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Aminoglycosides and renal magnesium homeostasis in humans

Rodo O. von Vigier[1], Anita C. Truttmann[1], Karin Zindler-Schmocker[1], Alberto Bettinelli[1]*, Carmen Casaulta Aebischer[1], Bendicht Wermuth[2] and Mario G. Bianchetti[1]

[1]Department of Pediatrics and [2]Department of Clinical Chemistry, University of Bern, Bern, Switzerland

Abstract

Background. The use of aminoglycosides has been linked with hypomagnesaemia in scattered reports. The objective of the study was to measure prospectively the effect of treatment with the aminoglycoside amikacin on renal magnesium homeostasis.

Methods. Twenty-four cystic fibrosis patients (aged 9–19 years) admitted because of exacerbation of pulmonary symptoms caused by *Pseudomonas aeruginosa* were treated with the aminoglycoside amikacin and the cephalosporin ceftazidime for 14 days. Renal values and plasma and urinary electrolytes were measured before and at the end of the systemic anti-pseudomonal therapy.

Results. In the patients with cystic fibrosis, treatment with amikacin and ceftazidime did not modify plasma creatinine or urea and plasma or urinary sodium, potassium and calcium. Treatment with amikacin and ceftazidime significantly decreased both plasma total magnesium (from 0.77 (0.74–0.81) to 0.73 (0.71–75) mmol/l; median and interquartile range) and ionized magnesium (from 0.53 (0.50–0.55) to 0.50 (0.47–0.52) mmol/l) concentration and increased fractional urinary magnesium excretion (from 0.0568 (0.0494–0.0716) to 0.0721 (0.0630–0.111)) and total urinary magnesium excretion (from 30.7 (26.5–38.0) to 38.5 (31.5–49.0) μmol/l glomerular filtration rate).

Conclusions. The present study demonstrates that systemic therapy with amikacin plus ceftazidime causes mild hypomagnesaemia secondary to renal magnesium wasting even in the absence of a significant rise in circulating creatinine and urea.

Keywords: aminoglycosides; cystic fibrosis; kidney disease; magnesium; magnesium deficiency

Introduction

Renal magnesium wasting is considered a rare complication of treatment with aminoglycosides. This complication of aminoglycosides, which is mostly associated with acute renal failure, has been documented in scattered anecdotal reports [1–5]. Recent observations in animals indicate the frequent occurrence of renal magnesium wasting even in the absence of both renal failure [6–8] and abnormalities in renal tubular morphology [8].

Studies on circulating magnesium have hitherto been hindered by the use of circulating total magnesium concentration, which does not estimate the biologically active fraction of circulating magnesium, that is, ionized magnesium [9,10]. Only recently have reliable techniques for ionized magnesium determination become available [11,12].

The objective of this study was to measure prospectively the effect of treatment with the aminoglycoside amikacin in combination with the cephalosporin ceftazidime on renal magnesium homeostasis in cystic fibrosis patients infected with *Pseudomonas aeruginosa* [13,14].

Subjects and methods

Experimental design

Between 1996 and 1998, twenty-four patients with cystic fibrosis admitted to the Department of Pediatrics, University of Bern, Switzerland because of exacerbation of pulmonary symptoms entered the study. There were 11 female and 13 male subjects aged between 9.0 and 19, median 14 years. They met the following criteria: isolation from their sputum of *Ps. aeruginosa* susceptible to amikacin and ceftazidime; no allergy to aminoglycosides or cephalosporins; no renal failure (circulating creatinine less than 88 μmol/l) or hepatic failure; no diabetes mellitus (glycosylated haemoglobin A_{1c} less than 0.057, and fasting plasma glucose less than 6.1 mmol/l); no treatment with any diuretic agent; and an interval since the last hospital treatment of 6 or more months.

