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Use of Gentamicin for Sepsis and Septic Shock in Anaesthesia-Intensive Care Unit: A Clinical Practice Evaluation

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Abstract

Objective: Numerous cases of gentamicin underdosing have been described in the literature in the context of sepsis and septic shock in anaesthesia-intensive care units (ICU). A survey of clinical practice was conducted with the aim to rationalise the use of gentamicin in the unit. The secondary objective was to propose a corrective formula for adjusting individual dosage.

Methods: A single-centre survey was used to determine the initial dose of gentamicin administered, in an anaesthesia-ICU, during the first hours of sepsis/septic shock. An initial retrospective phase allowed focusing on the points of improvement in terms of prescription. A second prospective phase enabled the evaluation of benefits following the implemented changes.

Results: Fifty-one patients were included during the retrospective phase (2014-2015) and 28 patients during the prospective phase (2016-2017). Out-of-guideline prescriptions significantly decreased between these two study periods (i.e., pulmonary infections decreased from 70.5% to 18%, $p<0.001$) and the mean±standard deviation administered dosage increased from 7.3±1.2 mg kg^{-1} to 9.5±1.5 mg kg^{-1} ($p<0.001$). Nevertheless, the proportion of Cmax (peak plasma concentration) ≥30 mg L^{-1} and the mean Cmax did not change significantly. A significant association ($p<0.05$) was found between Cmax, body mass index, haematocrit and creatinine, enabling a corrective formula to be proposed.

Conclusion: The present study allowed improvement in gentamicin prescription in an anaesthesia-ICU. A Cmax ≥30 mg L^{-1} remains difficult to achieve, but a Cmax ≥16 mg L^{-1} could be considered relevant for community infections and would be more attainable. A corrective formula could be used to adjust the dosage.

Keywords: Corrective formula, gentamicin, intensive care unit, peak plasma concentration (Cmax), sepsis

Introduction

The use of gentamicin in intensive care has been the subject of a number of recent reports (1, 2). This antibiotic from the aminoglycoside family presents the bactericidal activity based mainly on the inhibition of protein synthesis (3). It is a water-soluble molecule, with very little liposolubility, eliminated without metabolite by the kidneys, and for which there is no biliary or digestive secretion. It is characterised by a low volume of distribution, and therefore it diffuses poorly in tissues such as bronchial secretions, aqueous humour, or the central nervous system (4). During the acute care period, the individual variability in the volume of distribution increases due to disturbances of the capillary permeability. These disturbances are secondary to the haemodynamic instability, inflammatory state, vascular filling, hypoalbuminemia, respiratory insufficiency, and disorders of the renal function (2).

Maximal benefit of gentamicin is observed at the beginning of treatment, when the inoculum is potentially high, and germs are not yet identified (5, 6). It is always used in combination with beta-lactam for the purpose of bactericidal synergy, to broaden the spectrum of treatment activity, prevent the emergence of resistance, and induce a lasting inhibition of bacterial growth.

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The bactericidal action of gentamicin is concentration dependent rather than time dependent. The therapeutic effect is maximal if the inhibitory quotient (peak plasma concentration [Cmax] divided by minimal inhibitory concentration [MIC]) is 8-10. To reach this ratio, it is recommended to use an optimum dose of 7-9 mg kg^{-1} to reach a Cmax ≥30 mg L^{-1} (1, 2, 4). It is important achieve these goals quickly. Indeed, to reduce its nephrological and otological toxicity, gentamicin should be used as a single daily dose over a short period (<5 days). Importantly, adaptive resistance occurs at the first dose, inducing a decrease in the bactericidal rate, an increase in MICs and a decrease in the post-antibiotic effect duration.

Since 2014, several studies have shown that Cmax ≥30 mg L^{-1} was reached, at first injection, in only 10% of cases, despite the administration of a mean dose of 7 mg kg^{-1} of actual weight (7-11). Some teams investigated the clinico-biological risk factors for gentamicin underdosing (9, 10), which could allow for the development of a corrective formula to improve the use of gentamicin in the context of sepsis/septic shock.

Following a clinical practice evaluation, the present study aimed at improving the use of gentamicin in an anaesthesia-intensive care unit (ICU)/emergency unit. The secondary objective was to explore the association between Cmax and underdosing risk factors described in the literature to propose a corrective formula.

