REVIEW ARTICLE

Braz J Cardiovasc Surg 2006; 21(4): 444-452

Aminoglycoside nephrotoxicity

Nefrotoxicidade dos aminoglicosídeos

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RBCCV 44205-853

Abstract

Aminoglycoside are frequently used due to its high efficacy against gram-negative bacteria and positive synergism with other antibiotics against gram-positive organisms. They are commonly used for prevention and treatment of infection complications after cardiothoracic surgery. The principal side effect of this class of antibiotics is nephrotoxicity, which may occur in up to 20% of the exposed patients. Although usually reversible, aminoglycoside-induced renal injury prolongs hospitalization time and increase patients cost. Even more important, the occurrence of nephrotoxicity is associated with higher patient mortality. There are some known risk factors for nephrotoxicity development and some measures that may prevent it. This review will cover the most relevant aspects of this important side effect of aminoglycoside therapy.

Descriptors: **Aminoglycosides. Acute renal Insufficiency. Kidney, drug effects.**

Resumo

Aminoglicosídeos são antibióticos de amplo uso clínico, em função de sua eficácia contra bacilos gram-negativos e de seu sinergismo positivo com outros antibióticos no tratamento de infecções por agentes gram-positivos. São muito utilizados na prevenção e no tratamento de infecções pós-operatórias em cirurgia cardíaca. O principal efeito colateral desta classe de antibióticos é a nefrotoxicidade, que pode ocorrer em até 20% dos pacientes. Embora usualmente reversível, a lesão renal causa maior tempo de internação e, conseqüentemente, maiores custos. Ainda mais importante é o fato de nefrotoxicidade estar associada a maior mortalidade nestes pacientes. Existem alguns fatores de risco conhecidos para nefrotoxicidade, bem como algumas medidas de prevenção. Esta revisão irá descrever os aspectos mais relevantes deste importante efeito colateral do tratamento com aminoglicosídeos.

Descritores: **Aminoglicosídeos. Insuficiência renal aguda. Rim, efeitos de drogas.**

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Article received in May, 2006
Article accepted in September, 2006

Braz J Cardiovasc Surg 2006; 21(4): 444-452

INTRODUCTION

Aminoglycoside antibiotics are an important part of the antibacterial therapeutic arsenal since their discovery in the 1940s. The studies that culminated with the discovery of this new class of antibiotics started in 1939 in the Microbiology Department of the Experimental Agriculture Unit of Rutgers University in New Jersey, USA. In 1943, after examining several actinomycetes of the soil, Waksman et al. [1] isolated a strain of *Streptomyces griseus* which produced a substance that inhibited the growth of the tuberculosis bacillus as well as several gram-positive and gram-negative microorganisms leading to the isolation of streptomycin. From then on, a series of new substances derived from actinomycetes with antibacterial potential were discovered (Table 1) [2], as well as the semi-synthetic aminoglycosides, amikacin and netilmicin, derived from kanaminicin and sysomicin respectively.

Table 1. List of aminoglycosides, there origin and discovery

Name	Genero	Year discovered
Streptomycin	Streptomyces griseus	1944
Neomycin	Streptomyces fradiae	1949
Kanamycin	Streptomyces kanamyceticus	1957
Paromomycin	Streptomyces fradiae	1959
Gentamicin	Micromonospora purpurea	1963
Tobramycin	Streptomyces tenebrarius	1968
Amikacin	Streptomyces kanamyceticus	1972
Netilmicin	Micromonospora inyoensis	1975
Spectinomycin	Streptomyces spectabilis	1962
Sisomicin	Micromonospora inyoensis	1970
Dibekacin	Streptomyces kanamyceticus	1971
Isepamicin	Micromonospora purpurea	1978

The name aminoglycoside is due to the fact that the molecule is constituted of two or more amino sugars bound by glycidic links to hexose or aminocyclitol which normally take the central position. The name of the substance is related to its origin. Those that terminate in mycin are direct or indirect derivatives of Streptomyces and those that terminate in micin are direct or indirect derivatives of Micromonospora.

Aminoglycosides have a molecular weight that varies between 445 and 600 Daltons, they are highly soluble in water, stable at pHs of 6 to 8 and possess a cationic structure, which impedes their oral absorption and makes their penetration into the intercellular space or through the hematoencephalic barrier difficult. Their antimicrobial action mainly occurs in an aerobic medium and at alkaline pHs, as they require oxygen for active transportation in the microbial cells and are more active in alkaline than acid conditions.

The pharmokinetics of all aminoglycosides are very similar. Due to their polar nature, they are absorbed by the gastrointestinal tract, with less than 1% of the dose being absorbed after oral or rectal administration. The main administration via is hence parenteral, with the drug reaching the maximum plasma concentration 30 to 90 minutes after intramuscular application and 30 minutes after an intravenous injection.