Combined anti-pseudomonal treatment with amikacin (33 mg/kg daily in three divided doses) and ceftazidime (250 mg/kg daily in four divided doses) for 14 days was instituted in all patients [13]. The dose of amikacin was adjusted in the patients to achieve trough plasma concentrations less than 16.0 μmol/l [14]. Other aspects of hospital treatment included physiotherapy and inhalation therapy

Correspondence and offprint requests to: Dr M. G. Bianchetti, Inselspital, CH-3010 Bern, Switzerland.
* Present address: Second Department of Pediatrics, University of Milan, Italy.

three times daily, medication with pancreatic enzymes, and high-calorie diet.

Before and at the end of the 14 days treatment period a 2-h urine specimen was collected after overnight fasting, sitting (more than 10 min) blood pressure (first and fifth sounds), and heart rate were measured, and mid-point blood was taken anaerobically with minimal stasis and without movement of the forearm. Haemoglobin, pH, carbon dioxide pressure, urea, albumin, and ionized calcium and magnesium were assessed in blood, and total magnesium, sodium, potassium, chloride, uric acid, phosphate, creatinine and osmolality in both blood and urine, and total calcium in urine. In addition urinalysis (glucose and protein) and the excretion of *N*-acetyl-*β*-D-glucosaminidase were assessed.

Plasma and urine were also collected in a control group of 25 subjects (11 female and 14 males, aged between 4.1 and 19, median 12 years) with either nocturnal enuresis ($n=16$), dysfunctional voiding ($n=5$), or unstable bladder ($n=4$).

Data analysis

All measurements were performed in duplicate. Haemoglobin (cyanhaemoglobin method), uric acid (uricase–catalase assay), albumin (bromcresol purple method), total calcium (cresolphthalein complexone method), and magnesium (xylidil blue method) [15], phosphate (ammonium molybdate method), creatinine (kinetic alkaline picrate method), urea (Bertheloth–urease assay) and *N*-acetyl-*β*-D-glucosaminidase (cresolsulphonphthaleinyl *N*-acetyl-*β*-D-glucosaminide assay) [16] were measured colorimetrically. Osmolality was assessed by freezing point osmometry, glycosylated haemoglobin A_{1c} by a latex immunoagglutination inhibition assay, and circulating amikacin by fluorescence polarization assay. Urinary glucose and protein were determined using commercially available dipsticks. The susceptibility of isolated *Ps. aeruginosa* to amikacin and ceftazidime was assessed by conventional disk diffusion techniques. Ion-selective electrodes were used for the measurement of sodium, potassium, chloride, ionized calcium, pH, carbon dioxide pressure, and ionized magnesium. Plasma bicarbonate concentration was calculated using the Henderson–Hasselbalch equation. Plasma ionized magnesium was analysed within 15 min of collection in blood drawn into silicone-free tubes (heparin 1000 U/l) using a selective electrode, which has been recently characterized [11]. The electrode contains the neutral carrier-based membrane ETH 7025, which is incorporated in standard AVL electrode bodies by solvent casting (AVL 988–4/Mg Analyzer). The cell is provided with electrodes for sodium, calcium, pH, and magnesium together with a common reference electrode. The measuring cell is maintained at 37°C. Plasma or urinary electrolytes (P_x, U_x) and creatinine (P_{Cr}, U_{Cr}) were used to calculate the fractional clearance (1) or the excretion corrected for 1 litre of glomerular filtration rate (GFR) (2), using the following standard equations:

$$\frac{U_x \times P_{Cr}}{P_x \times U_{Cr}} \quad (1)$$

$$\frac{U_x \times P_{Cr}}{U_{Cr}} \quad (2)$$

The fractional clearance of magnesium and calcium was calculated from their plasma ionized concentrations. The maximal tubular reabsorption of phosphate was calculated from plasma (P_{Ph}) or urinary (U_{Ph}) phosphate and plasma (P_{Cr}) or urinary (U_{Cr}) creatinine as follows [17]:

$$P_{Ph} - \left(\frac{U_{Ph} \times P_{Cr}}{U_{Cr}}\right)$$

The urinary excretion of *N*-acetyl-*β*-D-glucosaminidase (unit, U/l) was factored by creatinine (unit, μmol/l). An estimate of aldosterone activity is the potassium concentration gradient between blood and nephron at the end of the cortical collecting tubule [18]. To assess the mentioned gradient and thereby the aldosterone activity, a non-invasive test has been designed. Consequently, the transtubular potassium concentration gradient was calculated from plasma and urinary potassium (P_K, U_K; in mmol/l) and osmolality (P_{osm}, U_{osm}; in mmol/kg) by the equation [18]:

$$\frac{U_K}{U_{osm}} \times \frac{P_{osm}}{P_K}$$

The results are expressed either as median and interquartile range or depicted as 'box and whisker plot' (boxes are median and interquartile ranges, vertical lines are ranges). The Wilcoxon matched-paired-signed rank test (non-parametric rank sum test for paired samples), the Wilcoxon–Mann–Whitney test (non-parametric rank sum test for two independent samples), and simple regressions with the non-parametric coefficient of correlation r_s were used for analysis. A P value of <0.05 was accepted as statistically significant.

Results

When studied before amikacin and ceftazidime, the group of 24 patients with cystic fibrosis slightly but significantly tended towards tachycardia, hypoalbuminaemia, hypocalcaemia, and hyperuricaemia (Table 1). Plasma total (0.77 (0.74–0.81) *vs* 0.80 (0.78–0.83 mmol/l) and ionized magnesium (0.53 (0.50–0.55) *vs* 0.54 (0.51–0.56) mmol/l), the fractional magnesium clearance (0.0568 (0.0494–0.0716) *vs* 0.0498 (0.0394–0.0591)), and the urinary excretion of this ion (30.7 (26.5–38.0) *vs* 26.9 (20.1–31.0) μmol/l GFR) were not statistically different in cystic fibrosis patients and in control subjects. Plasma total (0.75 (0.72–0.78) *vs* 0.77 (0.75–0.81 mmol/l) and ionized (0.53 (0.50–0.55) *vs* 0.52 (0.51–0.55 mmol/l) magnesium were similar in 16 cystic fibrosis patients with at least one treatment course with aminoglycosides in the past and in the eight patients without such a course.

Systemic treatment with amikacin and ceftazidime, intensive physiotherapy, inhalation therapy, and high-calorie diet did not significantly ameliorate the noted tendency towards tachycardia, hypoalbuminaemia, hypocalcaemia and hyperuricaemia (Table 1). Also blood pressure, body weight, haemoglobin, plasma creatinine and urea, blood acid–base balance, and plasma and urinary sodium, potassium and phosphate were unchanged following systemic anti-pseudomonal treatment with amikacin and ceftazidime for 14 days. None of the patients had a change in plasma creatinine concentration of more than 15 μmol/l. Treatment with amikacin and ceftazidime significantly increased the urinary excretion rate of *N*-acetyl-*β*-D-glucosaminidase (Table 1) and decreased plasma total magnesium (from 0.77 (0.74–0.81) to 0.73 (0.71–75), plasma ionized

Table 1. Clinical and laboratory findings in 24 patients (11 female and 13 male, aged between 9.0 and 19 years, median 14) with cystic fibrosis, before and after treatment with amikacin and ceftazidime for 14 days, and in a control group of 25 healthy subjects (11 female and 14 male, aged between 4.1 and 19 years, median 12). The results are given either as median (with interquartile range between brackets) or as relative frequency. Urinalysis failed to reveal pathological glucosuria and proteinuria in the 23 patients (both before and after amikacin and ceftazidime) and in the 25 control subjects