Methods

Study design

The present study was a single-centre survey of practices conducted according to the method validated by the French health authorities (*Haute Autorité de Santé*, HAS) (12), in the department of anaesthesia-ICU emergencies of the Desgenettes Military Teaching Hospital, in Lyon, France. The preliminary phase was performed retrospectively, and the second phase was performed prospectively. Results of the retrospective phase were presented orally and distributed electronically to the entire team of the anaesthesia-ICU (12 doctors). Formalised expert reviews, as well as the guidelines used for the study, were transferred to the team during a meeting and electronically. For development of the prospective phase, and in view of implementing a change in practice, a prescription help sheet, containing a summary of recommendations, was proposed. Following the implementation, the prospective phase of the study was completed.

Materials used for development of practice guidelines in the ICU

The choice of dosage and Cmax targets were based on the 2011 national medicines agency (*Agence française de securité sanitaire des produits de Santé*) (4) and the 2015 national resuscitation council (*Société de Réanimation de Langue Française*) (2) guidelines.

To rationalise prescriptions among physicians, we carried out a review of the guideline literature from different international and national learned societies (*Société Française d'Anesthésie et de Réanimation* (13, 14), *Société de Pathologie Infectieuse de Langue Française* (15), Infectious Diseases Society of America (16-18), European Society of Cardiology (19), and *Agence Nationale de Sécurité du Médicament et des produits de Santé* (4, 14). Formalised expert reviews, articles published on the subject (13, 20-22) and the Cochrane Database of Systematic Reviews (23) were also used.

Eligibility criteria

For the initial retrospective phase, all patients who received the first injection of gentamicin as part of a dual therapy for the treatment of sepsis or septic shock in the intensive care, with a Cmax reported in the medical or hospital biochemistry files, were included.

For the following prospective phase, all patients who received the first injection of gentamicin, as part of a dual therapy for the treatment of sepsis or septic shock in intensive care, but also in the anaesthesia unit with a Cmax documented by the hospital's biochemistry laboratory record, were included.

All patients who benefited from gentamicin outside the context of sepsis or septic shock were excluded. Stable patients who received gentamicin as a curative treatment in visceral surgery departments (treated for cholecystitis, appendicitis, diverticulitis or sigmoiditis), infectious diseases (treated for infective endocarditis or osteitis), or for antibiotic prophylaxis in the context of a set surgery (14) were excluded.

Data collection and Cmax measurement

Data collection for the retrospective phase was done using computerised medical records. During the prospective phase, all patients receiving gentamicin were recorded, based on exhaustive computerised medical recording and prescription sheets analyses. Feedback was obtained from the biochemistry department databases and the computerised medical files to ensure that all patients who had been dosed for the first gentamicin injection were included.

For each patient, the following information was collected: age, weight, height, body mass index (BMI), haematocrit (Ht), creatinine, Modification of Diet in Renal Disease clearance, the Simplified Acute Physiological Score (SAPS), mortality at Day 1 and Day 30, administered dose for the first gentamicin injection (in mg and mg kg^{-1}), corresponding Cmax and the site of infection treated. The proportion of gentamicin use for a given site of infection was calculated based on the ICU's data records.

A gentamicin assay was performed on plasma from whole blood collected on lithium heparin. The concentration of

gentamicin was determined by an indirect competitive immunoassay method (Cobas 'c', Roche Diagnostics, Swiss). The measurement range was 0.4-10 mg L^{-1}. If the result was greater than 10 mg L^{-1}, the sample was diluted (Preciset TDM I Diluent, Roche Diagnostics) at the ratio 1:1 and tested again. Variation coefficients of the repeatability and reproducibility tests were 3.8% and 4.5%, respectively. The assay method was accredited according to the International Organization for Standardization 15 189.

Statistical analyses

A comparison of the data collected during the retrospective phase and prospective phase was carried out. The distribution of quantitative data was determined using the Kolmogorov- Smirnov test; normally distributed data were compared using Student's t-test, and non-normally distributed data using the non-parametric Mann-Whitney U test. Qualitative data with a theoretical Size >5 were analysed using the chi-squared test, and those with a theoretical Size <5 were analysed using Fisher's exact test. An association between the Cmax and clinical and laboratory factors collected initially during the retrospective phase and then for the combined retrospective and prospective phase population was investigated using the multiple linear regression. The threshold of significance (p) was set at 0.05 for the initial analysis of data obtained during the retrospective phase. Data from the total population of both phases was then analysed, the Bonferroni correction was applied, and the significance level was divided by 2 (0.025).

Ethical approval

All procedures performed in the present study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study of clinical practice evaluation was approved by the ethics committee of the Desgenettes Military Teaching Hospital, in Lyon, France.