Their binding to plasma albumin is insignificant (= 10%) with the exception of streptomicin, which has proteic binding of about 30%. Since they are insoluble in lipids, their concentrations in secretions and in the tissues are reduced, as they do not easily pass biological membranes that do not have a transportation mechanism well. Their half life in blood is two to three hours in patients with normal renal function.

Elimination is by the kidney through glomerular filtration, with depuration at around 66% of simultaneous depuration of the creatinine due to tubular re-absorption. The half-life in the renal cortex is estimated at 30 to 700 hours, so there is still urinal elimination 20 to 30 days after the administration of the last dose.

All aminoglycosides act by the same mechanism exerting their bactericide effect on binding to the bacterial ribosome. Thus, it is necessary that they penetrate inside the bacterial cell for them to act. This occurs by means of the interaction of the aminoglycoside with the cellular surface, their transportation by means of the membrane and, finally their binding to the ribosome.

Interaction with the cellular surface occurs in a passive manner and without energy depletion. When aminoglycosides bind to negatively charged structures in the cellular wall, they competitively displace Ca^{2+} and Mg^{2+}, which hold the cells together thereby forming holes in the cellular wall and altering its permeability. Transport across the cellular membrane is dependent on energy and occurs in two phases (F1DE and F2DE). The energy utilized is generated by the transport of electrons to maintain the transmembrane potential. Once inside the cell, the aminoglycosides bind to the 30S subunit of ribosome, diminishing the proteic synthesis and leading to an incorrect measurement of the RNA messenger, causing alterations in the functioning of the cellular membrane with release of constituents essential to the functioning of the cell, thereby causing cell death.

Serum concentrations observed with the therapeutic doses are close to toxic levels (low therapeutic index). Cellular toxicity is a common characteristic of aminoglycosides (except for spectinomycin) due to their

absorption by the intercellular medium. Their most important toxic effects are nephrotoxicity, ototoxicity and neuromuscular blocks. The reported frequencies of these side effects are very variable due to the different criteria utilized for diagnosis. Neuromuscular blocks are rare, ototoxicity ranges from 0 to 62% (cochlear) and 0 to 19% (vestibular) and nephrotoxicity varies from 0 to 50% [2].

Several experimental studies have been performed in an attempt to elucidate the mechanisms of nephrotoxicity. The existence of genetic factors was suggested due to differences in the susceptibility to nephrotoxicity of rats, rabbits and other animals [3]. The starting point for nephrotoxicity is the binding of the pharmacological agent to the proximal tubule. It is believed that there are specific receptors in the proximal tubule where endocytosis of the aminoglycoside occurs (in the same manner as amino acids, small peptides and perhaps polyamines are absorbed) [4]. The binding in the tubular membrane occurs with megalin, an endocytotic receptor expressed in the apical membrane of the proximal tubular epithelium. It is responsible for the re-absorption of glomerular filtrate and also binds to low molecular weight proteins [5]. Once bound to megalin, the aminoglycoside-megalin complex is transported inside the cell and joins to lysosome, where it fuses to preexistent structures causing progressive deposition of polar lipids, that adopt concentric lamellar disposition [6], forming the so-called myeloid body. Additionally, several other alterations occur in the organelles and enzymes, such as in the ribosomes, mitochondria and Na/K-ATPase pump [7,8]. It should be stressed that the formation of myeloid bodies is not exclusive of aminoglycosides; this also occurs with other cationic drugs. The aminoglycosides gradually accumulate in the lysosomes and induce morphological alterations. The mechanisms through which the aminoglycosides alter glomerular filtration are not totally understood yet. Several factors were incriminated such as the release of vasoconstricting hormones [9], the release of platelet aggregating factor [10], deposition of cellular remains obstructing individual nephrons [11] and reduction in the glomerular surface and/or alterations in the glomerular permeability with decreases in the glomerular ultrafiltration coefficient [12,13].

INCIDENCE

Medical literature describes an increase in nephrotoxic acute renal failure (ARF), with antibiotics being responsible for the majority of cases, among which the most common are the aminoglycosides [14,15]. The incidence of ARF associated with the use of aminoglycosides varies widely due to the differences in the diagnostic criteria and the studied populations. In fact, the frequency of nephrotoxicity with these drugs varies from 0 to 50% [16-18]. In a small group of young healthy volunteers, the incidence was zero [19], whilst in elderly patients with multisystemic diseases it reached 50% [20]. In patients hospitalized in the ICU, the incidence may reach 76% depending on the criteria utilized for the diagnosis of nephrotoxicity by aminoglycoside [21].

In the clinical practice, this group of antibiotics has wide-spectrum use both for prophylaxis [22-24] and in the treatment of infections (mediastinitis and endocarditis) associated to cardiovascular surgery [25,26]. Thus, they may cause significant renal damage.

