Observed concentrations of amikacin and gentamycin in the setting of burn patients with gram-negative bacterial infections: Preliminary data from a prospective study

Therapies

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Résumé:	Aim of the Study Critically ill populations often have shown subtherapeutic aminoglycosides' concentrations mostly because of unavoidable changes in drug volume distribution and clearance. We present a real life prospective study evaluating plasma concentrations for once-daily dosing foramikacin and gentamycin among a population of severe burn adults. Methods We conducted a real life prospective study on the plasma concentrations of amikacin and gentamycin among severe burn patients, using aminoglycoside as combination therapy. Antibiotics were prescribed at the standard doses of 15-20 mg/kg/day for amikacin and 3-5mg/kg/day for gentamycin Results Eight patients (4 in amikacin and 4 in gentamycin groups, respectively) were enrolled in the study. All subjects were admitted for severe burns. The most common site of infection was bloodstream (5; 62.5%) and pneumonia (4; 50%). Pseudomonas aeruginosa , followed by Klebsiella pneumoniae and multi-drug resistant Acinetobacter baumannii were the most prevalent agents isolated. Amikacin and gentamycin never achieved the target peak concentration of 60mg/L and 30mg/L: in our study C max , for amikacin, was 33.1 ±15.6mg/L (SD), while for gentamycin was 14.3 mg/L ±9. C max and total body surface area have shown a strong negative correlation with borderline statistical significance (amikacin: ρ= 0.922, p=0.078; gentamycin: ρ=0.937, p=0.063). At the standard dosage, the pharmacokinetic/pharmacodynamic (PK/PD) target of Cmax > 8 x highest MIC was reached for 8 (53.3%) out of 15 isolated pathogens. Conclusions The present study found that, in a population of septic burn patients, standard doses of

	gentamycin and amikacin most often lead to plasma concentrations under the PK/PD target
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UNIVERSITÀ DEGLI STUDI DI TORINO
DIPARTIMENTO DI SCIENZE MEDICHE

Turin, September 19th 2020

Dear Editor,

Thanks for the opportunity to revise our manuscript. Please find the response to reviewers' comments on our manuscript entitled "**Observed concentrations of Amikacin and Gentamycin in the Setting of Burn Patients with Gram-Negative Bacterial infections: preliminary data from a prospective study**" to be considered for publication in *Therapies*

Reviewer comments

Thanks you for your revision which improve the manuscript. Few issues are still remaining.

1) Discussion section: Please modify the following sentence in order to improve understanding : "Thirdly, we use exact MIC value and clinical breakpoints in the pharmacological analysis, despite that using ECOFF as MIC value is more appropriate in ICU than the use of clinical breakpoints for defining PK-PD targets of an antibiotic treatment" to "Thirdly, in the PK-PD analysis we use clinical breakpoints when exact MIC value were not available, despite that using ECOFF as MIC value is more appropriate in ICU population (Guilhaumou et al., Critical Care, 2019)."

Thank you for these corrections. The sentence was modified in the text.

2) Conclusion: Line 20-21 page 5 : Please correct « concetrations ».

Thank you for these correction. The word was corrected in the text.

3) Ethics approval: Please correct the discrepancy between "Ethics approval and consent to participate section" ("Informed consent was waived due to the retrospective nature of the study. The study was performed by ICH-GCP guidelines and the declaration of Helsinki")

and "Methods" section ("The study was approved by the local ethical committee (PROT. N.0063741) and written informed consent was obtained from all patients before the sampling").

Thank you for this suggestion that improve the manuscript. Right formi s the second one, presented in method section. We have modify also ethics approval.

Sincerely,

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THERAPIES

HEADING: Pharmacokinetics

Observed concentrations of amikacin and gentamycin in the setting of burn patients with gram-negative bacterial infections: preliminary data from a prospective study

Pharmacokinetics of amikacin and gentamycin

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Summary

Aim of the study.- Critically ill populations often have shown subtherapeutic aminoglycosides' concentrations mostly because of unavoidable changes in drug volume distribution and clearance. We present a real life prospective study evaluating plasma concentrations for once-daily dosing for amikacin and gentamycin among a population of severe burn adults. *Methods*.- We conducted a real life prospective study on the plasma observed concentrations of amikacin and gentamycin among severe burn patients, using aminoglycoside as combination therapy. Antibiotics were prescribed at the standard doses of 15-20 mg/kg/day for amikacin and 3-5mg/kg/day for gentamycin. *Results*.- Eight patients (4 in amikacin and 4 in gentamycin groups, respectively) were enrolled in the study. All subjects were admitted for severe burns. The most common site of infection was bloodstream (5; 62.5%) and pneumonia (4; 50%). *Pseudomonas aeruginosa*, followed by *Klebsiella pneumoniae* and multi-drug resistant *Acinetobacter baumannii* were the most prevalent agents isolated. Amikacin and gentamycin never achieved the target peak concentration of 60mg/L and 30mg/L: in our study C_{max}, for amikacin, was 33.1 ±15.6mg/L (SD), while for gentamycin was 14.3 mg/L ±9. C_{max} and total body surface area have shown a strong negative correlation with borderline statistical significance (amikacin: ρ= 0.922, p=0.078; gentamycin: ρ=0.937, p=0.063). At the standard dosage, the pharmacokinetic/pharmacodynamic (PK/PD) target of C_{max} > 8 x highest MIC was reached for 8 (53.3%) out of 15 isolated pathogens. *Conclusions*.- The present study found that, in a population of septic burn patients, standard doses of gentamycin and amikacin most often lead to plasma concentrations under the PK/PD target