Results

Study population

A total of 51 patients were included in the retrospective phase, from April 2014 to September 2015 (17 months), and 28 patients in the prospective phase, from November 2016 to August 2017 (10 months). Unlike the retrospective phase, which included a 100% of patients from the ICU, the prospective phase included 79% (n=22) of patients from the ICU, and 21% (n=6) from the operating theatre.

Between the two periods of study, the patients included differed significantly in terms of mean age, mortality at Day 30 and SAPS. There was no significant difference for the other parameters collected (Table 1).

Primary objective

Among the total population treated with gentamicin, there was a significant decrease in the proportion of gentamicin prescriptions administered out of guidelines for pulmonary infections between the first phase (70.5%) and the second phase of the survey (18%, p<0.001). The administration of gentamicin following recommendations was significantly increased for intra-abdominal infections between the initial phase (13.5%) and the second phase (50%, p=0.001; Table 2). Of note, between the retrospective phase and the prospective phase, the proportion of gentamicin-treated patients in the ICU increased for intra-abdominal infections (20% vs. 48%) and decreased for pulmonary infections (22% vs. 6%) and urinary tract infections (5% vs. 0%).

Between the two study periods, the mean dosage (mg kg^{-1}) increased significantly (7.3±1.2 vs. 9.5±1.5, p<0.001). However, there was no significant increase in the proportion of patients achieving a Cmax ≥30 mg L^{-1} or ≥16 mg L^{-1} (Table 3).

Secondary objectives

The linear regression analysis performed on data from the retrospective phase (n=51) showed an association between gentamicin Cmax and BMI, Ht, and creatinine (p<0.05).

Table 1. Description of the population for the two periods studied

Description and comparison of the population	Retrospective phase (n=51)	Prospective phase (n=28)	p
Mean age (years)±SD	69±15	59±22	0.01
Mean SAPS (points)±SD	46±15	36±13	0.006
Mortality at Day 30 (%)	26	4	0.01
Mortality at Day 1 (%)	6	4	ns
Mean BMI (kg m^{-2})±SD	26±6	24±6	ns
Mean haematocrit (%)±SD	33.5±6	36±7	ns
Mean creatinine (µmol L^{-1})±SD	98±86	116±106	ns
Mean MDRD (mL min^{-1} 1.73 m^2)±SD	99±63	85±55	ns

SAPS: Simplified Acute Physiological Score; BMI: body mass index; MDRD: Modification of Diet in Renal Disease; SD: standard deviation; ns: non-significant

Table 2. Description of sites of infections treated with gentamicin

Site of infection	Retrospective phase (n=51) % (n)	Prospective phase (n=28) % (n)	p
Out-of-guideline administration			
Pulmonary	70.5 (36)	18 (5)	<0.001
Urinary tract	4 (2)	0	ns
Recommended administration			
Intra-abdominal	13.5 (7)	50 (14)	0.001
Neurological	2 (1)	10.5 (3)	ns
Skin	8 (4)	10.5 (3)	ns
Bone	0	3.5 (1)	ns
Otolaryngology	0	3.5 (1)	ns
Not specified	2 (1)	3.5 (1)	ns

n: number of patients; ns: non-significant

Table 3. Description of gentamicin dosages used and cmax rates obtained

	Retrospective phase (n=51)	Prospective phase (n=28)	p
Mean dosage (mg kg^{-1})±SD	7.3±1.2	9.5±1.5	<0.001
Mean dosage (mg)±SD	543±137	610±193	ns
Mean Cmax (mg L^{-1})±SD	20.1±6	22.0±7.1	ns
Cmax ≥30 mg L^{-1} % (n)	10 (5)	15 (4)	ns
Cmax ≥16 mg L^{-1} % (n)	72 (37)	76 (20)	ns

Cmax: peak plasma concentration; SD: standard deviation; ns: non-significant; n: number of patients

Association relationship between Cmax, BMI, Ht and creat:

- Cmax=constant+0.17*BMI+0.34*Ht+0.02*creat
- Δ Cmax=0.17*(BMI–mean BMI)+0.34*(Ht–mean Ht)+0.02*(creat–mean creat)

Association relationship between Cmax and dosage:

- Cmax=constant+1.94*Dosage
- Corrected dosage=Mean dosage+*Δ Cmax*/1.94
- Corrected dosage=mean dosage–[0.17*(BMI–mean BMI)+0.34*(Ht–mean Ht)+0.02*(creat–mean creat)]/1.94

Corrected dosage=**9**–[0.17*(BMI–**27**)+0.34*(Ht–**36**)+0.02* (creat–**141**)]/1.94

