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Original article

Guidelines for aminoglycoside use and applicability to geriatric patients

Recommandations de bon usage des aminosides et applicabilité aux patients gériatriques

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Abstract

Objectives. – The authors had for objective to evaluate the applicability of AFSSAPS guidelines for aminoglycoside use to geriatric patients.

Methods. – Theoretical doses and dosing regimens allowing reaching target concentrations in this population were calculated by applying a pharmacokinetic model to 30 geriatric patients treated by amikacin.

Results. – The dose allowing reaching a maximum concentration of 60 mg/L was 1.217 mg on average. The time required to reach a blood concentration lower than or equal to 2.5 mg/L was 62.5 ± 70.4 hours. Forty-six percent of patients had a trough concentration greater than 2.5 mg/L, 48 hours after administration. For these patients, the time between critical minimum inhibitory concentration (MIC) and toxicity threshold concentration was 21.9 ± 14.9 hours.

Conclusion. – Reaching a target concentration can be problematic in geriatric patients. It is frequently necessary to use dosing intervals greater than 48 hours. The effectiveness and safety of these regimens remain uncertain.

Keywords: Amikacin; Bayesian forecast; Geriatrics; Guidelines; Pharmacokinetic

Résumé

Objectifs. – Évaluer l'applicabilité des cibles proposées par les recommandations Afssaps de bon usage des aminosides à une population gériatrique.

Méthodes. – En appliquant un modèle pharmacocinétique sur 30 patients gériatriques traités par amikacine, les doses et intervalles posologiques théoriques permettant de respecter les concentrations cibles dans cette population ont été calculés.

Résultats. – La dose permettant d'atteindre une concentration maximale de 60 mg/L était de 1217 mg en moyenne. Le temps nécessaire pour obtenir une concentration sanguine inférieure ou égale à 2,5 mg/L était de 62,5 ± 70,4 heures. Une concentration résiduelle supérieure à 2,5 mg/L 48 heures après l'administration était retrouvée chez 46 % des patients. Chez ces patients, le temps passé entre la CMI critique et la concentration seuil de toxicité était de 21,9 ± 14,9 heures.

Conclusion. – L'atteinte des concentrations cibles en gériatrie peut poser problème. Un espacement supérieur à 48 heures des administrations semble fréquemment nécessaire. L'efficacité et l'innocuité de ces schémas demeurent incertaines.

Mots clés : Amikacine ; Recommandations de bon usage ; Gériatrie ; Méthode bayésienne ; Pharmacocinétique

1. Introduction

Amikacin is an antibiotic of the aminoglycoside family, the main indications of which are Gram-negative bacterial infections and empirical treatments for severe infections [1–2]. Aminoglycosides are prescribed in most cases in a combination to obtain bactericidal synergy (with beta-lactams), to prevent the emergence of resistance and broaden the treatment's activity spectrum [3–4]. The pharmacodynamics of aminoglycosides is characterized by a first rapid "concentration-dependent" bactericidal phase followed by an post-antibiotic effect of variable

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duration (0.5 to 8 hours in vitro) during which bacterial growth is stopped [5–7].

The toxicity of aminoglycosides is mainly renal, auditory, and vestibular. The nephrotoxicity is explained by the active reabsorption and the accumulation of a fraction of the antibiotic in the tubules [8–10]. The incidence of aminoglycoside nephrotoxicity ranges from 5 to 10% according to authors, but may reach 50% in specific populations (in case of renal insufficiency, sepsis, prolonged aminoglycoside treatment, etc.) [8]. Aminoglycosides present risks for geriatric patients, who often present with multiple diseases and consequently receive multiple treatments, because of a frequent alteration of the renal function [11–12].

The French Agency for the safety of Health Products (french acronym for afssaps now called ansm) published guidelines for the good use of injectable aminoglycosides, in March 2011 [13]. These recommend the prescription of aminoglycosides so as to optimize their effectiveness and safety, and prevent the emergence of resistance. Thus, it is recommended to administer a dose allowing to reach a maximum concentration of 60 to 80 mg/L and to make sure that the trough concentration, predictive of toxicity, does not exceed 2.5 mg/L, in case of treatment for more than 5 days, or in case of renal insufficiency.

The important prevalence of renal insufficiency [14–15] in geriatric patients associated its pharmacokinetic specificities (usually delayed and more variable absorption, increased fat mass and alteration of the distribution volume of lipophilic drugs, decreased blood flow in organs and especially in hepatic blood flow, alteration of plasma protein concentration, alteration of the renal function [16]). We had for objective to assess, on a cohort of geriatric patients, the applicability of targets suggested by these recommendations with a pharmacokinetic assessment of this population.