KEYWORDS

Pharmacokinetic; Burn; Amikacin; Gentamicin; Gram-negative; Infections

Abbreviations

AGs: aminoglycosides

AMK: amikacin

Cmax: peak drug concentration

EUCAST: European Committee on Antimicrobial Susceptibility Testing

GEM: gentamycin

IV: intravenous

MIC: minimum inhibitory concentration

PD: pharmacodynamic

PK: pharmacokinetic

TBSA: total body surface area

TDM: therapeutic drug monitoring

Vd: volume distribution

Introduction

Aminoglycosides (AGs) have been commonly used as a part of the combination regimen for managing bacterial infections in severe burn patients, increasing the chance of initial effective therapy [1]. Infection is the most frequent complication encountered by burn patients, with a high risk of gram-positive isolates immediately after hospital admission and a risk of gram-negative bacteria that increases with the length of hospital stay [2-3]. AGs display a concentration-dependent killing activity; thus, the rate and extent of bacterial killing are driven by peak drug concentrations (i.e., C_{max}) [4]. Pharmacodynamic, bacteriological and toxicological expertise have allowed for increasingly higher usage of aminoglycosides in once-daily dosing regimens, due to its ability to achieve desirable antibiotic blood concentration and potentially reduce the risk of nephrotoxicity [5]. Severe burn patients often show subtherapeutic AG concentrations, mostly due to changes in volume distribution (Vd) and clearance [6]. Hence, the pharmacodynamic (PD) target – the ratio of C_{max} to the minimum inhibitory concentration (MIC) $\geq$8 (notably by eight-fold to twelve-fold) after the first dose – is often difficult to achieve [6]. A weight-based dose adjustment scheme, commonly known as the Hartford nomogram, has been recommended for the treatment of gram-negative infections; dosing correction was based on pharmacokinetic (PK) data derived from the general patient population [7]. However, the recommended AG dose is likely to be insufficient to achieve target peak drug concentrations in critically ill patients due to differences in PK compared with the general patient population. PK parameters AG are much more variable in critically ill patients, and in the severe burn patients themselves, than in the general population. Therefore, treatment of critically ill patients requires

frequent dose changes and therapeutic drug monitoring (TDM) practice to achieve therapeutic antibiotic concentrations and maximise effectiveness and safety [8-11].

We aimed to describe observed concentrations of amikacin (AMK) and gentamycin (GEM) in a population of severe burn patients.

Methods

We conducted a real life prospective study on the plasma concentrations of AMK and GEM among severe burn patients. Antibiotics were prescribed at the standard, in label, doses of 15-20 mg/kg/day for AMK and 3-5 mg/kg/day for GEM. The target peak concentrations (C_{max}) for AMK and GEM were, respectively, 60 mg/L and 30 mg/L, according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) definitions, and the target pharmacokinetic/pharmacodynamic (PK/PD) ratio was defined as a C_{max} >8 x highest MIC [12]. Both drugs were given intravenously (IV) over 30 minutes, either as empirical or targeted therapy. The study was approved by the local ethical committee (PROT. N.0063741) and written informed consent was obtained from all patients before the sampling. All subjects admitted to the Burn Center of Turin, Italy from January 2016 to April 2018 and treated with AMK or GEM, either empirically or as target therapy, were enrolled in the study. Complete demographic characteristics, medical histories and clinical parameters were collected from each subject, including days of hospitalisation, blood chemistries, renal function and specific burn indices. Sepsis and septic shock were classified according to the Third International Consensus Definition (Sepsis-3) [13]. Microbiological data, where available, were also collected.

Plasma aminoglycosides concentrations were determined at steady-state ≥48 h after the beginning of therapy. The first blood sampling was performed immediately before the antibiotic administration (T0) and, another sample was obtained at the end of the infusion (T1). The C_{max} is defined as the concentration at the end of the infusion. Blood samples were collected in lithium heparin tubes (7 mL) and plasma was obtained by centrifugation at 1400 *X* g for 10 min at 4 °C (ALC PK 130R refrigerated centrifuge; DJB Labcare Ltd., Newport Pagnell, UK). Each sample was stored at - 20 °C until analysis (<3 weeks). Stability tests performed during method validation reported drug stability (<5% degradation) within 1 month (data not shown). AMK and GEM concentrations were

determined in the setting of routine clinical care via the HPLC-photodiode method (HPLC-photodiode array).

