitalised and ambulant patients treated with potassium supplements may be explained by more aggressive potassium supplementation and by a higher prevalence of other risk factors for hyperkalaemia in hospitalised patients.

In our study, the majority (142 or 71%) of the 200 patients treated with potassium supplements had an additional 'major risk factor' for hyperkalaemia, such as severe renal impairment, use of potassium-sparing diuretics, use of ACE inhibitors or ARBs and/or diabetes mellitus.

Several studies about hyperkalaemia highlight the risk of the potential drug interaction between spironolactone and ACE inhibitors or ARBs.[10,19] Palmer et al.[4] recommends that the dose of spironolactone should not exceed 25 mg/day when used in combination with an ACE inhibitor or ARB. In agreement with this recommendation, the use of high-dose potassium-sparing diuretics (daily doses of spironolactone >25mg or of amiloride >10mg) significantly accelerated the velocity of the development of hyperkalaemia in our study, whereas no such effect was observed for high-dose ACE inhibi-

tors or ARBs. Our study therefore supports the statements of Palmer et al. that the dose of spironolactone should not exceed 25 mg/day when used in patients with heart failure, in particular in patients with other risk factors for hyperkalaemia such as treatment with ACE inhibitors, ARBs or potassium supplements and in patients with renal failure.[4] In our study, 20.5% of the patients (n = 60) treated with an ACE inhibitor or ARB in combination with potassium-sparing diuretics had severe renal impairment at the beginning of the observation period and of the 106 patients treated with spironolactone, 57 (53.8%) were treated with daily doses >25mg. In this context, it is important to realise that in the RALES study, spironolactone was investigated using a daily dose of 25mg and not at higher doses.[4]

Although not identified as risk factors for a fast development of hyperkalaemia in this study, drugs associated with hyperkalaemia including NSAIDs (table III) could contribute to the development of hyperkalaemia, especially when combined with major risk drugs (ACE inhibitors, ARBs, potassium-sparing diuretics and potassium supplements) or in patients with pre-existing major risk factors (diabetes mellitus or renal impairment).

Kaliuretics (loop diuretics or thiazides) are effective in reducing the risk for hyperkalaemia. Patients at risk for hyperkalaemia could therefore be treated with kaliuretics. In our study, the potassium-lowering effect of kaliuretics could be confirmed in patients with severe renal impairment and in patients treated with ACE inhibitors, ARBs, potassium-sparing diuretics and/or potassium supplements. The velocity of the development of hyperkalaemia in these patients was significantly lower, if they were treated also with kaliuretics. However, the risk of hyponatraemia should be taken into consideration and the patients should be monitored closely when loop diuretics or thiazides are prescribed.[20]

The strength of this study is the analysis of the velocity of the development of hyperkalaemia. Therefore we used an observational study design without a control group. This is different to the other studies in this field, which assessed only the occurrence of hyperkalaemia with the objective of identifying risk factors for hyperkalaemia.[15,16] Our study reveals that the velocity of the development of hyperkalaemia is influenced almost by the same risk factors as the occurrence of hyperkalaemia. The only exception is the treatment with potassium supplements, which is a more pronounced risk factor for the velocity of the development of hyperkalaemia than for the occurrence of hyperkalaemia. The exposure to two or more risk factors further enhances the velocity. Since the velocity is correlated with the extent of hyperkalaemia, patients with two or more risk factors should be monitored very closely for the development of potentially life-threatening hyperkalaemia.

Some limitations of this study merit discussion. First, the study sample was recruited on four general wards in one university hospital, representing patients of one single community with long hospitalisation stay (18 days). The findings may therefore not be generalised and be transferred to other hospital or ambulatory settings. Second, the Cockroft-Gault formula[17] may overestimate the CrCl. A comparison with other methods estimating the CrCl reveals, however, that the differences are small, suggesting that other methods would not change our findings.[21] Third, the study was retrospective and the way we calculated the velocity of the development of hyperkalaemia did assume a linear rise of serum potassium. We did not judge the linearity of the increase, even in patients where multiple serum potassium determinations were available in the observation period. Fourth, hospitalised patients are closely monitored and hyperkalaemia is normally quickly detected and can therefore be treated immediately. Similar to previous in-hospital studies,[16] only a small number of patients (5.4%) developed severe hyperkalaemia (serum potassium levels >6.5 mmol/L) and more than half of the patients developed only mild hyperkalaemia (serum potassium levels <5.5mmol/L). The situation for outpatients might be different. In these patients, less intense monitoring may result in an increased risk of hyperkalaemia, which can be fatal.[22]

The relatively high mortality (14.7%) of patients in this study is comparable to other in-hospital studies.[16] This may be explained by the polymorbidity (seven diagnoses per patient) of the patients studied and their advanced age (72.2 years). None of the deaths could directly be attributed to hyperkalaemia. Nevertheless, patients who died showed a significantly higher maximal serum potassium level than

the entire study population and cardiac diseases were the most frequently reported cause of death.

Conclusions

Risk factors associated with a high velocity of the development of hyperkalaemia are use of potassium supplements > severe renal impairment > use of ACE inhibitors or ARBs > use of potassium-sparing diuretics > diabetes mellitus. The presence of two or more of these risk factors is associated with an even faster development of hyperkalaemia. Since the velocity is correlated with the extent of hyperkalaemia, the serum potassium levels in patients with two or more risk factors should be monitored closely to avoid life-threatening hyperkalaemia. A rapid increase in serum potassium (>0.5 mmol/L/day) should alert clinicians to identify and possibly remove risk factors for hyperkalaemia.

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