2. Material and methods

The study was made in two stages. In the first stage, the individual pharmacokinetic parameters of a cohort of 30 geriatric patients, previously treated by amikacin, were determined by Bayesian forecasting. In the second stage, these pharmacokinetic parameters were used to simulate administration of doses allowing reaching a maximum concentration of 60 mg/L in these patients. The necessary time to reach a concentration inferior to the threshold of toxicity between two administrations, as well as the trough concentrations after repeated administrations were studied as described below.

2.1. Study population

A cohort of 30 patients treated by amikacin and hospitalized in a geriatric unit of the Lyon teaching hospital was built randomly from files of patients treated by amikacin between 2008 and 2011, having benefited from therapeutic follow-up of amikacin blood levels in our unit. The administered doses of amikacin and the peak and trough concentrations were documented for each patient, (as well as the time of sampling and of administration), along with their age, sex, weight, and creatininemia. The possible weight and creatininemia changes during treatment were also documented. The renal function was assessed by calculating creatinine clearance according to Jelliffe's equation for unstable creatininemia [17].

Table 1
Anthropometric characteristics of the cohort.
Caractéristiques anthropométriques de la cohorte.

Male/Female Ratio	13/17
Age (mean ± standard deviation)	83 ± 8 years of age
Weight (mean ± standard deviation)	65 ± 4 kg
Creatinine clearance (mean ± standard deviation)	55 ± 21 mL/min

2.2. Modelization and simulations

The individual pharmacokinetic parameters of each patient were calculated with Bayesian forecasting, with a bicompartmental pharmacokinetic model.

This model included the following parameters: volume of distribution of the central compartment (Vd), elimination rate constant (Kel), and two intercompartmental transfer constants (Kcp and Kpc).

The volume of distribution of the central compartment was related to the patient's weight by the equation: $Vd = Vs \times Weight$, with Vs: slope parameter.

Elimination and renal function were related by the equation: $Kel = Knr + (Kr \times Ccr)$, with Knr: non-renal elimination rate constant, Kr: renal elimination rate constant, Ccr: creatinine clearance (estimated with Jelliffe's equation).

The theoretical dose allowing to reach a maximum concentration of 60 mg/L was calculated for each patient. A simulation was made, after fictive administration of this dose; the length of time with a concentration inferior to critical minimum inhibitory concentration (MIC) (8 mg/L – superior critical concentration defined by the European Committee for Antibiomicrobial Susceptibility Testing (EUCAST) for amikacin [13]) but superior to the toxicity threshold concentration of 2.5 mg/L was determined on one hand, and on the other hand the delay before reaching a blood concentration inferior or equal to 2.5 mg/L. The percentage of patients for whom this delay was superior to 48 hours was calculated. The linear correlation coefficient between the delay before reaching a blood concentration inferior or equal to 2.5 mg/L and creatinine clearance was determined.

A one-week treatment with administration of the dose allowing to reach the target peak every 48 hours was simulated for these patients. The trough concentration before readministration could be superior to 2.5 mg/L. The trough concentration reached 48 hours after the last administration was determined so as to check if the recommendation of a trough concentration inferior to 2.5 mg/L, in case of treatment for more than 5 days or of renal insufficiency, was taken into account.

3. Results

The anthropometric characteristics of the cohort used are listed in Table 1. The volume of distribution of amikacin was 0.31 ± 0.11 L/kg and the clearance of amikacin was and

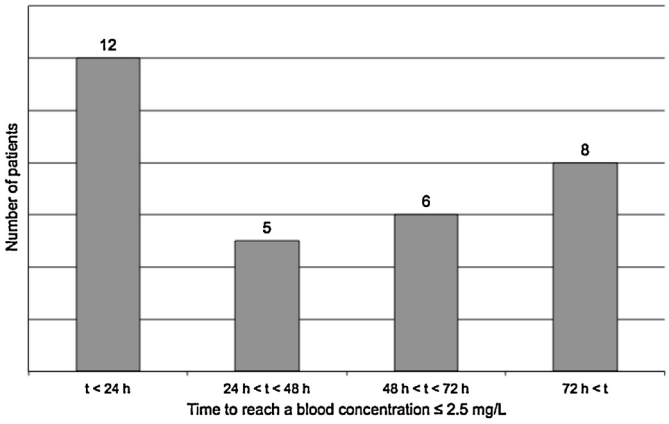

Fig. 1. Distribution of patients according to time required to obtain a blood concentration inferior or equal to 2.5 mg/L.
Répartition des effectifs en fonction du temps nécessaire pour obtenir une concentration sanguine inférieure ou égale à 2,5 mg/L.

