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Pharmacology applied to geriatric medicine

Rejuvenating aminoglycosides usage in geriatric patients with gram-negative infections

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ABSTRACT

Aminoglycosides still represent an important antimicrobial class for the treatment of gram-negative infections. Their spectrum of activity and the possibility to act synergistically with β-lactams offer the opportunity of being used in severe infections or infections sustained by resistant pathogens. However, the fear of side effects, related to their narrow therapeutic index and toxicodynamic profile, limits sometimes the use of aminoglycosides, especially in old or very old patients. Improved knowledge of antimicrobial pharmacokinetics and pharmacodynamics in the last years has allowed improving regimens and dosing on an individual basis, according to the patient's pathophysiological conditions and pathogen's susceptibility profile. Optimised aminoglycoside use yields to a more rapid bacterial killing and, likely, prevention of resistance development. Some advances toward an improved aminoglycoside usage and application of pharmacodynamic concepts to avoid or limit toxicity are herein briefly discussed.

1. Introduction

Despite the introduction into clinical practice some six decades ago, aminoglycosides remain one of the most potent, broad-spectrum classes of antimicrobials and still an important therapeutic option for life-threatening infections. Aminoglycoside class features a predictable activity against *Pseudomonas aeruginosa* and other aerobic gram-negative bacilli and shows an additive or synergistic activity to that of penicillins or cephalosporins against aerobic gram-negative bacilli and aerobic gram-positive cocci. Their bactericidal efficacy, however, is seldom fully exploited in aged patients due to the fear of potential toxicity: aminoglycosides exert their toxicodynamic profile mostly at renal level and many elderly patients show a physiological decrease in kidney function that can be strongly worsened by the administration of these drugs. As a result of our improved understanding of pharmacokinetic and pharmacodynamic principles and their application in clinical practice over the last decade, however, the application of newer dosing schedules not only has led to an enhanced antibacterial effectiveness, but also proved to minimize aminoglycoside toxicodynamic profile in aged patients.

2. Pharmacological background

Injectable aminoglycosides commonly used in clinical practice – amikacin, gentamicin, and tobramycin – are typical hydrophilic drugs, with very poor bioavailability (absorption from gastrointestinal tract) and metabolic transformation that are exclusively eliminated through renal clearance. From a pharmacokinetic point of view they share many properties, amikacin being the only with slight differences to others (Table 1). Due to their hydrophilicity, they have a small volume of distribution (Vd) ranging from 0.25 to 0.4 L/kg, which roughly represents the volume of extracellular fluid. However, the percentage of body weight attributed to extracellular fluid changes according to physiologic or pathologic conditions: aged people have often decreased extracellular fluid, which may consequently increase aminoglycoside concentration, whereas critically ill septic patients who are fluid overloaded may have increased apparent Vd, with resulting aminoglycoside peak serum level (Cmax) decreased [1]. Protein binding is around 20%, and elimination half-life ($t_{1/2}$) is around 2 hours (h) in patients with normal renal function. Due to poor protein binding, aminoglycoside concentration is virtually unaffected by decreased serum albumin level, which is quite frequent in older patients. Aminoglycosides do not diffuse well into tissues and fluids, and are unable to cross lipid bi-layer cell membranes and enter cells. In particular, their diffusion is very limited in brain tissues, bronchial tree and aqueous humour [2] and they show a very poor activity in

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Table 1
Expected blood levels of aminoglycosides according to conventional dosing (thrice a day) or once-daily (OD) dosing (high single doses with extended interval).

Drug	Expected trough level conventional dosing	Expected trough level once-daily dosing	Expected peak level conventional dosing	Expected peak level once-daily dosing
Amikacin	<5–10 ug/ml	Undetectable	15–40 ug/ml	40–60 ug/ml
Gentamicin	<2 ug/ml	Undetectable	4–10 ug/ml	>20 ug/ml
Tobramycin	<2 ug/ml	Undetectable	4–10 ug/ml	>20 ug/ml

Levels foreseen with normal renal function (creatinine clearance >80 ml/min), normal Vd (0.25–0.5 L/kg), and consequent normal $t_{1/2}$ (2–3 hours). Targeted peak levels should be at least 10 ug/ml for MIC ≤1; 20 ug/ml for MIC = 2 and 40 ug/ml for MIC ≤4.

abscesses or empyema, as they are chemically inactivated by acid pH. Despite their short $t_{1/2}$, bactericidal activity is exerted through a concentration-dependent mechanism – which facilitates also tissue distribution because of higher plasma/tissue concentration gradients – and a powerful and prolonged post-antibiotic effect (PAE). This leads to:

- the therapeutic effect is the highest if the dose used allows reaching Cmax equal to at least 8–10 times the minimum inhibitory concentration (MIC), that is Cmax/MIC ratio ≥ 8 to 10;
- the bactericidal activity continues for a prolonged time, even when the blood level has fallen far below the MIC of the targeted pathogen [2,3].