Descriptive and correlation statistical analysis were performed using SPSS 24.0 software (IBM).

Results

Eight patients were enrolled in the study – four in the AMK treatment group and four in the GEM treatment group. Patients' characteristics are shown in Table 1. All subjects were admitted for severe burns, involving 10–55% of their total body surface area (TBSA), with a mean Revised Baux Score of 104.5 ± 50.4. Six patients (75%) required mechanical ventilation and two had septic shock [13]. The most common sites of infection were the bloodstream (5; 62.5%) and pneumonia (4; 50%). In three cases (37.5%), infection involved more than one site. The most frequently isolated bacteria were *Pseudomonas aeruginosa*, followed by *Klebsiella pneumoniae* and multidrug-resistant *Acinetobacter baumannii* (Table 2). The administration of 15–20 mg/kg of AMK and 3–5 mg/kg of GEM never achieved the respective target peak concentrations of 60 mg/L and 30 mg/L (Table 2). The mean C_{max} was 33.1 ± 15.6 mg/L (SD) for AMK and 14.3 mg/L ±9 (SD) for GEM. C_{max} values for both AMK and GEM were negatively correlated with burn surface area (e.g., TBSA), with borderline statistical significance (AMK: $\rho = 0.922$, $p = 0.078$; GEM: $\rho = 0.937$, $p = 0.063$). At the standard dosage, the PK/PD target of C_{max} >8 x highest MIC was reached for 8 (53.3%) out of 15 isolated pathogens. No incidents of acute kidney failure were reported during aminoglycosides treatment.

Discussion

Complex haemodynamic changes occurring in critically ill burn patients may be different depending on the phase after the burn injury [8]. In the early phase, there is a greater volume of distribution (Vd) that may be due to weight gain secondary to aggressive IV fluid resuscitation (i.e., Parkland formula), flanked by hypoalbuminemia and a variable glomerular filtration rate [6]. The latter is one of the most

predictive markers for AG clearance, along with Vd, and it is linked to the presence of renal dysfunction: decreased urine output may denote low renal blood flow and AG clearance, on the other hand in the absence of organ dysfunction, AG output could result consistently increased [6-7]. Altered pharmacokinetics in burn patients may affect antibiotic plasma concentrations and, in most studies, the C_{max} for aminoglycosides was always below therapeutic plasma level, with high interindividual variability [10]. However, these changes are generally not considered when deciding upon antibiotic doses for these patients, despite Beaucaire et al. showing a worse outcome in critically ill patients when the C_{max} remained at < 40 g/mL [13]. We reported the PK /PD characteristics of a single daily dose of AMK and GEM, at the standard doses of 15-20 mg/kg and 3-5 mg/kg, respectively, in a small population of burn patients with severe infections caused by gram-negative bacteria. We observed that the standard doses of AMK and GEM never achieved the respective target peak concentrations of 60 mg/L and 30 mg/L, with low mean C_{max} values (33.1 mg/L and 14.3 mg/L, respectively). Conil and colleagues [14] showed that administration of higher doses, particularly of AMK, (e.g., 20 mg/kg) was insufficient to ensure the goal of C_{max}/MIC ratio up to six-fold, achieved in only 47% (18/28) of cases. Several studies used TDM with dose modification to achieve concentrations within a predefined range in the general population: AMK at a standard dosage of 14–15 mg/kg has reached target concentration range in 91–100% [15], while GEM at a dosage of 5–7 mg/kg has reached target concentration range in 96–98% [16]. In Jenkins et al. [15] and Plajer et al. [16] studies target concentrations were achieved with satisfactory percentages through higher dosages of aminoglycosides compared to this cohort and with the use of TDM. Our population statistical analysis demonstrated a negative relationship between C_{max} and the area of the burn for AMK and GEM, as previously reported by Conil et al. [14], with a strong correlation but with borderline statistical significance, likely due to the low number of patients. Moreover, in this small sample, PK/PD target for efficacy (C_{max}/MIC ≥8) was reached in 53.3%. of subjects No theoretical drug or drug interactions have been observed with concomitant therapies. Higher doses of AG were investigated in a subsequent study by Roger et al. in a non-burnt critically ill population: only 59% of patients led to target peak serum concentrations after the administration of 30 mg/kg and 8 mg/kg of AMK and GEM, respectively [10]. Low peak AG concentrations were also confirmed in other studies that proposed higher dosages or intensive TDM [5-7]. This study had several limitations. First, the number of patients receiving AMK or GEM was too small for the assessment of the impact of confounding factors, such as co-morbidities or synergism or drug interactions with chronic or concomitant therapies, that might have led to further reductions or modifications in peak concentrations. Secondly, we did not evaluate the impact of those antibiotics on clinical outcomes and renal function. Thirdly,

in the PK-PD analysis we use clinical breakpoints when exact MIC value were not available, despite that using ECOFF as MIC value is more appropriate in ICU population [17].

