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Risk calculation for hyperkalaemia in heart failure patients

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ABSTRACT

Background: We aimed to develop a model to estimate the risk of hyperkalaemia in patients treated for heart failure in a tertiary reference hospital and to identify precipitating factors.

Methods: 125 congestive heart failure (CHF) patients were studied retrospectively. Thirty of these patients developed episodes of hyperkalaemia (K ≥5.5 mmol/l). Both groups were compared for possible risk factors for hyperkalaemia (age, glomerular filtration rate (GFR), New York Heart Association (NYHA) class, diabetes mellitus (DM), ejection fraction and medication use (ACE inhibitors, angiotensin receptor blockers, aldosterone antagonists).

Results: On multivariate logistic regression analysis DM (OR 2.9, 95% CI = 1.05 to 8.3, p=0.041), GFR <45 ml/min (OR 4.1, 95% CI = 1.6 to 10.5, p=0.004) and NYHA class III-IV (OR 2.4, 95% CI = 0.9 to 6.3, p=0.086) were independently associated with hyperkalaemia, whereas age, ejection fraction and medication sort and dose were not. Of the episodes of hyperkalaemia, 38% were precipitated by periods of dehydration (diarrhoea, fever) or change of medication.

Conclusion: We identified kidney function, diabetes mellitus and heart failure class as independent risk factors of hyperkalaemia. The majority of the hyperkalaemic episodes develop without a precipitating factor. This implies that heart failure patients in a tertiary reference hospital should be very closely monitored to minimise the risk for hyperkalaemia.

KEYWORDS

Diabetes mellitus, heart failure, hyperkalaemia, renal failure, risk factors

INTRODUCTION

Adverse drug reactions are a major cause of hospitalisation. Recently it was reported that 6% of all hospitalisations are due to adverse drug reactions. Despite the fact that angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are viewed as safe drugs, they can be found in the top five of drugs leading to hospitalisation because of adverse drug reactions, leading to renal dysfunction and electrolyte disturbances.[1]

In 1999 it was found that adding spironolactone to ACE inhibitors reduced morbidity and mortality in patients with congestive heart failure (CHF)[2] and since than this combination has been used more and more. The combined use of ACE inhibitors and spironolactone, however, increases the risk of hyperkalaemia, as was found a few years after this policy had been generally accepted.[3-6] This was partly due to the fact that also patients with severe kidney failure (who were excluded from the RALES study) were treated with this combination. In addition advanced age, diabetes mellitus (DM), volume depletion, severity of chronic heart failure (NYHA) and use of nonsteriodal anti-inflammatory drugs (NSAIDs) are possible risk factors for hyperkalaemia in CHF patients on combined ACE inhibitors and aldosterone antagonists. Since all of these risk factors are linked to diminished kidney function, renal dysfunction appears to be a pivotal factor for this risk. Especially in older patients, renal dysfunction is often underestimated, since in these patient creatinine tends to be lower due to loss of muscle mass.

The purpose of this study is to provide the clinician with tools to identify patients at risk for hyperkalaemia in an outpatient setting so that he can take measures to prevent it or decide to monitor these patients more closely. To this end we aim to identify and quantify risk factors for hyperkalaemia. Secondly we aim to identify precipitating factors that are responsible for hyperkalaemic episodes.

METHODS

Study population

This is a retrospective study performed at the heart failure outpatient clinic of the Radboud University Medical Centre (a tertiary reference hospital). Only patients treated for at least three months between January 2002 and April 2006 were included. From these, a random sample of 128 patients was taken. Patients were excluded if they were under eighteen years (no patients) or on haemodialysis (three patients). This yielded a study group of 125 patients. In all patients, the diagnosis of heart failure had been made in the past.

