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ORIGINAL ARTICLE

Serum tobramycin concentrations in ICU patients treated with SDD: a prospective study

H. Dijkstra[1], J. de Zee[1,2], A.C. Reidinga[3], M. van Hulst[1], M. Luinstra[1], N.D. Holman[3]
The first two authors contributed equally
[1] Department of Clinical Pharmacy, Martini Hospital, Groningen, the Netherlands
[2] Department of PharmacoTherapy, Epidemiology & Economics, University of Groningen, the Netherlands
[3] Department of Intensive Care, Martini Hospital, Groningen, the Netherlands

Correspondence
N.D. Holman - n.holman@mzh.nl

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Abstract

Background: Selective decontamination of the digestive tract (SDD) is used in intensive care units to prevent nosocomial infections. The antibiotics used are considered safe as they are not absorbed from the gastrointestinal tract. However, tobramycin has been detected in the serum of critically ill patients receiving SDD. The aim of this study was to evaluate the prevalence of SDD-treated patients with tobramycin levels >1 mg/l. The secondary aim was to identify risk factors that may contribute to detectable tobramycin levels.

Methods: Patients receiving SDD were asked to participate in the study. Blood was drawn on the day 3, 7, 10 and 14 after the start of SDD. Tobramycin was determined using a Roche immunoassay.

Results: Six of the 45 patients (13%; 95% CI 3-23%) had detectable tobramycin levels, none of which had a level >1 mg/l. Patients with detectable tobramycin levels significantly more often had CVVH (p=0.028) and impaired renal function (p=0.043). Three models were evaluated with logistic regression. These models indicated that continuous venovenous haemofiltration and APACHE III (Chi2(2) =16.6, p=0.0002; Nagelkerke R2=0.567), impaired renal function and APACHE III (Chi2(2)=14.8, p=0.0006; Nagelkerke R2=0.517) and abdominal sepsis and APACHE III (Chi2(2)=23.1, p=0.000010; Nagelkerke R2=0.738) were predictors for detectable tobramycin levels.

Conclusion Tobramycin was detected in 13% of the patients receiving SDD; none had levels of >1 mg/l. This study is an indication that absorption may be a factor to consider in relation to measurable tobramycin levels.

Introduction

Selective decontamination of the digestive tract (SDD) is used in intensive care units (ICU) to prevent nosocomial infections by eradicating aerobic potential pathogenic gram-negative bacteria and yeasts from the digestive tract. To prevent overgrowth with resistant micro-organisms, the intestinal anaerobic flora is left intact. SDD treatment consists of tobramycin, amphotericin B and colistin, applied in the mouth and stomach. In patients with an ileostomy or colostomy, a suppository is added to the regimen.[1] Treating ICU patients with SDD reduces mortality.[2,3]

The antibiotics used in SDD are considered safe as they are not absorbed from the gastrointestinal tract. However, the literature shows that tobramycin serum levels have been detected in critically ill patients.[4-9] Oudemans-van Straaten et al. concluded that traces of tobramycin were present in the blood of the majority of acute critically ill patients after treatment with SDD. Tobramycin absorption was associated with severe shock, inflammation and subsequent acute kidney injury.[4] Mol et al. studied absorption of tobramycin in patients with acute renal failure treated with continuous venovenous haemofiltration (CVVH). SDD treatment in these patients can lead to detectable and potentially toxic serum concentrations.[5] In addition, there are case reports of ICU patients with toxic tobramycin serum levels (>2.0 mg/l).[7-9] One of these patients was admitted to Martini Hospital and formed the initiative for conducting this study.[7] It is known that prolonged high tobramycin serum trough concentrations are correlated with nephrotoxicity.[10] When used intravenously, a therapeutic tobramycin trough concentration should not be higher than 1.0 mg/l; concentrations of >2.0 mg/l are considered toxic.[11,12]

In the Dutch National SDD Guideline (Stichting Werkgroep Antibioticabeleid (SWAB)), it is advised to monitor aminoglycoside levels in patients with impaired renal function (≤30 ml/min) and/or undergoing CVVH or haemodialysis.