Hence, this review aims at evaluating the risk factors related to nephrotoxicity by aminoglycosides and the measures that can be taken to reduce the incidence of this complication.

RISK FACTORS

In animal models, several factors related to the nephrotoxicity of aminoglycosides have been reported: multiple doses [27], male animals [28], infection, acidosis, volume depletion, sodium depletion [29], hyperkalemia [30], hypomagnesemia, hepatic disease [31] and concomitant use of other drugs including vancomycin [32], teicoplamin [33], cyclosporin [34] and cisplatin [35]. The factors that experimentally reduce nephrotoxicity were: single doses [36], female animals [37], alkalosis [38], thyroid hormone [39], calcium overload [39], diabetes mellitus [40,41], concomitant use of wide-spectrum penicillin [42] and polyaspartic acid [43]. The concomitant use of cephalotin presents conflicting results with one group reporting a worse effect and another an improvement in nephrotoxicity [44,45].

Clinically there are few studies that evaluate risk factors for nephrotoxicity due to aminoglycosides. They may by divided into studies related to the patient, related to aminoglycosides and to the use of concomitant drugs (Table 2).

Table 2. Risk factors for nephrotoxicity related to the patient, to aminoglycoside and to the use of other drugs

Patient	Aminoglycosides	Other drugs
Age	Recent use	Vancomycin
Prior renal disease	High doses	Amphotericin B
Gender male / female	Treatment for more than 3 days	Furosemide
volume depletion	Chosen drug	Cephalosporin
Hepatic dysfunction	Interval of dose	Contrasts

Among the factors related to patients are advanced age [46], preexistent renal disease [47], hypotension, volume depletion and hepatic dysfunction [48,49]. Factors related to aminoglycoside are high doses [2], the use of the drug for more than three days [2], reduction in the interval between doses [2], recent use of aminoglycosides and the administration of the drug between midnight and 7 o'clock a.m. [50]. The concomitant use of vancomycin, amphotericin B, furosemid, clindamycin, piperacilin, cephalosporin, foscarnet and the use of iodine contrast are also clinically associated with greater nephrotoxicity [2]. Similar to animal experiments, the concomitant use of cephalotin presented conflicting results with reports of worse nephrotoxicity or absence of an additional effect. It is worthwhile stressing that none of these works assessed different factors concomitantly.

CLINICAL ASPECTS

Nephrotoxicity due to aminoglycoside causes nonoliguric renal failure and a drop in the glomerular filtration, generally occurring seven days after treatment. The evolution to oligoanuric renal failure and/or dialysis dependency is rare.

Apart from reducing glomerular filtration, aminoglycosides may cause enzymuria, proteinuria, amino aciduria, glycosuria and diverse electrolytic alterations including hypomagnesemia, hypocalcemia and hyperkalemia, and may even cause Fanconi's-like [51] or Bartter-like syndrome [52]. Urine examinations are little characteristic; sometimes with leukocyturia, proteinuria and cylindruria [53]. The increased output of tubular enzymes in the urine suggest tubular lesion by aminoglycoside (alanine aminopeptidase, β-D-glucosamine and phosphatase alcaline) [54]. The urine sodium concentration and sodium output fraction are generally high (greater than 40 mEq/L and 1%, respectively), as is common in other forms of NTA. As alterations in the urine volume do not occur, nephrotoxicity is frequently detected by an increase in serum creatinine. The most sensitive method of early diagnosis is the detection of an increase at the "de vale" moment and not at the aminoglycoside peak which antecedes an elevation in creatinine [53].

The serum concentration of creatinine usually returns to normal within 21 days of cessation of aminoglycoside administration. Irreversible tubulointersticial injury is uncommon with acute nephrotoxicity, but it can occur with prolonged therapy using low doses [55] and in those patients with previously altered renal function [56]. The resolution of acute events may be delayed if the patient remains hypovolemic, septic or catabolic.

In the majority of cases there is recovery of the renal function. Evolution to chronic renal injury is rare but my happen if other factors involved. Cases of incomplete recovery due to interstitial fibrosis have been reported both in animals [57] and humans [58].

Treatment of nephrotoxicity caused by aminoglycoside is basically support, consisting on cessation of the use of the drug (if possible) substituting it for another non-nephrotoxic antibiotic. When this is not possible, the dose of aminoglycoside should be corrected (increase in the interval between doses). It is important to avoid the use of other nephrotoxicity drugs in this period to adequately maintain the balance of electrolytes and fluids.

PREVENTION OF NEPHROTOXICITY

Experimental studies

Prevention of nephrotoxicity by aminoglycoside can be focused on reducing or preventing the accumulation of aminoglycosides in the kidney, reduce or prevent aminoglycoside-induced phospholipids, protect against necrosis and other cellular alterations, protect against vascular and glomerular effects and/or increase the capacity of regeneration of the kidney.