Procedures

Medical records were reviewed, and the following parameters were collected: age, gender, NYHA class, left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVEDD), a diagnosis of diabetes mellitus (DM), medication use and dose (ACE inhibitors, ARBs, aldosterone antagonists, β-blockers and diuretics) and laboratory variables (serum potassium and creatinine). Creatinine clearance was calculated using the Cockcroft-Gault formula.[7] In order to be able to compare different drugs within a class the prescribed daily dose was divided by the defined daily dose (ddd) of that class. In addition, it was assessed whether episodes of transient deterioration in kidney function occurred during the study period. Transient renal failure was defined as a 25% increase and subsequent decrease in serum creatinine within a period of three months, with a creatinine peak >110 μmol/l. Next patients were identified who had a potassium of ≥5.5 μmol/l during the study period. This 'case' group was compared with a control group that had no hyperkalaemia during the study period. For this latter group the most recent data available in the medical records were used for the subsequent analysis. For the case group the most recent episode of hyperkalaemia was taken and data were collected at three months, both prior to this episode and during the episode itself. An episode of hyperkalaemia was defined as any episode of elevated potassium (K ≥5.5 μmol/l). High potassium values occurring within a period of two weeks were considered to belong to the same episode of hyperkalaemia. In this way it was possible to both assess risk factors that lead to a hyperkalaemic episode and which precipitating factors directly provoke hyperkalaemia. Since we were interested in out-of-hospital risk factors of hyperkalaemia, episodes that were the consequence of renal failure due to radiocontrast were not included in the analysis.

Statistical analysis

A desktop computer equipped with SPSS 12.0.1 for windows was used for data analysis. Fisher's exact test and independent t-test were used for dichotomous and continuous variables respectively, comparing cases and controls on each of the collected variables. Variables found to have a p value <0.05 were incorporated into the logistic regression model. Variables independently associated with hyperkalaemia were identified. Based on the multivariate analysis a model was developed to predict the risk of hyperkalaemia in individual patients.

RESULTS

Thirty patients had 52 episodes of hyperkalaemia; 19 patients had one episode of hyperkalaemia, five patients had two episodes, four patients had three episodes, one patient had four episodes and one patient had seven episodes. In *table 1* data on the study population and findings in the case and control group can be found.

On multivariate logistic regression analysis DM (OR 2.9, 95% CI = 1.05 to 8.3, p=0.041), GFR <45 ml/min (OR 4.1, 95% CI = 1.6 to 10.5, p=0.004) and NYHA class III or IV (OR 2.4, 95% CI = 0.9 to 6.3, p=0.086) were independently associated with hyperkalaemia. Age, ejection fraction and medication sort and dose, were not independently associated with hyperkalaemia. All of the patients were taking at least one potassium-increasing drug (ACE inhibitor, ARB or aldosterone antagonist). None of them were treated by all three drug classes. There was no association between the number of potassium-modulating drugs and the occurrence of hyperkalaemia. Based on these ORs a model was designed, assigning 1 point to DM, 1 point to NYHA class III or IV and 2 points to GFR <45 ml/min. In *table 2* a prediction model is shown for if this point scoring system is applied on the study group.

In *figure 1* precipitating factors for the 52 hyperkalaemic episodes are depicted; 38% of the episodes of hyperkalaemia were precipitated by periods of dehydration (diarrhoea, fever), change in medication or others. In 62% no precipitating factor for the episode of hyperkalaemia could be found.

DISCUSSION

The favourable outcome of the RALES study has led to the widespread use of aldosterone antagonists in heart failure on top of high doses of ACE inhibitors or ARBs. This has resulted in an increase in the incidence of hyperkalaemia leading to hospitalisation and even death, although the combined therapy has proven to be safe if serum potassium is controlled frequently. In our study we found episodes of hyperkalaemia in 24% of patients. It is important to note that in this retrospective study only living subjects were included. It is possible that we missed patients who had died because of hyperkalaemia. A second shortcoming of this study is that potassium was routinely analysed