However, the guideline provides no guidance if high tobramycin concentrations are detected.[13]

The aim of this study was to evaluate the prevalence of SDD-treated ICU patients with tobramycin levels of >1.0 mg/l. Furthermore, we hypothesise that there should be a reason why tobramycin is absorbed from the gastrointestinal tract. The secondary aim is to identify risk factors that may contribute to an increased risk of absorption of tobramycin.

Materials and Methods

After receiving permission from the Medical Ethics Review Committee (RTPO Leeuwarden, the Netherlands) we performed a single-centre observational prospective cohort study. The trial was registered in the Dutch trial register (NTR) as trial number NTR5661.

All patients admitted to the ICU and receiving treatment with SDD were asked to participate in the study. Patients were informed about the research through a patient information letter. If the patient agreed to participate, he or she had to sign informed consent. A representative had to provide permission if the patient was unable to due to sedation and/or severe illness.

Inclusion criteria

- Patients admitted to the ICU
- Patients receiving SDD four times daily

Exclusion criteria

- Patients admitted to the burns ICU
- Patients receiving tobramycin concurrently or 72 hours prior to SDD treatment
- Patients not treated with the regular schedule

The SDD treatment in the Martini Hospital is administered four times daily and consists of:

- 1 g cefotaxime intravenously four times daily for the first four days
- 0.5 g mouth paste (in ventilated patients) with 2% colistin, 2% tobramycin and 2% amphotericin B
- 10 ml suspension with 100 mg colistin, 80 mg tobramycin and 500 mg amphotericin B

If a patient met the inclusion criteria and permission was obtained, the patient was included in the study. Patients received SDD according to a four-times daily schedule, therefore continuous tobramycin levels were to be expected. On day 3, 7, 10 and 14 after the starting SDD a blood sample was drawn during the standard blood collection round at 6 am. If a patient was discharged within 14 days, blood samples were taken as long as the patient was admitted to the ICU. Tobramycin serum concentrations were determined using a Roche immunoassay (Cobas c502, Roche diagnostics, Almere, the Netherlands). The limit of quantification was 0.3 mg/l. Patient data were obtained from the electronic medical records (Chipsoft). The glomerular filtration rate (GFR) was estimated using the Cockcroft and Gault formula.[14]

Data were analysed with IBM SPSS Statistics 25.0 (IBM Corporation, New York, USA). Descriptive statistics (such as frequencies, percentage, mean and standard deviation) were used to show patient characteristics. The primary outcome of our study was the number of patients with a tobramycin level >1 mg/l. The secondary outcome was the number of patients with measurable tobramycin concentrations. To explore and test differences between groups the Student's t-test was used. The Mann-Whitney U test was used for not normally distributed values. The Fisher exact test was used for nominal values. To adjust for multiplicity, we used the Holm-Bonferroni procedure. Furthermore, logistic regression was used to explore if tobramycin cases could be predicted by risk factors of absorption and reduced excretion. As pre-specified risk factors for absorption we defined: abdominal surgery, sepsis, and number of routes of SDD administration. Risk factors for reduced excretion were: impaired renal function defined as a GFR <30 ml/min and CVVH. To correct for the severity of illness, the APACHE III score at admission was introduced in the model.

Results

Between March and October 2016, 50 patients were included. Due to incomplete data five patients were excluded from the data analysis. *Figure 1* shows the consort flow diagram of this study. Patient characteristics and an overview of the SDD treatment of the included 45 patients are shown in *table 1*.