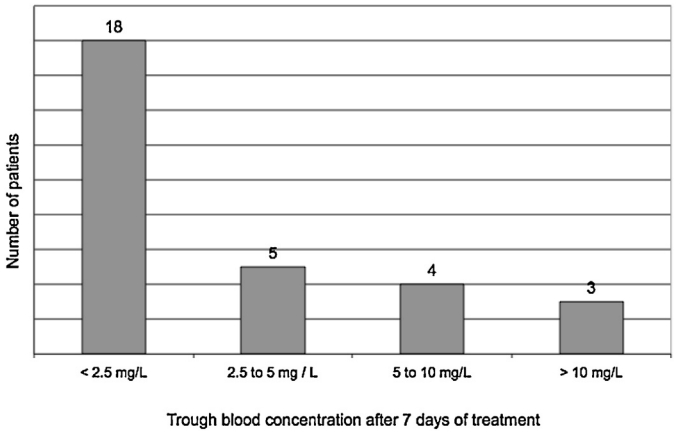

Fig. 2. Distribution of patients according to trough blood concentration after 7 days of amikacin treatment (administration every 48 hours of a dose providing a peak concentration of 60 mg/L).
Répartition des effectifs en fonction de la concentration sanguine résiduelle retrouvée après sept jours de traitement par amikacine (avec administration toutes les 48 heures d'une dose assurant un pic de concentration de 60 mg/L).

average 45.2 ± 36.1 mL/min. The dose allowing to reach a maximum amikacin concentration of 60 mg/L was an average 1.217 mg ± 447 mg.

The delay before coming back to a blood concentration inferior or equal to 2.5 mg/L after having reached a peak concentration of 60 mg/L was 62.5 ± 70.4 hours. The distribution of patients according to the time needed to come back to a blood concentration inferior or equal to 2.5 mg/L is shown on Fig. 1. The linear correlation coefficient r^2 between creatinine clearance and the time needed to come back to a blood concentration inferior or equal to 2.5 mg/L was 0.4.

Thirteen patients (46%) had a trough concentration greater than 2.5 mg/L 48 hours after administration. The time spent with a concentration inferior to the critical MIC (8 mg/L) but superior to the toxicity threshold concentration of 2.5 mg/L was 21.9 ± 14.9 hours for the 13 patients who would need a delay between administrations superior to 48 hours, and 6.8 ± 3.1 hours for the 17 other patients.

The 13 patients with a trough concentration greater than 2.5 mg/L after 48 hours, had an estimated trough blood concentration of 7.3 ± 5.8 mg/L with a median at 6.35 mg/L, after 7 days of treatment with administration every 48 hours of a dose allowing to reach the peak concentration of 60 mg/L. The distribution of patients according to trough blood concentration after 7 days of treatment is shown in Fig. 2.

4. Discussion

Our study results show that for more than 40% of geriatric patients, the target concentration peak proposed in the latest AFSSAPS recommendations cannot be reached without obtaining potentially toxic trough concentrations, even after 48 hours, or without increasing the delay between administrations beyond 48 hours. The time spent with a concentration inferior to the MIC but beyond the toxicity threshold may be considerably increased, when such an option is chosen.

The effectiveness of reaching the highest plasmatic peak concentration peak has been demonstrated: amikacin is considered as having a concentration-dependent speed of bactericidal action, and the Cmax/MIC ratio is the pharmacodynamic index best correlated to clinical effectiveness. A Cmax/MIC ratio between 8 and 10 [18] or between 10 and 12 is often considered optimal [19–21]. Reaching higher concentrations does not seem to increase effectiveness [22]. Likewise, toxicity (especially renal) is related to trough concentrations reached [2,13].

Many authors, for several years, have reported the benefit of dosing regimens with single daily dose, instead of treatments with two or three daily administrations. These regimens seem to decrease the risk of toxicity while maintaining or increasing clinical effectiveness [23]. They also allow, in patients with a normal renal function, intervals of 7 to 8 hours without measurable concentrations, the post-antibiotic effect explaining the clinical effectiveness [24]. The validity of such regimens for some patients remains controversial, especially in geriatric patients [25–26], and in patients presenting with cystic fibrosis [27]. Furthermore, administrations may be delayed even more when renal elimination is failing [28].

Our study results prove that for a great number of geriatric patients ages treated by amikacin, it would be necessary to extend the dose interval beyond 48 hours in case of repeated administrations, to be able to reach the target concentrations suggested by the AFSSAPS. These dose regimens have never been validated, as far as we know, and many problems may occur.

First of all, these treatments with long intervals between administrations, will allow reaching a peak concentration much less frequently than with the usual regimen. Contrary to switching from a regimen with several daily injections to the regimen "single daily dose", this larger delay between administrations will not require increasing the single dose (eg an interval between administrations increased to 72 hours because of insufficient elimination will not require administration of a three-fold weaker dose). Thus, the effectiveness of this regimen may be discussed. Indeed, as reported by Tam et al., aminoglycosides present a non-linear relation between blood concentration and

speed of bactericidal action: at some levels of concentrations, a slight variation of concentration will induce a strong variation in the speed of bactericidal action [29]. There is a risk that reaching high concentration peaks may not be equivalent to prolonged maintaining of a weaker concentration as observed in case of slower elimination.