	Patients with cystic fibrosis		Control subjects
	Before amikacin and ceftazidime	After amikacin and ceftazidime	
Blood pressure (mmHg)	100 (96–104)/58 (55–70)	102 (96–103)/58 (51–70)	106 (90–121)/65 (54–76)
Heart rate (b.p.m.)	82[a] (78–110)	75[a] (63–91)	68 (62–74)
Body weight (kg)	40.6 (28.3–44.8)	41.4 (31.1–46.6)	42.4 (25.2–53.2)
Haemoglobin (g/l)	128 (116–135)	130 (120–136)	133 (119–142)
Plasma albumin (g/l)	35.0[a] (33.0–37.0)	35.2[a] (33.3–36.5)	38.5 (39.3–42.4)
Plasma creatinine (μmol/l)	68 (64–76)	64 (58–70)	66 (60–78)
Plasma urea (mmol/l)	4.0 (3.8–4.7)	3.9 (3.6–4.3)	4.3 (3.8–5.0)
Blood pH	7.40 (7.38–7.42)	7.38 (7.36–7.40)	7.39 (7.37–7.41)
Plasma carbon dioxide pressure (kPa)	5.64 (5.11–6.17)	5.83 (5.36–6.10)	5.76 (5.12–6.02)
Plasma bicarbonate (mmol/l)	24.9 (23.9–25.7)	24.9 (23.1–25.9)	24.2 (22.6–27.7)
Plasma sodium (mmol/l)	139.0 (137.6–141.0)	140.1 (139.1–141.8)	140.4 (138.5–141.31
Fractional sodium clearance (10^{-2})	0.57 (0.34–0.84)	0.63 (0.43–0.95)	0.48 (0.25–1.02)
Plasma potassium (mmol/l)	4.02 (3.90–4.25)	4.18 (3.90–4.41)	4.01 (3.89–4.20)
Fractional potassium clearance (10^{-2})	10.8 (7.2–18.9)	9.5 (6.3–14.2)	12.1 (8.0–14.3)
Transtubular potassium gradient	6.7 (5.8–7.5)	6.5 (5.7–7.6)	6.6 (5.5–7.3)
Plasma chloride (mmol/l)	98 (96–101)	100 (98–102)	99 (96–102)
Fractional chloride clearance (10^{-2})	0.95 (0.65–1.25)	1.19 (0.83–1.50)	0.92 (0.71–1.36)
Plasma ionized calcium (mmol/l)	1.22[a] (1.18–1.24)	1.23[a] (1.20–1.25)	1.26 (1.24–1.28)
Fractional calcium clearance (10^{-2})	2.96 (0.79–5.40)	1.93 (0.53–3.24)	1.60 (0.51–3.18)
Urinary calcium excretion (μmol/l GFR)	29.7 (16.7–38.7)	23.5 (14.1–32.1)	19.3 (14.6–33.2)
Plasma uric acid, μmol/l	305[a] (250–393)	286[a] (248–338)	216 (190–237)
Fractional uric acid clearance (10^{-2})	9.20 (7.31–11.3)	8.74 (7.18–10.2)	8.50 (7.03–11.8)
Plasma phosphate (mmol/l)	1.25 (0.98–1.36)	1.30 (1.04–1.40)	1.32 (1.16–1.50)
Maximal tubular phosphate reabsorption (mmol/l)	1.13 (0.96–1.27)	1.14 (0.99–1.33)	1.19 (1.02–1.37)
Urinary *N*-acetyl-*β*-D-glucosaminidase (U/μmol creatinine)	215 (118–265)	910[a,b] (664–1568)	154 (52–208)

GFR, glomerular filtration; [a]$P<0.05$ *vs* control group; [b]$P<0.02$ *vs* before amikacin and ceftazidime.

magnesium (from 0.53 (0.50–0.55) to 0.50 (0.47–0.52) mmol/l), as shown in Figure 1. The tendency towards hypomagnesaemia was associated with a significantly increased fractional magnesium clearance (from 0.0568 (0.0494–0.0716) to 0.0721 (0.0630–0.111)) and urinary magnesium excretion (from 30.7 (26.5–38.0) to 38.5 (31.5–49.0) μmol/l glomerular filtration rate (GFR)). In patients no correlation was observed between the changes in the urinary excretion of magnesium and those in the urinary excretion of *N*-acetyl-*β*-D-glucosaminidase.