Table 1. *Data on study population and cases and controls*

Study population	Total (n=125)	Control (n=95)	Case (n=30)	P value
Binominal variables				
Gender (male)	76 (61%)	55 (58%)	21 (70%)	0.29
HF class (severe)	62 (50%)	40 (42%)	22 (73%)	<0.01
DM	26 (21%)	15 (16%)	11 (37%)	0.02
Creatinine jump	52 (42%)	24 (25%)	28 (93%)	<0.01
Medication use				
Aldosterone antagonist	81 (65%)	60 (63%)	21 (70%)	0.66
ACEi	103 (83%)	77 (81%)	26 (87%)	0.59
ARB	23 (19%)	18 (19%)	5 (17%)	1.00
Diuretics	102 (82%)	75 (79%)	27 (90%)	0.28
β-inhibitor	120 (96%)	91 (96%)	29 (97%)	1.00
Two RAAS-i	82 (66%)	60 (63%)	22 (73%)	0.31
Continues variables mean (±sd)				
Age (years)	65 (±14)	64(±14)	68 (±13)	0.17
GFR (ml/min)	69 (±38)	76 (±40)	45 (±17)	<0.01
LVEDD (cm)	5.70 (±0.9)	5.69 (±1.0)	5.72 (±0.8)	0.87
LVEF (%)	39.2 (±13)	39.4 (±13)	38.4 (±11)	0.74
Potassium (mmol/l)	4.5 (±0.9)	4.1 (±0.4)	5.9 (±0.4)	<0.01
Medication dose (mean pdd/ddd)				
Aldosterone antagonist	0.46 (±0.25)	0.46 (±0.26)	0.45 (±0.22)	0.91
ACE inhibitor	2.26 (±1.38)	2.26 (±1.37)	2.26 (±1.44)	0.98
ARB	1.3 (±0.56)	1.25 (±0.52)	1.5 (±0.71)	0.39

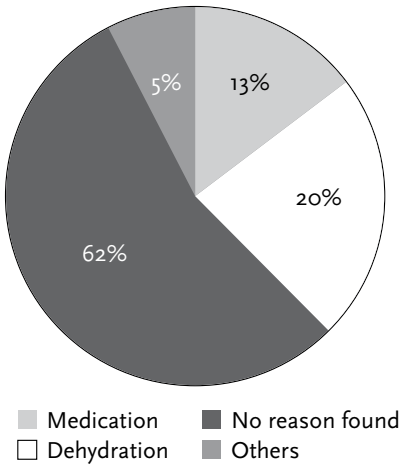
HF class (severe) = New York Health Association (NYHA) class III-IV; DM = diabetes mellitus type 2; creatinine jump = 25% rise and 25% fall of creatinine above 110 µmol/l within three months time; pdd/ddd = prescribed/defined daily dose; ACEi = angiotensin converting enzyme inhibitor; ARB = angio-tensin receptor antagonist; two RAAS-i = use of two potassium-increasing drugs (ACEi, ARB or aldo-a); GFR = glomerular filtration rate; LVEDD = left ventricular end-diastolic dimension; LVEF = left ventricular ejection fraction. p<0.05 is considered statistically significant.

Table 2. *Prediction model hyperkalaemia*

Total points	Control	Case	Total
0	45	3	48
1	20	6	26
2	16	8	24
3	13	9	22
4	1	4	5
Total	*95*	*30*	*125*

Based on the multiple regression a prediction model was developed. A patient with 0 points has NYHA class I or II, GFR >45 ml/min and no diabetes mellitus. Three of these patients developed hyperkalaemia. A patient with 4 points has all risk factors for hyperkalaemia. In one of them no hyperkalaemia was found.

Figure 1. *Precipitating factors for hyperkalaemia*



Precipitating factors for the 52 episodes of hyperkalaemia. In 62% no precipitating factor for the episodes of hyperkalaemia is found. In 38% the possible reason for hyperkalaemia is dehydration, change of medication or others.

every three months, but if a patient had problems, more outpatient clinic visits were scheduled, which led to more frequent blood sampling and hence to bias. This bias is inevitable in a retrospective study. In fact it will even be difficult to circumvent it in a prospective set-up.

