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BRIEF REPORT

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Systemic tobramycin concentrations during selective decontamination of the digestive tract in intensive care unit patients on continuous venovenous hemofiltration

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Abstract *Objective:* To study whether selective decontamination of the digestive tract (SDD) results in detectable serum tobramycin concentrations in intensive care unit (ICU) patients with acute renal failure treated with continuous venovenous hemofiltration (CVVH). *Design and setting:* Prospective, observational, single-center study in a mixed medical–surgical ICU. *Patients:* Adult ICU patients receiving SDD for at least 3 days and being treated with CVVH because of acute renal failure. *Measurements and results:* Tobramycin serum concentrations were measured at the 3rd day after start of CVVH and every 3 days thereafter. Detectable serum concentrations of tobramycin were found in 12 (63%) of 19 patients and in 15 (58%) of the 26 samples. With a toxic tobramycin concentration defined as more than 2.0 mg/l, we found one patient with a toxic concentration of 3.0 mg/l. In three other patients tobramycin concentrations of $\geq$ 1.0 mg/l were found. *Conclusions:* In patients with acute renal failure treated with CVVH, administration of SDD with tobramycin can lead to detectable and potentially toxic serum tobramycin concentrations.

Introduction

Selective decontamination of the digestive tract (SDD) is an infection-prophylaxis regimen in intensive care unit (ICU) patients, aiming at eradicating the potentially pathogenic micro-organisms from the mouth and stomach, while preserving the intestinal anaerobic flora to prevent overgrowth with resistant bacteria and yeasts. Most SDD regimens use the combination of topically applied tobramycin, colistin and amphotericin B. These antibiotics are given topically in the mouth and through a gastric tube in the stomach four times daily. Some regimens combine this local therapy with systemic antibiotic prophylaxis for the first couple of days. All three of the topical antibiotics mentioned above are regarded as non-absorbable and therefore safe [1].

After prolonged use, however, minimal enteral absorption of tobramycin might lead to potentially toxic serum concentrations in patients with impaired renal function [2]. Normally, more than 90% of tobramycin is eliminated by glomerular filtration. Renal replacement therapy by continuous venovenous hemofiltration (CVVH) leads to only limited drug clearance [3]. Thus, ICU patients with renal failure are at highest risk of developing toxic serum concentrations of tobramycin after enteral administration.

Serum concentrations of tobramycin are commonly monitored to minimize the risk of toxicity after systemic administration, aiming at a trough concentration of less than 2.0 mg/l [2].

The aim of this study was to determine whether enteral administration of tobramycin as part of the SDD regimen can lead to detectable and potentially toxic serum concen-

trations in ICU patients with acute renal failure requiring CVVH.

Materials and methods

Study design

We conducted a prospective single-center observational study. From June 2006 to October 2006, all eligible patients were included in the study. Eligible patients were older than 18 years, admitted to our 28-bed mixed medical–surgical ICU, receiving SDD and treated with CVVH. Patients with systemic use of tobramycin or another aminoglycoside within the previous 5 days were excluded from the study.

Because the study involved no interventions, and because measuring serum tobramycin concentrations in patients on CVVH was part of routine patient care, the local medical ethics review board waived the requirement for informed consent.

The SDD regimen consisted of four times daily treatment with approximately 0.5 g of a paste, applied to the oral cavity, containing 2% colistin, 2% tobramycin, and 2% amphotericin B. Patients also received 100 mg colistin sulfate, 80 mg tobramycin, and 500 mg amphotericin B administered through a gastric tube four times daily. Patients with blind loops (e.g., after colostomy) additionally received suppositories containing 42 mg amphotericin B, 42 mg colistin sulfate, and 64 mg tobramycin (as sulfate).