Discussion

When magnesium intake is curtailed or when there is intestinal magnesium malabsorption the normal kidney reduces magnesium excretion to very low values. When renal magnesium handling is impaired, hypomagnesaemia ensues because, unlike with calcium, equilibration with cellular stores does not occur for several weeks [9,10,19,20]. In the present study, treatment with amikacin plus ceftazidime for 14 days very often caused subtle changes in the renal magnesium homeostasis. However, the treatment was not associated with changes in circulating creatinine and urea, a relatively common complication of aminoglycoside therapy [21]. Consequently the study demonstrates that in cystic fibrosis, systemic therapy with the aminoglycoside amikacin plus the cephalosporin ceftazidime causes mild and probably transient [1–5] hypomagnesaemia secondary to inappropriate renal magnesium wasting even in the absence of a rise in circulating creatinine and urea.

In cystic fibrosis the drawbacks of hypomagnesaemia on respiratory symptoms have not been addressed. Data from the literature suggest that in humans, hypomagnesaemia may reduce respiratory muscle power and cause airflow obstruction [22]. Our findings of hypoalbuminaemia, hypocalcaemia, and hyperuricaemia in advanced cystic fibrosis before and at the end of systemic anti-pseudomonal therapy concur with the literature [23–26]. Hypoalbuminaemia and hypocalcaemia reflect the severity of exocrine pancreatic insufficiency that leads to malabsorption of fat, fat-soluble vitamins (such as vitamin D), and protein [23–25]. On the other hand, hyperuricaemia is secondary to the purine contamination of the pancreatic replacement therapy [26]. None of our cystic fibrosis patients was on treatment with diuretics, the drugs most frequently associated with hyperuricaemia [26].

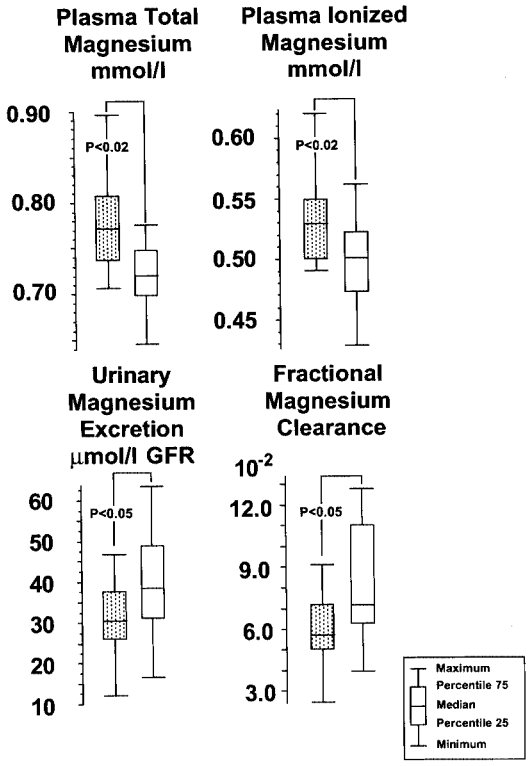

Fig. 1. Plasma total and ionized magnesium, magnesium excretion rate corrected for 1 litre of GFR, and fractional magnesium clearance in 24 patients with cystic fibrosis before (shaded boxes) and at the end (clear boxes) of systemic treatment with amikacin and ceftazidime for 14 days.