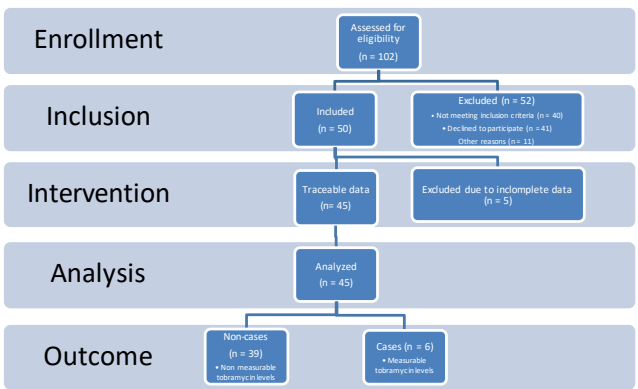

Figure 1. The consort flow diagram

Primary aim: prevalence

Of the 45 patients included in this study, none had a tobramycin level of >1 mg/l. Six patients (13%; 95% CI -23) had detectable tobramycin levels. In *table 2*, an overview is given of the

Table 1. Characteristics of patients and SDD use

Characteristic	Value*
General parameters	
Male - no. (%)	30 (67)
Age - years	67 ± 14
Duration of stay - days	18 ± 19
APACHE III score at admission	76 ± 23
Type of admission	No. (%)
Elective	7 (16)
Emergency	39 (84)
Cause of admission	No. (%)
Medical	22 (49)
Emergency surgery	15 (33)
Elective surgery	8 (18)
Events during stay	No. (%)
Abdominal surgery	22 (49)
Sepsis	27 (60)
Abdominal sepsis	9 (20)
Impaired renal function (GFR <30 ml/min)	12 (27)
CVVH	11 (24)
Haemodialysis	1 (2)
Type of SDD treatment	No (%)
Suspension	45 (100)
Mouth paste	35 (78)
Suppository	2 (4)
Duration of treatment	Days
Total	18 ± 18
Suspension	16 ± 18
Mouth paste	13 ± 19
Suppository	15 ± 13

* scale variables: mean ± standard deviation, nominal variables: number and percentage

Table 2. Tobramycin levels in patients with detectable tobramycin levels in mg/l. The limit of quantification is 0.3 mg/l, values below this limit are reported as <0.3.

Patient*	Tobramycin level (mg/l)			
	Day 3	Day 7	Day 10	Day 14
1	<0.3	<0.3	<0.3	0.8
2	<0.3	<0.3	0.7	0.4
3	0.5	0.6	<0.3	Discharged
4	<0.3	<0.3	0.4	<0.3
5	<0.3	<0.3	0.7	Discharged
6	<0.3	<0.3	<0.3	0.4

*Only the 6 patients with detectable levels out of in total 45 patients are displayed. All other patients had levels below the limit of quantification.

tobramycin levels for the six patients with detectable tobramycin. As shown, the occurrence of tobramycin absorption is not consistent. For example, patient 3 had detectable tobramycin on day 3 and day 7 of treatment, however, the levels were undetectable on day 10. No high (≥1.0 mg/l) tobramycin serum concentrations were found, which suggests that no dose adjustments were necessary. The question arises whether therapeutic drug monitoring (TDM) of tobramycin as propagated by the SWAB guideline is useful for patients receiving SDD treatment. Nevertheless, tobramycin levels during the full SDD treatment remain unknown; we only measured serum levels during the first 14 days, on 4 set days. Further research should be done to confirm that TDM is necessary and which cut-off levels should be used to adjust of SDD.

Table 3. Patient characteristics and use of SDD in patients with and without detectable tobramycin levels. To control for the family wise error rate due to multiple testing, the Holm-Bonferroni correction was applied to p values.