Figure 1. Description of the corrective formula obtained
Cmax: peak plasma concentration; BMI: body mass index; Ht: haematocrit; Creat: creatinine

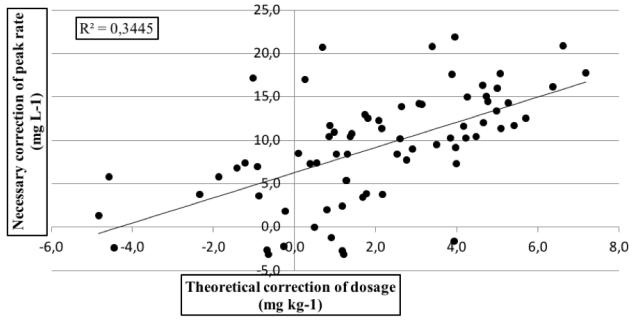

Figure 2. Retrospective testing of the proposed corrective formula: Correlation between observed Cmax and the required correction dosage given by the formula (79 patients).

- **The upper right points (X positive and Y positive) represent patients with Cmax <30 mg L^{-1} for whom the corrective formula did advocate an increase in the initial dose.**
- **The lower left points (X negative and Y negative) represent patients with Cmax >30 mg L^{-1} and for whom the correction formula recommended a reduction in the initial dose.**
- **The lower right points (X positive and Y negative) represent patients with Cmax >30 mg L^{-1}, but for whom the corrective formula still recommended an increase in the initial dose.**
- **The upper left points (X negative and Y positive) represent patients with Cmax <30 mg L^{-1}, but for whom the corrective formula recommended a decrease in the initial dose.**

The multiple linear regression analysis, performed on total population data (n=79), of the Cmax as a function of BMI, Ht and creatinine found to be significant in the analysis of variance (p=0.001). The coefficients of the regression were very close to the coefficients found for the retrospective phase. However, only creatinine and Ht remained significantly associated with Cmax when the effect of each coefficient was analysed separately.

The mean values used for establishing a corrective formula were selected using the mean values of BMI, Ht and creatinine of patients with a Cmax 25-35 mg L^{-1} (n=18). The con-

structed formula was then tested on the total population at the end of the study to evaluate the suggested dosage to be administered to obtain a Cmax ≥30 mg L^{-1}, in an individual manner according to BMI, haematocrit and creatinine. The corrective formula proposed is described in Figure 1. These data allowed us to obtain a correlation coefficient for the formula, R^2=0.34 (Figure 2).

Discussion

The present study showed a good adherence to the rationalised prescription protocol accompanied by a drastic decrease in gentamicin administration for non-recommended infections. Despite a significant increase in gentamicin dosage, there was no significant increase in the proportion of patients with a Cmax ≥30 mg L^{-1}. Regarding secondary objectives, a significant association between Cmax, BMI, Ht and creatinine was found. This association allowed a corrective formula to be proposed.

The main clinical impact of the present survey was to reduce the use of gentamicin for pulmonary and urinary tract infections. When an aminoglycoside is recommended for these infections, amikacin should be preferred (15, 24). In addition, despite its proven efficacy on Cocci gram-positive (CG+) organisms, gentamicin has no indication in the probabilistic or documented treatment of staphylococcal pneumopathies, mainly due to its poor pulmonary diffusion. The recommended anti-staphylococcal antibiotics are glycopeptides, rifampicin, clindamycin and linezolid (15). In the current practice of the unit studied herein, gentamicin is now mainly used to treat community intra-abdominal infections, in accordance to French guidelines (2, 4).

Among pharmacological models studied previously, Torkmani et al. (10) found BMI and creatinine to be risk factors for gentamicin underdosing. In the present study, a significant association between Cmax, BMI, Ht and creatinine was found. However, the association between Cmax and BMI was significant only for the population in the retrospective phase and not for the overall population, probably due, in part, to the inclusion and analysis of a morbidly obese patient (BMI>40 kg m^{-2}) in the overall population.

Based on the CASFM-EUCAST 2017 data (25) (*Comité de l'Antibiogramme de la Société Française de Microbiologie-European Committee on Antimicrobial Susceptibility Testing*), the critical concentrations to which Enterobacterales, *Pseudomonas aeruginosa* or *Staphylococcus aureus* (*S. aureus*) are considered sensitive to gentamicin treatment, are 4 mg L^{-1}, 4 mg L^{-1} and 1 mg L^{-1}, respectively. Moreover, with a mean gentamicin Cmax of 15 mg L^{-1}, a Cmax-to-MIC >8 ratio was only reached for *S. aureus*.