Initiation of CVVH in our department is considered in patients who are oliguric despite adequate fluid resuscitation and/or display a persistent steep rise in plasma creatinine in addition to persistent shock. Vascular access was obtained by insertion of a double-lumen catheter (Duo-Flow 400XL, 14F × 6 in. (15 cm); Medcomp, Harleysville,

Table 1 Patient characteristics

Patient	Age (years)	Sex (male/female)	Weight (kg)	APACHE II	SOFA	Creat. start CVVH	Diuresis (ml/h)	Days CVVH	Diagnosis
1	59	M	90	18	12	284	29	9	Cardiac shock with ARDS
2	42	M	100	22	16	287	6	3	Necrotizing fasciitis and ischemic large bowel
3	44	M	85	8	13	124	2,5	6	Abdominal sepsis
4	68	F	56	36	15	367	25	3	Decompensated liver cirrhosis
5	36	F	75	23	8	318	5	3	Fluxus postpartum
6	77	M	75	23	9	131	17	6	Cardiac shock after acute myocardial infarct
7	83	M	75	37	14	180	5	6	Out of hospital cardiac arrest
8	68	M	90	29	14	244	12	10	Septic shock caused by necrotic pancreatitis
9	51	F	70	23	17	422	0	6	Medication induced liver failure
10	72	M	84	27	12	265	31	5	Complicated cardiac surgery
11	56	M	99	25	11	260	25	8	Postoperative after thymectomy
12	66	F	70	20	7	143	67	2	Cardiac and mesenteric ischemia
13	61	M	80	26	13	327	13	4	Intra-abdominal arterial bleeding
14	55	F	74	31	15	243	3	9	Abdominal sepsis caused by fecal peritonitis
15	74	F	65	18	13	84	25	3	Abdominal sepsis caused by ischemia from the small bowel
16	72	M	73	25	11	614	0	3	Respiratory failure caused by fluid overload
17	61	F	58	22	13	162	26	9	Cardiac shock after massive acute myocardial infarct
18	54	M	95	15	12	157	59	6	Respiratory failure caused by pneumonia
19	72	M	80	22	14	136	108	6	Cardiac shock caused by mitral valve insufficiency due to acute myocardial infarct

APACHE II, APACHE II score on the day of admission to ICU; *SOFA*, SOFA score on day of admission to ICU; *Diuresis*, urine production (ml/h) in the last 24 h before starting CVVH; *Days CVVH*, number of days on CVVH at time first blood sample was drawn

PA, USA) into a large vein (femoral, subclavian, or internal jugular vein). CVVH was performed using a Diapact hemofiltration machine (B. Braun Melsungen, Melsungen, Germany) and a cellulose triacetate hemofilter (CT-190G; Baxter Healthcare, Deerfield, IL, USA). The ultrafiltration rate was set at 35 ml/kg/h.

Blood samples for the measurement of tobramycin concentrations were scheduled for the 3rd day after start of CVVH and every 3 days thereafter. Patients had to have received SDD for at least 3 days.

Given the slow absorption and elimination of tobramycin and the frequent (four times daily) dosing, tobramycin concentrations were assumed to be steady state, and serum samples were taken randomly (not as trough or peak concentrations).

Tobramycin concentrations were determined with a validated fluorescence polarization immunoassay (FPIA; Axsym®, Abbott Laboratories, IL, USA). The lower limit of determination using this technique is 0.2 mg/l. Toxic serum concentrations of tobramycin were defined as more than 2.0 mg/l [2].

Results

A total of 26 samples were obtained from 19 patients. Baseline characteristics of the patients included are shown in Table 1. Patients were treated with CVVH for median 6 days (interquartile range, IQR, 3–8 days). Serum concentrations of tobramycin and the doses of SDD administered are shown in Table 2. Patients were treated with SDD for median 6 days (IQR 3–9 days). Three patients received SDD suppositories as additional prophylaxis.

Detectable serum concentrations were found in 12 (63%) of 19 patients and in 15 (58%) of the 26 samples. We found one patient with a toxic concentration of 3.0 mg/l. In three other patients tobramycin concentrations of $\geq$ 1.0 mg/l were found.

The three patients with highest tobramycin concentrations all had ischemic bowel disease. In contrast, no patients with concentrations < 1 mg/l had intestinal ischemia (Table 1).

In six patients more than one sample was drawn. In three of them, consecutive samples showed a rise in concentration with prolonged SDD use. One patient showed a tobramycin concentration of 1.1 mg/l after 6 days of CVVH, rising to 1.7 mg/l 4 days later.