Conclusions

We reported preliminary data from a small, single-centre, real life prospective study on PK/PD of aminoglycosides in burn patients. In literature, most of data on PK/PD and observed concentrations of aminoglycosides are retrospective analysis and no prospective trial. In our prospective study we found that in a population of septic burn patients, standard doses of GEM and AMK most often lead to plasma concentrations under the PK/PD target and peak concentrations might be significantly lower in burn patients compared to those described in critically ill patients [5, 14]; therefore, it may be helpful using higher doses of AMK and GEM, using TDM in clinical practice to avoid sub-optimal therapies and to avoid overexposure and toxicity.

Funding

None to declare

Ethics approval and consent to participate

The study was approved by the local ethical committee (PROT. N.0063741) and written informed consent was obtained from all patients before the sampling

Availability of data and material

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Disclosure of interest

The authors declare that they have no competing interests or conflicts of interest.

Authors' contributions

SC and FGDR conceived the study, AP, FVG, RCL, TL collected, analyzed and interpreted the data, and elaborated the manuscript. MS, AD, FGDR supervised the study, corrected the final version of the manuscript. All authors read and approved the final version of the manuscript. We state that the results presented in this paper have not been published previously in whole or part, except in abstract format.

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Table 1. Patient characteristics and plasma concentrations

Table 2. Microbiological features and observed concentrations

Tables

Table 1: Patient Characteristics and Plasma Concentrations

Patient Code	Antibiotic	Gender	Age	BMI	TBSA (%)	RBS	Septic Shock	Creatinine clearance (ml/min)	CVVH	Cmin (mg/L)	Cmax (mg/L)
1	GEM	F	78	25	30	125	No	39	Yes	3,2	13,9
2	GEM	F	46	25	25	71	No	170	No	<0,2	23,7
3	GEM	M	43	29.4	55	115	No	100	Yes	2,2	5,7
4	GEM	M	64	27.8	45	127	Yes	95	No	0.5	8.9
5	AMK	M	67	26	30	114	No	106	No	<1,0	33,9
6	AMK	M	25	22	50	92	Yes	87	No	<1,0	23,9
7	AMK	M	81	27.8	40	138	No	279	No	<1,0	19,7
8	AMK	F	26	19.5	10	54	No	187	No	1,4	54,7
Mean ± S.D.			53.8 ± 22	25.3 ± 3.2	35.6 ± 14.7	104.5 ± 29.5		132.9 ± 75.4			GEM: 14.3 ± 9; AMK: 33.1 ± 15.6
Median			55	25.5	114.5	114.5		103			GEM: 13.9; AMK: 28.9

Legend (Table 1): S.D. : standard deviation; GEM: gentamicin; AMK; amikacin; BMI: body mass index; M: male; F: female; TBSA: total burn surface area; RBS: revised BAUX score; CVVH: continuous veno-venous hemofiltration; MIC: minimum inhibitory concentration; C: concentration

Table 2: Microbiological Features and Observed Concentrations

Patient Code	Aminoglicosides (AG)	Pathogens Isolated	Site of infections	MIC (exact)	Breakpoint for AG	Cmax/MIC
1	GEM	MSSA E.cloacae P.vulgaris	Wound Swab	1 2 4	S ≤1 S ≤2 R >2	6,9 6,9 3,4
2	GEM	E.Coli P.aeruginosa	Blood Culture	2 2	S ≤2 IE	11,8
3	GEM	K.pneumoniae	Blood Culture	2	S ≤2	2,8
4	GEM	S.marcescens	Blood Culture	2	S ≤2	4,4
5	AMK	P.Aeruginosa A.baumannii MDR	Bronchial Aspirate	8 16	S ≤16 R > 8	4,2 2,1
6	AMK	P.Aeruginosa S.Marcescens M.morganii	Wound Swab	8 8 8	S ≤16 S ≤8 S ≤8	2,9
7	AMK	A.baumannii MDR	Blood Culture	8	R > 8	2,4
8	AMK	K.pneumoniae	Blood Culture	4	R >2	13,6

Legend (Table 2): GEM: gentamicin; AMK; amikacin; MIC (exact): minimum inhibitory concentration; C: concentration; MSSA: Methicillin-susceptible S.aureus; S: sensible; R: resistant; AG: aminoglycosides