Characteristic	Detectable tobramycin levels*		
	No (n=39)	Yes (n=6)	p value†
General parameters			
Male - no. (%)	26 (67)	4 (67)	n.a. [1.000]
Age - years	67 (61-76)	76.5 (73-81.5)	0.091 [0.021]
Duration of stay - days	11 (7-16)	23 (13-30)	0.085 [0.014]
APACHE III score at admission	72±6.5	99±30	0.077 [0.006]
Type of admission - no. (%)			
Elective	6 (15)	1 (17)	n.a. [1.000]
Emergency	33 (85)	5 (83)	
Cause of admission - no. (%)			
Medical	21 (54)	1 (17)	0.232 [0.151]
Emergency surgery	11 (28)	4 (67)	
Elective surgery	7 (18)	1 (17)	
Events during stay - no. (%)			
Abdominal surgery	18 (46)	4 (67)	0.312 [0.414]
Sepsis	21 (54)	6 (100)	0.106 [0.067]
Abdominal sepsis	5 (13)	4 (67)	0.082 [0.010]
Impaired renal function (GFR <30 ml/min)	7 (18)	5 (83)	0.043 [0.003]
CVVH	6 (15)	5 (83)	0.028 [0.002]
Haemodialysis	1 (3)	0 (0)	n.a. [1.000]
Type of SDD treatment			
Suspension - no. (%)	39 (100)	6 (100)	n.a., all patients
Mouth paste - no. (%)	29 (74)	6 (100)	0.302 [0.312]
Suppository - no. (%)	0	2 (33)	0.097 [0.015]
Number of routes of administration of SDD	2 (1 - 2)	2 (2 - 3)	0.093 [0.011]
Duration of treatment (days)			
Total	9 (5 - 14)	22 (12 - 45.8)	0.091 [0.008]
Mouth paste	5.5 (2 - 10.5)	12.5 (5.8 - 40.8)	0.268 [0.077]
Suppository	-	14.5 (5.0 - 14.5)	n.a.

*scale variables with non-normal distribution: median and IQR, Mann-Whitney U test; scale variables with normal distribution: mean ± 95% confidence interval, t-test; nominal variables: number and percentage, Fisher exact or Chi2 test. †p value with Holm-Bonferroni correction applied to 14 tests, unadjusted p-value between brackets. Tests with an unadjusted p value of 1 were excluded from the Holm-Bonferroni correction. n.a. = not applicable.

Secondary aim: identification of risk factors

Table 3 shows the differences in patient characteristics and use of SDD between patients with and without detectable tobramycin. CVVH (two-sided Fisher's exact test, Holm-Bonferroni p=0.028) and impaired renal function (two-sided Fisher's exact test, Holm-Bonferroni p=0.043) were significantly more frequent in patients with detectable tobramycin than in patients without detectable levels. Moreover, all patients with detectable tobramycin levels had impaired renal function and / or CVVH during the study period. In the univariate analysis, the frequency of risk factors for absorption, such as abdominal sepsis (two-sided Fisher's exact test, Holm-Bonferroni p=0.082) and abdominal surgery (two-sided Fisher's exact test, Holm-Bonferroni p=0.312), was not significantly different between patients with and without detectable tobramycin. Interestingly, detectable tobramycin was found in all patients who received suppositories as part of SDD.

Logistic regression analyses were conducted to predict detectable tobramycin levels using the APACHE III score at admission, abdominal surgery, sepsis, number of routes of SDD administration, CVVH and impaired renal function as predictors. Due to the limited number of patients with detectable tobramycin, three separate models were evaluated *(table 4)*.

Table 4. Logistic regression models to predict patients with detectable tobramycin levels

	Coefficient	Standard error	Odds ratio
CVVH and APACHE III model			
Constant	-9.011	3.623 (p=0.013)	-
CVVH	3.431	1.340 (p=0.010)	30.9
APACHE III score	0.066	0.038 (p=0.082)	1.07
Chi^2 16.615, p=0.0002, degrees of freedom=2; Nagelkerke R^2=0.567			
Impaired renal function and APACHE III model			
Constant	-7.868	2.990 (p=0.009)	-
Impaired renal function	2.997	1.248 (p=0.017)	19.6
APACHE III score	0.054	0.032 (p=0.088)	1.06
Chi^2 14.847, p=0.0006, degrees of freedom=2; Nagelkerke R^2=0.517			
Abdominal sepsis and APACHE III model			
Constant	-17.143	6.793 (p=0.012)	-
Abdominal sepsis	6.302	2.487 (p=0.011)	545
APACHE III score	0.145	0.063 (p=0.022)	1.16
Chi^2 23.1, p=0.00001, degrees of freedom=2; Nagelkerke R^2=0.738			