Subcutaneous administration has been advocated in older patients with poor venous accesses, but this route alters pharmacokinetic and pharmacodynamic profile of aminoglycosides and has been associated with unacceptable local toxicity and necrosis phenomena [4]. Subcutaneous administration of aminoglycosides should be therefore strongly discouraged.

3. Clinical use of aminoglycosides

Aminoglycosides are used in case of severe infections since they exert a strong bactericidal activity against several gram-negative and gram-positive bacteria.

Aminoglycoside clinical indications include the treatment of multi-drug resistant gram-negative organisms, empiric double gram-negative coverage in critically ill patients, and combination therapy with a β-lactam whenever synergistic activity is required. Among gram-negative pathogens their spectrum of activity includes *Enterobacteriaceae* (*E. coli, Klebsiella* spp., *Proteus* spp., *Enterobacter* spp., *Morganella* spp., *Citrobacter* spp., *Serratia marcescens*) and non-fermenters gram-negative rods (*P. aeruginosa, Acinetobacter* spp.). Their activity is not strictly superimposable: indeed, tobramycin and amikacin are more active than gentamicin against *P. aeruginosa* (tobramycin > amikacin), whereas gentamicin is normally more active than others against *S. marcescens*. These differences should be kept in mind in balancing clinical efficacy and toxicity, mostly when dealing with severe infections in aged or very aged patients.

Due to their hydrophilic properties, aminoglycosides are unable to enter cells, and are therefore completely inactive against intracellular pathogens, such as *Chlamydia* or *Mycoplasma*. Moreover, their bactericidal activity requires oxygen-mediated processes and, therefore, they are completely inactive against anaerobe pathogens as well [2].

Aminoglycosides are historically the drugs acting synergistically with the backbone drug for staphylococcal, streptococcal or enterococcal endocarditis or complicated bacteraemia. Overall, severe to very severe gram-positive infections require aminoglycoside combination therapy, but the pharmacological basis and efficacy determinants are different in case of gram-positive infections [5]. As a matter of fact, administration of aminoglycosides in severe gram-positive infections is usually refracted twice- or thrice-daily. However, Bassetti et al. recently found that gentamicin once-daily was as effective as with split doses in 21 patients with gentamicin-susceptible enterococcal endocarditis [6]. Moreover, some relevant experiences have recently opened a thorough appraisal of aminoglycoside usage in enterococcal endocarditis [7–11]. The activity of aminoglycosides against gram-positive pathogens, therefore, will not be reviewed, as it is beyond the aim of this work.

The efficacy of aminoglycoside monotherapy against gram-negatives has been clearly assessed, even with short-courses [12], particularly in urinary tract infections that are the commonest infections among elderly patients [13]. Urine concentrations of aminoglycoside exceed plasma Cmax 25- to 100-fold within one hour after injection and remain above therapeutic levels for several days after a single dose [14]. Therefore, one single shot of aminoglycoside may probably be adequate to treat uncomplicated urinary tract infections. Recommendations and evidences on appropriate use of this drug class have been recently published by different European groups, also overviewing available experiences on optimized usage [15,16]. To briefly summarise, current aminoglycoside treatment of gram-negative infections should be stopped after 48 to 72 hours (which is about the time required for antibiogram results) in almost all situations except endocarditis. At least, it should be carefully reassessed at that time, especially when there is not microbiological documentation. Proven gram-negative infective endocarditis usually requires prolonged aminoglycoside courses (up to 2 weeks) along with the primary drug chosen, but their usage must be carefully assessed and blood levels monitored. Febrile neutropaenic patients or patients in severe sepsis or septic shock may benefit from a maximum of 5 days, depending on the clinical course of the disease, in association with a cell wall-active drug (β-lactams or vancomycin) [17,18]. However, Paul et al. performed a systematic review and meta-analysis of randomised controlled trials comparing any β-lactam antibiotic monotherapy with any combination of a β-lactam and an aminoglycoside antibiotic, for the initial empirical treatment of febrile neutropaenic cancer patients: all-cause mortality was the primary outcome assessed and β-lactam monotherapy was found advantageous compared with β-lactam-aminoglycoside combination therapy with regard to survival, adverse events and fungal super-infections [19]. Likewise, the same Israeli group very recently compared any β-lactam monotherapy versus any combination of a β-lactam with an aminoglycoside for sepsis, and they concluded that the addition of aminoglycosides to β-lactams should be discouraged, as all-cause mortality rates remain unchanged but combination treatments carry a significant risk of nephrotoxicity [20].

It should be pointed out that in none of the studies included in the analyses the usefulness of these drugs has been assessed against an optimized dosing according to therapeutic drug monitoring (TDM) or in relationship with the MIC of the infecting pathogen. It is therefore likely that inappropriate administration may have played a role either because of a sub-therapeutic Cmax or for an excessive trough level (Cmin) with consequent toxicity (see below).