Pseudomonas aeruginosa is a major cause of bronchopulmonary morbidity in cystic fibrosis [13,14]. Aggressive chest physiotherapy, nutritional management, and intravenous antibiotics for 14 days have been largely responsible for the increased life-span of patients with cystic fibrosis. In most centres the standard antibiotic regimen for acute exacerbation includes a β-lactam (e.g. ceftazidime) and an aminoglycoside (e.g. amikacin) [13,14]. Ceftazidime is a recognized anti-pseudomonal agent [27,28]. No report mentions a possible link between ceftazidime or other β-lactams and magnesium wasting. Aminoglycosides are a mainstay in the management of severe Gram-negative infection but are nephrotoxic [21].

Acute renal failure is a relatively common complication of aminoglycoside therapy that can occur even if drug levels are closely monitored [21]. Aminoglycosides undergo uptake into the proximal tubular cells, accumulate within lysosomes, and cause a histologically detectable damage and renal failure [21]. None of the patients included in this study developed acute renal failure. The results of our study concur with those of investigations in rats. In this animal aminoglycosides acutely decrease the tubular reabsorption of magnesium [6–8] and increase the excretion of *N*-acetyl-β-D-glucosaminidase [8]. However, glomerular filtration rate remains unaffected [6–8] and no abnormalities in renal tubular cell morphology are detectable [8]. Our data and the literature do not provide information on the nephron site and on the cellular site at which aminoglycosides interfere with the magnesium transport. *N*-acetyl-β-D-glucosaminidase is a large lysosomal enzyme that does not undergo glomerular filtration [21,29]. Since this enzyme is located predominantly within the proximal tubule, an increased excretion is generally interpreted as evidence of proximal tubular injury and has been shown to occur in humans 2–3 days after onset of aminoglycoside therapy [21,29]. In the experimental animal, however, an increased excretion of this enzyme occurs before the development of histologically detectable tubular injury, suggesting that aminoglycosides simply interfere with the cellular cycling of the enzyme [8]. In the present study the urinary magnesium excretion did not parallel that of *N*-acetyl-β-D-glucosaminidase. Furthermore data from the literature indicate that the reabsorption of magnesium predominantly occurs by paracellular diffusion in the thick ascending loop of Henle [19,20]. Recent studies disclosed the gene encoding paracellin-1, a protein found exclusively in the tight junctions of the thick ascending loop of Henle that mediates the paracellular reabsorption of magnesium and calcium [30]. Available data do not provide information on the possible interaction between aminoglycosides and the paracellular reabsorption of magnesium. Whatever the underlying mechanisms, the results of the present study indicate that in our patients, inappropriate renal magnesium wasting was brought about by amikacin.

In cystic fibrosis some further causes of renal magnesium wasting deserve mention, including intestinal malabsorption, the use of diuretics, diabetes mellitus and aldosteronism [9,10]. In the present study, however, cystic fibrosis patients on treatment with diuretics or with diabetes mellitus were excluded. Furthermore, we failed to disclose signs consistent with aldosteronism, as indicated by the transtubular potassium gradient [18]. These factors probably account for the rather mild degree of magnesium deficiency noted in our patients after aminoglycosides. Hence we assume that aminoglycosides may cause a more severe magnesium deficiency in cystic fibrosis patients with poorly controlled intestinal malabsorption or secondary diabetes mellitus, in those treated with diuretics, or in those with aldosteronism. It behoves us to be alert for the possible occurrence of hypomagnesaemia among cystic fibrosis patients so that severely affected subjects can be given replacement.

Hypokalaemia, hypocalcaemia, or hypophosphataemia sometimes occur in patients with severe hypomagnesaemia [9,10]. In the cystic fibrosis patients presented in this study mild renal magnesium wasting was not linked with hypokalaemia. A tendency towards hypocalcaemia, however, was observed both before as well as after treatment with amikacin and ceftazidime. It is therefore speculated that hypocalcaemia is related directly to cystic fibrosis, as discussed above.

It has been known for many years that aminoglycosides sometimes cause renal magnesium wasting [1–5].

This prospective study indicates that in cystic fibrosis treatment with amikacin plus ceftazidime for 14 days often causes renal magnesium wasting.

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