The logistic regression model with CVVH and APACHE III was tested to have a better fit compared with a constant-only model ($Chi^2_{(2)}$ =16.6, p=0.0002; Nagelkerke R^2=0.567). This indicates that CVVH and APACHE III are predictors for patients to have detectable tobramycin. Only CVVH was found to be a significant predictor (p=0.01). A test of a model with impaired renal function and APACHE III against a constant-only model was statistically significant ($Chi^2_{(2)}$=14.8, p=0.0006; Nagelkerke R^2=0.517). Therefore, impaired renal function and APACHE III are predictors for patients with detectable tobramycin. Only impaired renal function was a significant predictor (p=0.017). A model with abdominal sepsis and APACHE III as predictors was significant compared with a constant-only model ($Chi^2_{(2)}$=23.1, p=0.000010; Nagelkerke R^2=0. 0.738). The combined information about abdominal sepsis (p=0.011) and APACHE III (0.022) could predict whether patients had detectable tobramycin. We could not evaluate a valid model with CVVH, impaired renal function and abdominal sepsis as predictors. Also, it was not possible to test the interaction of abdominal sepsis and impaired renal function.

Discussion

The primary aim of our study was to estimate the prevalence of patients with a tobramycin level of above 1 mg/ml in SDD-treated ICU patients. In our study, no patients reached the primary outcome of a tobramycin level above 1 mg/l. Tobramycin levels were detected in 13% of patients. Within the group of patients with detectable tobramycin, highly variable levels were found.

The secondary aim of our study was to identify risk factors for detectable tobramycin. All patients with detectable tobramycin levels had a GFR of <30 ml/min and/or CVVH. Only CVVH and impaired renal function were found to be significant predictors of detectable tobramycin levels in the univariate analysis. This is in line with previous research.[4-6] In multivariate analyses, CVVH, impaired renal function and abdominal sepsis were found to predictors of detectable tobramycin in addition to APACHE III in three separate logistic regression models.

Because tobramycin is renally cleared, impaired renal function and/or CVVH is related to measurable tobramycin levels.[4-6] However, this does not explain how the tobramycin entered the bloodstream, since it is not readily absorbed from the gastrointestinal tract. We think that the presence of detectable tobramycin is due to a combination of an increase in absorption on the one hand, and a lack of excretion of the absorbed tobramycin on the other hand. Previous studies focused mainly on the elimination part.[4-6] Therefore, we looked at potential risk factors for the absorption of tobramycin, such as abdominal surgery, sepsis (associated with intestinal barriers loss[15]), abdominal sepsis and number of routes of administration. Unfortunately, mainly due to the limited number of cases and/or patients included in our study we were not able to detect or to rule out a significant contribution of risk factors for absorption in the occurrence of detectable tobramycin levels. Also, it was not possible to construct a valid logistic regression model to explore the influence of absorption in addition to reduced renal clearance on the possibility of detectable tobramycin levels.

Moreover, we were not able explore the interaction between factors of absorption and reduced renal clearance on the possibility of detectable tobramycin levels. Although we were able to construct a valid logistic regression model to predict detectable tobramycin levels with APACHE III at admission and abdominal sepsis as a risk factor for absorption, we find this less clinically plausible as the elimination of tobramycin is omitted. Interestingly, only two patients received suppositories, with tobramycin being detected in both patients. This may be a lead for future studies.

This study has several limitations. The study was conducted in a single centre. Furthermore, the population of ICU patients studied was heterogeneous. We used the APACHE III score as a proxy for severity of illness; one could argue that a daily severity of illness score should be used. Only a small number of patients were included, which could potentially explain the small number of patients in whom tobramycin was detected. As no cases with toxic or even high tobramycin serum levels were found, more patients are needed to draw valid conclusions. Future research should be carried out with a larger group of patients. We recommend to include factors such as abdominal sepsis and number of routes and type of SDD administration, so new risk factors may be potentially added to the SWAB guideline.

Conclusion

In our study, no patients reached the primary outcome of a tobramycin level above 1 mg/l. Tobramycin was detected in 13% (95% CI 3-23%) of the patients receiving SDD. This study is an indication that absorption may be a factor to consider in relation to measurable tobramycin levels. Further research is necessary to provide more information about the necessity and frequency of measuring tobramycin serum levels, the risk factors for detectable levels and how to manage detectable or high tobramycin levels.

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Disclosures

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