For Enterobacterales, the CASFM sets a low critical concentration at 2 mg L^{-1}, to define sensitivity. Considering this target and a gentamicin Cmax of 15 mg L^{-1}, the ratio then approaches 8. In addition, the sensitivity to gentamicin is variable depending on the species of Enterobacterales. If the prevalence of gentamicin sensitivity is greater than 90% for *E. coli*, it varies between 70% and 88% according to studies for *Klebsiella pneumonia* (26). This difference results in a higher MIC 50 and 90 for *Klebsiella* compared to *Escherichia coli*. If the distribution of MICs of the susceptible strains is of a Gaussian distribution type, it is possible to consider that, with respect to *E. coli* (the enterobacteria most frequently involved in an infectious process), the Cmax-to-MIC ratio will generally be >8 for a Cmax of 15 mg L^{-1}.

For *P. aeruginosa*, however, the previous reasoning is difficult to apply. Indeed, even if there is a significant decrease in resistance to aminoglycosides from this species (27), a Cmax of 15 mg L^{-1} will not allow to systematically obtain an inhibitory quotient >8, with a critical concentration defining the threshold of sensitivity at 4 mg L^{-1}.

In conclusion, a gentamicin Cmax of 15 mg L^{-1} could be considered acceptable in the context of probabilistic antibiotic therapy in community-acquired sepsis when the involvement of *P. aeruginosa* is supposed to be infrequent. Similar results have been described in previous studies (9).

The results herein and the data from the literature (7-10), support the idea that guidelines (2,4) aimed at reaching a Cmax ≥30 mg L^{-1} with doses of 7-9 mg kg^{-1} seem difficult to be applied in clinical practice. To increase the proportion of initial Cmax ≥30 mg L^{-1}, dosages would have to be increased systematically to 10-15 mg kg^{-1}. This would likely be at the cost of more significant nephrotoxic and ototoxic complications. This approach is therefore currently not justifiable, especially due to the possibility of alternate antibiotic use.

In the proposed prescription corrective formula, the correlation coefficient was low. To be applicable in clinical practice, this correlation coefficient should be improved. Future studies are necessary to improve its reliability and evaluate its application in clinical practice.

The present study has some limitations. First, it focused only on the initial Cmax. The first gentamicin injection is the most important since it occurs during the phase of haemodynamic instability and major bacterial inoculum. To reduce renal toxicity and according to guidelines (2, 4), patients received only one to three injections of gentamicin. Because of pre-existing renal insufficiency and therefore decreased clearance, the second injection usually did not occur during the 48 first hours (time required for the residual rate to allow a new in-

jection). In the context of sepsis, survival depends, in part, on the rapid establishment of an effective antibiotic therapy (5). Second, the use of the real weight rather than the lean mass for calculating dosage, has been previously discussed in a similar study on amikacin (28). The main advantages include avoiding underestimation of the volume of distribution and ease of implementation. The main risk, however, would be overdose, particularly in a population of obese patients. No overdose (Cmax >40 mg L^{-1}) was observed herein. Third, the delay between the start of antibiotic therapy and the Cmax was not controlled for, but the administration in the unit was strictly protocoled according to international recommendations: infusion of gentamicin using an electric syringe set at 30 minute injection time and Cmax dosing on blood sample collected 30 minutes after the end of infusion, i.e. 1 hour after the beginning of the injection (2). Fourth, the study patients from the two phases were not comparable. They were significantly different in terms of the mean age, sites of infections, SAPS, and mortality at Day 30. Lastly, the small size of the study population and the single-centre design of the study likely impacted the low correlation coefficient of the corrective formula proposed.

Conclusion

The present study improved the prescription of gentamicin in an anaesthesia-ICU. A Cmax ≥30 mg L^{-1} remains difficult to achieve, but a Cmax ≥16 mg L^{-1} could be considered for community infections and would be more attainable. A corrective formula could be used to adjust the dosage in an individual manner.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of the Desgenettes Military Teaching Hospital.

Informed Consent: Written informed consent was obtained from patients or the parents of the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – C.P., W.P.F., P.G.; Design – C.P., W.P.F., A.C.; Supervision – C.P., W.P.F.; Materials – P.G.; Data Collection and/or Processing – C.P., P.G.; Analysis and/or Interpretation – C.P., A.L., A.C.; Literature Search – C.P., A.L., P.G.; Writing Manuscript – C.P., P.G., A.C.; Critical Review – W.P.F., A.L.

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