Furthermore, even if the post-antibiotic effect is very favorable in case of a regimen of the "single daily dose" type, since it allows suppressing bacterial growth between two administrations [30], it may not be prolonged enough to maintain this effect for treatment regimens with more than 48 hours between administrations. Our results show that the time spent with a concentration inferior to the MIC is on average 21.9 hours (for a MIC at 8 mg/L), whereas the duration of the post-antibiotic effect is 0.5 to 8 hours in vitro [6,31], which would allow bacterial regrowth. Moreover, the adaptive resistance phenomenon, which results in a temporary decrease of the bacterium susceptibility, around 2 hours after administration and for 6 hours [30], may be more unfavorable. Indeed, this resistance does not seem problematic in case of regimens of the "single daily dose" type in a patient with adequate elimination: the blood concentration decreasing rapidly, the patient has already benefited from a great part of the dose's bactericidal effect when this resistance occurs. In case of failing elimination, this resistance could appear even if concentrations are still important, and decrease the bactericidal activity during this period.

Finally, a prolonged maintenance of the concentration superior to the 2.5 mg/L set by the AFSSAPS, and especially the absence of windows during which blood concentration would be null, may present a risk of toxicity, especially renal. Part of the renal toxicity is mediated by a saturation phenomenon (tubular reuptake [8,32–33]), explaining the benefit of regimens of the "single daily dose" type for patients with a normal renal function: the increase of maximum concentrations does not induce an increased toxicity because of this saturation [34–35]. But, even when no threshold concentration has been identified, this saturation phenomenon does not allow preventing toxicity in case prolonged maintenance of non-null concentration. It should be noted that the study of correlation between creatinine clearance and the time needed to come back to a concentration inferior to 2.5 mg/L give a relatively weak linear coefficient ($r^2 = 0.4$). Alteration of the renal function only partly explains the slow elimination of amikacin in some patients. It is probable that other physiological modifications of geriatric patients (loss of muscular mass, hypoproteinemia, alteration of the hepatic function, etc.) have an impact on the pharmacokinetics of aminoglycosides.

Auditory toxicity, less studied, seems related to the area under the curve (AUC) of blood concentration [36]. The AUC of a regimen including repeated administrations, as long as blood concentration is inferior to 2.5 mg/L in a patient with failing elimination, is necessarily equal or superior to that of a patient who can benefit from standard treatment. The risk of ototoxicity could be at least equal or superior in this population.

This study has a few limitations that should be discussed. First of all, the number of included patients is small. Thus, some potentially rare conditions (unusual pharmacokinetic characteristics) may not have been observed in our population. Furthermore, the estimations of pharmacokinetic parameters and calculation of doses and intervals were made by using a bicompartmental model: other models could have been used, nevertheless bicompartmental models seemingly allow a good prediction of amikacin concentrations [9,37]. Moreover, some potentially useful information, such as possible coprescription of diuretics, was not available for the analysis. Finally, these results obtained by simulations should be confirmed by a prospective study. Nevertheless, conducting such a study would be limited by the use of potentially toxic doses.

Finally, even if the benefit of reaching high blood levels at the peak concentration is certain, reaching these target levels may be problematic in geriatric patients. An important interval between administrations, sometimes superior to 48 hours, seems frequently necessary because of elimination disorders observed in this population. The effectiveness and the safety of these regimens with long intervals between administrations remain uncertain.

5. Conclusion

Aminoglycosides are a major class of antibiotics, the use of which is limited by toxicity. Their great speed of bactericidal action, all the higher that the maximum concentration reach is elevated, the presence of saturable toxicity and post-antibiotic effect have led to suggesting regimens including strong single doses (guarantying effectiveness) with delayed administrations (to limit toxicity).

Our study results show that the currently recommended target concentrations for amikacin are difficult to reach for a great number of geriatric patients, while keeping an acceptable interval between administrations, because of renal elimination disorders, frequent in this population.

Increasing the interval between administrations beyond 48 hours, a possible solution for patients for whom elimination of the aminoglycoside is difficult, raises the question of microbiological effectiveness and development of resistance. Nevertheless, the emergence of bacteria resistant to most available anti-infectious agents stresses the major position of aminoglycosides in the therapeutic armamentarium [23].

Globally, as suggested by Jacobs et al., we should assess the capacity of a given dose regimen to reach pharmacokinetic-pharmacodynamic targets, ensuring effectiveness and limiting the emergence of resistance, before prescribing it [38]. These regimens, with long intervals between administrations, should be assessed, to be able to offer safe and effective management for this population presenting with an important iatrogenic risk.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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