In most episodes of hyperkalaemia hospitalisation was not necessary and medication was adjusted to reduce the potassium. In these cases firstly the dose of the aldosterone antagonist was reduced or it was discontinued. Secondly the dose of the ACE inhibitor (or ARB) was reduced. The major risk factor for development of hyperkalaemia was renal failure, which was already recognised in the RALES study, where patients with severe renal failure were excluded (creatinine >221 µmol/l). It is thought that the increase in incidence of hyperkalaemia is partly due to the fact that in daily practice aldosterone antagonists are

also applied in renal failure. In our patients 25 out of 125 patients had a GFR ≤40 ml/min and 14 of these patients received spironolactone. Second, we found that diabetes mellitus is an independent risk factor for hyperkalaemia. This might be due to the fact that insulin is needed for postprandial intracellular disposition of potassium or to the fact that in diabetic patients hyporeninism-hypoaldosteronism is often observed, which leads to poor renal excretion of potassium. As third factor (although not statistically significant) we identified the severity of heart failure as defined by NYHA class III or IV. This can be explained by the fact that kidney perfusion is impaired in severe heart failure, which makes these patients at risk for a transient deterioration in kidney function in periods of (subtle) dehydration. This is confirmed by the fact that in all but one patient there was a transient deterioration in kidney function during the episode of hyperkalaemia, which is probably due to renal hypoperfusion during periods of (subtle) dehydration. Interestingly, a cause for dehydration was only identified in a minority of the patients. Unexpectedly, we did not find that treatment with aldosterone antagonists or renin-angiotensin-aldostonone system (RAAS) inhibitors, or the dose of these drugs, was related to the risk of hyperkalaemia, and change in medication only provoked the hyperkalaemia in 13% of the episodes of hyperkalaemia. In an earlier study on multivariate analysis, these drugs were identified as risk factors (use of spironolactone (OR = 4.18), and use of ACE inhibitors (OR = 2.55)).[8] This may be explained by the fact that in our heart failure outpatient clinic these patients are very intensively monitored, which may lead to withdrawal or lower dosage of these drugs in high-risk patients, because of imminent hyperkalaemia. In our opinion there are two effects. On the one hand aldosterone antagonists and RAAS inhibitors lead to hyperkalaemia. This happens in a vulnerable group of patients with kidney failure, severe heart failure and diabetes. In these patients it is impossible to give the full dose of ACE inhibitors and aldosterone antagonists. This will lead to a lower dosage in this vulnerable group and paradoxically, lower dosage of these drugs in patients at risk for hyperkalaemia and thus lower dosage in patients who have episodes of hyperkalaemia. We feel that this latter effect will be most prominent in a high-risk group that is intensely monitored, i.e. in a tertiary heart failure outpatient clinic. So our results may not be applicable in situations where monitoring is less strict. As in our study the other two independent risk factors identified by these authors are diabetes mellitus (OR = 2.42), and creatinine clearance <40 ml/min (OR = 8.36).[8] We did not find a relationship between the risk of hyperkalaemia and ejection fraction or LVEDD either. In fact, there was no relationship between echocardiographic parameters and NYHA class, which reflects that in the majority of our patients diastolic heart failure is present. It is important to note that despite the identification of the risk factors, the model we have developed based on these risk factors was only a weak predictor of hyperkalaemic episodes. For instance, one out of the five patients who had all risk factors did not develop hyperkalaemia and three out of the 48 patients who had no risk factors still developed hyperkalaemia. Importantly, a clear provoker of the hyperkalaemic episode could only be identified in a minority of patients, and in these cases this was most often due to dehydration. Alteration of drugs or drug dose only caused hyperkalaemia in a very few patients, which is probably due to our policy to check potassium three days after introduction of a drug or dose increment. In conclusion, we identified kidney function, diabetes mellitus and severity of heart failure (as defined by the NYHA class) as independent risk factors for hyperkalaemia. Nevertheless, the model based on these risk factors only gives a weak prediction of hyperkalaemia. In addition, most episodes of hyperkalaemia develop without a clear precipitating factor. These findings imply that heart failure patients in a tertiary reference hospital should be very closely monitored to minimise the risk for hyperkalaemia. This study confirms the notion that these patients should be treated in a specialised heart failure outpatient clinic.[9,10]

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