Attempts to form an extracellular complex with aminoglycoside have been made utilizing polyanionic compounds such as dextran sulfate [59] or acidic drugs (piperacilin and phosphomycin) [60,61]. Also a reduction in the binding with brush-border of the membrane has been tried, altering the pH of the urine using bicarbonate [62] and using competitors to bind on the brush-border such as calcium [63] and lysine [64]. All these studies proved to have little clinical applicability as they diminished the efficacy of the drug or caused high toxicity.

In the 1970s, aminoglycoside were developed derived from gentamicin and kanamycin, starting from an alteration in the N1 chain, with the aim of obtaining molecules resistant to bacterial enzymes. Long-term analyses showed that these drugs (amikacin, isepamicin and arbekacin) reduced the binding to phospholipid acid together with a lower inhibition of lysosomal phospholipase [65] thereby diminishing toxicity [66-68].

The co-administration of polyaspartic acid with gentamicin protected against phospholipidosis and phospholipiduria [69], attenuating the nephrotoxicity of aminoglycosides [70].

The formation of free ions has also been implicated as a cause of renal injury due to aminoglycosides. This was presupposed because of the observation that these antibiotics increase the production of hydrogen peroxide by the renal cortex in rats and also due to indirect evidence linked to the fact that agents similar to aminoglycosides that inhibit the synthesis of phospholipase A2 and glutation

[71], also cause ARF. Previously tested antioxidant agents include deferoxamine, methimazole, vitamin C, vitamin E and selenium [72]. Medicinal plant extracts with antioxidant properties also protect against or improve nephrotoxicity induced by aminoglycosides. These plants include garlic [73] and Ginkgo biloba [74]. However these natural antioxidants present problems in their clinical use as they are not specific and contain impurities.

The concomitant administration of other antibiotics with aminoglycosides may also reduce nephrotoxicity. It was demonstrated in rats that the use of aminoglycosides with cephalosporin or cephtriaxone reduces the intracortical concentration of tobramicin. This protective effect was also noted with the use of fleroxacin (fluoroquinolone) [75] or isepamicin [76] with gentamicin. However, other studies show an aggravation of nephrotoxicity when aminoglycoside was associated with first-generation cephalotin.

Clinical trials

There is a circadian variation of nephrotoxicity induced by aminoglycoside. This was first noted by Nakano & Ogawa [77], who observed a greater renal toxicity in rats when gentamicin was administered during resting than in the period of activity. This was proven in a study involving 179 patients with severe infections treated with gentamicin or tobramicin. The nephrotoxicity was 34.6% during periods of resting (midnight to 7:30 a.m.) against 12.5% (8:00 a.m. to 3:30 p.m.) and 9.3% (4:00 p.m. to 11:30 p.m.) during active periods [50]. This variation is related to alterations in urinary pH, as there is greater interaction of aminoglycosides and anionic phospholipids when the pH is low [78]. It was seen, both in animals and humans, that the urinary pH is higher during activity and after eating and lower during rest and low food intake [79].

The use of aminoglycosides as a single daily dose diminishes its nephrotoxicity [27] providing at least the same effectiveness as a similar dose divided in two or three applications per day [80]. The rationale for this is due to two pharmacodynamic characteristics of the drug: the post-antibiotic effect and the bactericide power dependent on concentration. The post-antibiotic effect is the persistent inhibitory effect after drug removal or metabolization and elimination observed with many gram-negative organisms [81]. Bactericide power depends on concentration and is related to the plasma level of the drug [82]. Several metanalyses were carried out to compare the nephrotoxicity and the efficacy of single-dose administration showing the same efficiency with lower nephrotoxicity and ototoxicity [83]. The lower nephrotoxicity is probably due to a reduced accumulation of the drug in the renal cortex as with a single larger dose, more of the drug is excreted and not reabsorbed in the tubule because of the transportation speed of the tubular cells [84].

Measurement of the serum level has become routine in some centers, but clinical data showing reductions in nephrotoxicity are conflicting. Measurement may be important to guarantee an adequate therapeutic level and to avoid toxic concentrations. Measurement of the peak level should be made 30 minutes after venous infusion and one hour after intramuscular injections to guarantee that the therapeutic level is reached. Measurement of the trough (valley) level should be taken immediately before administration of the next dose. An increase in the trough level significantly reduces the glomerular filtration rate and is the first indication of nephrotoxicity caused by aminoglycosides, although the amount of accumulation varies between patients [85].

CONCLUSION

In conclusion, in spite of the risk of nephrotoxicity, aminoglycosides continue to be an important therapeutic option in the treatment of infections due to their efficacy and cost. Their correct dosage can considerable reduce or attenuate toxicity. Hence, it is essential to understand which risk factors are related to nephrotoxicity and to try to correct them when ever possible.

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