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BRIEF REPORT

Kees H. Polderman
Armand R.J. Girbes

Piperacillin-induced magnesium and potassium loss in intensive care unit patients

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K.H. Polderman (✉) · A.R.J. Girbes
Department of Intensive Care,
Vrije Universiteit Medical Centre,
PO Box 7057, 1007 MB Amsterdam,
The Netherlands
e-mail: k.polderman@vumc.nl
Tel.: +31-20-4443912
Fax: +31-20-6392125

Abstract *Objective:* Broad spectrum penicillins such as piperacillin are used extensively in the intensive care unit (ICU) because of their wide bacterial spectrum and low level of toxicity. Although some cases of interstitial nephritis induced by piperacillin have been reported, this problem is thought to be rare. However, in view of the large number of other risk factors for renal disorders that are frequently present in ICU patients, we speculated that ICU patients might be more at risk for renal side effects. We therefore decided to measure serum electrolyte levels in patients before and after piperacillin administration. *Design:* Prospective observational study. *Setting:* University teaching hospital. *Patients and participants:* Forty-three consecutive patients with normal renal function treated with piperacillin; 40 patients treated with other antibiotics. *Results:* Serum levels of magnesium (Mg), potassium (K) and, to a lesser degree, calcium (Ca) decreased significantly in patients treated with piperacillin, but not in patients treated with other antibiotics ($p<0.01$). This decrease was especially pronounced in a subgroup of patients concurrently treated with furosemide. *Conclusions:* We conclude that treatment with piperacillin may cause or aggravate electrolyte disorders and tubular dysfunction in ICU patients even when serum creatinine levels remain normal.

Keywords Piperacillin · Electrolyte depletion · Tubular dysfunction · Electrolyte loss

Introduction

Patients in the intensive care unit (ICU) are at increased risk for the development of acute renal disorders, tubular dysfunction and interstitial nephritis, which may be present even when serum levels of creatinine and urea are normal. Various medications frequently used in the ICU (including dopamine and catecholamines) can induce or exacerbate electrolyte disorders and/or tubular dysfunction. The use of certain types of antibiotics may also affect renal function; this may be an important factor due to the high incidence of (nosocomial) infections and the frequent use of antibiotics in ICU patients.

In recent years beta-lactam antibiotics such as piperacillin have gained popularity due to their wide bacterial spectrum and low level of toxicity [1, 2]. Piperacillin is excreted by both renal and biliary mechanisms, but the primary route of elimination is by glomerular filtration. Although some case reports have described the occurrence of interstitial nephritis associated with piperacillin administration [3, 4], it is generally well tolerated and manifest renal problems occur infrequently. However, in view of the numerous risk factors for renal disorders in ICU patients, we surmised that renal side effects of piperacillin might be more prevalent in ICU patients. Subclinical interstitial nephritis and tubular dysfunction may first become apparent through increased urinary loss of electrolytes. To test our hypothesis, we therefore decided to measure serum electrolyte levels in patients before and during piperacillin administration.

Methods

Serum levels of magnesium (Mg) and potassium (K) were measured in 43 ICU patients before and after 36 h of piperacillin administration (group 1). Forty patients treated with different antibiotics (mostly cephalosporins or ciprofloxacin) were used as controls (group 2). All antibiotics were dissolved in saline (NaCl 0.9%). Indications for antibiotic use were similar in the two groups of patients and consisted mainly of upper airway infections, pneumonia or abdominal infections. Patients with pre-existing renal disorders (defined as serum creatinine levels ≥120 µmol/l or known renal disease prior to ICU admission) were excluded from the study.

Results

Patients and controls were comparable in regard to age and severity of disease (Table 1) and all patients had normal serum creatinine levels before inclusion in this study.

Serum electrolyte levels (before and after 36 h of antibiotic administration, group 1 versus group 2, in mmol/l; see Table 2) were as follows: Mg: 1.01±0.21 to 0.69±0.17 (p<0.01) versus 0.98±0.27 to 0.96±0.14 (p<0.01); K: 4.15±0.52 to 3.5±0.44 (p<0.01) versus 4.2±0.44 to 4.3±0.38 (p<0.01); Ca: 2.09±0.47 to 1.99±0.36 (p<0.05) versus 2.02±0.48 to 2.08±0.22 mmol/l (p=NS). Electrolyte loss was especially pronounced in 17 patients of group 1 who also received furosemide during the study period; during piperacillin administration Mg levels decreased in all of these 17 patients from 1.04±0.19 to 0.62±0.16 mmol/l (p<0.01). Sixteen patients in group 2 were also treated with furosemide; Mg levels did not change significantly in this subgroup (from 1.09±0.21 to 1.00±0.23, p= NS).