Discussion

We show that in ICU patients receiving enteric tobramycin as part of SDD, detectable serum concentrations of tobramycin are found in more than half of patients with

Table 2 Treatment with SDD and tobramycin serum concentrations

Patient	SDD (orally and via gastric tube)	SDD suppositories	Days on SDD	Tobramycin serum concentrations (mg/l)
1	+	–	24	< 0.2
	+	–	27	0.2
2	+	–	3	0.2
	+	–	6	1.1
	+	–	10	1.7
3	+	+	6	0.5
	+	+	9	0.5
4	+	–	3	0.2
5	+	–	3	< 0.2
6	+	–	19	< 0.2
7	+	–	6	< 0.2
8	+	–	9	0.7
9	+	–	6	0.3
10	+	–	6	0.2
11	+	–	6	< 0.2
12	+	–	3	3.0
13	+	–	3	0.2
14	+	+	9	< 0.2
15	+	+	3	1.1
16	+	–	3	< 0.2
	+	–	6	0.3
17	+	–	7	< 0.2
	+	–	9	< 0.2
18	+	–	6	< 0.2
	+	–	9	< 0.2
19	+	–	6	1.0

< 0.2: below quantification limit

acute renal failure treated with CVVH. We found one patient with a toxic serum concentration of tobramycin.

These findings are in contrast to the general belief that tobramycin is not absorbed from the gastrointestinal tract and that SDD may be safely used in all patients [4].

Our findings, however, are supported by two previous reports. In 1991 Gastinne et al. measured serum tobramycin concentrations in 15 mechanically ventilated ICU patients on SDD. Detectable tobramycin concentrations were found in 9 patients and in 50% of the serum samples. In two patients with renal failure, toxic serum concentrations > 2.0 mg/l were found [5]. In a more recent investigation, Camus also reported systemic tobramycin concentrations exceeding 2 mg/l using SDD. In their study comparing two different decontamination regimens, they found toxic tobramycin serum concentrations in 21 of 74 (28%) patients. In all these patients creatinine clearance was < 30 ml/min [6].

Toxicity of tobramycin includes nephrotoxicity and ototoxicity, which may be seen respectively in 10–20% and 10% of the patients with serum trough concentrations > 2.0 mg/l [2]. However, accumulation of tobramycin in renal cortical cells is seen even when trough concentrations do not exceed this limit, potentially resulting in damage to proximal tubuli [7]. Thus, it cannot be excluded that prolonged detectable serum concentrations of tobramycin are toxic even if lower than 2.0 mg/l.

The major limitation of our study is its small size. Furthermore, we only studied patients with acute renal failure requiring CVVH. Tobramycin clearance by CVVH may be approximately 80% of ultrafiltrate rate (35 ml/h in our study) [8]. In patients with renal failure not treated with renal replacement therapy, the likelihood of accumulation of tobramycin in serum may be even higher. Although the risk of toxic serum concentrations will be lower in patients with no major impairment of renal function, prolonged use of SDD may lead to detectable serum tobramycin concentrations in these patients too [2, 5, 6]. We did not study factors that influence the enteric absorption of tobramycin. It may be hypothesized that tobramycin absorption is higher in patients with a decreased gut barrier function. Indeed, increased absorption of polyethylene glycol has been shown in patients with inflammatory bowel disease [9]. In normal conditions enteral absorption of tobramycin in humans is very low due to active efflux of the drug by P-glycoprotein in the brush border of the intestinal mucosa [10]. If the intestinal mucosa is damaged for any reason, this efflux pump may not function optimally and tobramycin absorption is then increased. Interestingly, in our study the highest tobramycin concentrations were exclusively found in patients with intestinal ischemia.

In conclusion, administration of SDD can lead to detectable and potentially toxic serum concentrations of tobramycin in patients with renal failure. More studies are needed to identify factors related to increased enteral absorption of tobramycin. We recommend determination of plasma concentrations of tobramycin in all ICU patients with severely impaired renal function and on prolonged treatment with SDD.

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