In addition, amounts of intravenous and oral potassium supplementation during the study period were significantly higher in group 1 (average 6.8 mmol/h) than in group 2 (3.2 mmol/h). Serum creatinine and urea levels remained constant during the study period. Average urine production over a 6-hour period before and a 6-hour period after 36 h of antibiotic administration did not change significantly in either group (group 1: 115±78 versus 121±84 ml/h, p= NS; group 2: 107±64 versus 111±68 ml/h, p= NS; p= NS for group 1 versus group 2). Phosphate levels were low in both groups at the beginning of the observation and were corrected for clinical reasons.

Acid-base status remained unchanged in all patients in both groups who did not receive furosemide (Table 2). In patients treated with furosemide, average pH also remained unchanged but base excess increased slightly in both groups (group 1: from –0.1±1.8 to +2.1± 3.7 mmol/l; group 2: from –0.4±0.9 to +1.8±2.4; p=NS for group 1 versus group 2).

Discussion

Our results show that piperacillin is associated with electrolyte depletion in ICU patients, probably induced by subtle effects of the antibiotic on tubular function, as has been described in some case reports [3, 4]. There were no manifest changes in renal function in our patients, as shown by the fact that serum creatinine levels remained

Table 1 Patient data

	Group 1 (piperacillin)	Group 2 (other antibiotics)
Number of patients	43	40
Age (years)	58±18.2 (range 26–77)	56±21.4 (range 22–78)
APACHE II score	19.6±12.0	18.2±8.2
Creatinine levels (µmol/l)	88±42	94±32
No. of patients receiving furosemide during study	17	16

Table 2 Serum electrolyte levels and acid-base status in groups 1 and 2

	Group 1 (piperacillin) n=43			Group 2 (other antibiotics) n=40			
	T=0	T=36 h	p value T_0 versus T_{36}	T=0	T=36 h	p value T_0 versus T_{36}	p value group 1 versus group 2
Mg (mmol/l)	1.01±0.21	0.69±0.17	<0.01	0.98±0.27	0.96±0.14	<0.01	NS
K (mmol/l)	4.15±0.52	3.5±0.44	<0.01	4.2±0.44	4.3±0.38	<0.01	NS
Ca (mmol/l)	2.09±0.47	1.99±0.36	<0.05	2.02±0.48	2.08±0.22	NS	NS
Creatinine (µmol/l)	88±42	90±33	NS	94±32	91±36	NS	NS
pH	7.39±0.12	7.38±0.16	NS	7.38±0.19	7.41±0.18	NS	NS
Bicarbonate	23.9±2.9	24.1±3.9	NS	24.1±3.3	23.8±4.2	NS	NS
Base excess	–0.3±1.6	–0.1±2.6	NS	0.0±2.1	0.2±1.8	NS	NS

unchanged and urine production remained normal. However, even subtle electrolyte disorders can have harmful effects, especially in ICU patients. Low levels of Mg can cause cardiac arrhythmias, neuromuscular irritability, hypertension, strokes and vasoconstriction [5] and hypomagnesemia is associated with increased mortality in the ICU [6, 7]. Hypokalemia can also induce cardiac arrhythmias (especially in patients with ischemic heart disease and left ventricular hypertrophy) and is associated with muscle weakness, rhabdomyolysis and hyperglycemia. Moreover, the effects may be cumulative if both Mg and K are depleted.

Thus, electrolyte disorders induced by piperacillin administration may have serious consequences, especially in ICU patients. Various risk factors that are often present in ICU patients may contribute to the development of electrolyte disorders and/or renal dysfunction. These include nasogastric suction, diarrhea, administration of diuretics such as furosemide and mannitol, administration of dopamine, which can enhance renal excretion of sodium and other electrolytes [8], and administration of potentially nephrotoxic medications such as aminoglycosides. In addition, the risk of developing electrolyte disorders may be increased in patients with impairments of renal function caused by their underlying disease or with pre-existing renal disorders.

The potentially harmful effects of electrolyte loss are, of course, easily preventable by replacing these electrolytes through infusion or enteral supplementation. However, serum levels of many electrolytes including magnesium are not routinely measured in most ICUs, and many physicians may be unaware of the possibility that piperacillin can induce interstitial nephritis. Moreover, the results of our study demonstrate that the incidence of electrolyte disorders associated with piperacillin use is surprisingly high.

In conclusion, we found that treatment with piperacillin is associated with severe electrolyte disorders in ICU patients, even when serum creatinine levels remain normal. The mechanism is probably exacerbation of preexisting tubular dysfunction. Doctors treating ICU patients with beta-lactam penicillins should be aware of this potential problem and electrolytes including Mg should be regularly monitored and, if necessary, supplemented in these patients.

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