The indiscriminate use of antibiotics and the selective pressure exerted by them has led to an increase in bacterial resistance, so that the antimicrobials that were previously the first choice for treating certain pathologies have to be replaced by others of less frequent use, such as the aminoglycosides.

The chemical structure of aminoglycosides is composed of amino-sugars bound by glycoside bonds to a hexagonal cyclic alcohol with amino-groups (aminocyclitol). Depending on whether the aminocyclitol component is streptidine or deoxystreptamine, they are classified into two large groups. The first is composed only of streptomycin while the second one includes most of the compounds used in clinical practice (kanamycin, amikacin, tobramycin, gentamicin, neomycin).

Aminoglycosides are not absorbed by the gastrointestinal tract, so they must be administered parenterally.

They are freely distributed into the vascular space and into the interstitial fluid of most tissues due to their poor protein binding and high solubility level. They scarcely cross the biological membranes with the exception of renal tubular cells and those of the inner ear, which show saturable aminoglycoside uptake kinetics. One hour post-administration, the urine concentration ranges from 25 to 100 times higher than the plasma concentration and remains elevated for several days.

All aminoglycosides are excreted by glomerular filtration without metabolic change. Over 90% of the administered dose is recovered unchanged in the urine over the first 24 h; the rest is slowly recycled in the tubular lumen.

Its cationic structure, which depends on the number of amino-groups and their distribution within the molecule, seems to play an important role in the nephrotoxicity and ototoxicity. Despite its undesirable effects, they are an effective therapeutic alternative against germs insensitive to other antibiotics due to their chemical stability, fast bactericidal effect, low resistance and low cost.

Aminoglycoside antibiotics are used in the treatment of infections caused by aerobic gram-negative bacilli. However, its association with antimicrobials acting on the bacterial wall (penicillin, cephalosporin, carbapenem) shows synergic activity against several microorganisms. Its activity against Gram-positive bacteria includes staphylococci, enterococci and streptococci and resides in the synergy exhibited associated with beta-lactams.

The action of aminoglycosides comprises the interaction with the outer surface of the bacterial cell membrane, transport through the inner membrane and binding to the 30S subunit of ribosomes, which inhibits the synthesis of proteins, leading to the death of the microorganism. The mechanisms of resistance developed by microorganisms against aminoglycosides are: enzymatic modification of the molecule, alteration of diffusion and ribosomal mutation.

The incidence of nephrotoxicity by aminoglycosides in human medicine ranges between 5 and 25%. In the majority of patients it is manifested as a non-oliguric renal failure, the need for dialysis being very rare. Single-dose administration reduces the risk of nephrotoxicity.
Gentamicin induces cytotoxicity in the cells in which it accumulates (proximal tubule, distal tubule and collecting duct). This lesion can be lethal, giving rise to apoptosis and necrosis of the cells; or sublethal, altering the mechanisms involved in the transport of water and solutes from both the brush border and the basolateral membrane.

Damaged cells accumulate in the tubular lumen causing partial or complete obstruction and reduction of the excretory function. In addition, this obstruction increases tubular hydrostatic and Bowman's capsule pressure, thus causing decreased filtration pressure and glomerular filtration.

The tubular lesion is reversible and in some patients recovery of renal function occurs despite continuing the administration of aminoglycosides. Some factors such as advanced age, hypovolemia, pre-existing nephropathy, associated liver disease, hypothyroidism, pregnancy, metabolic acidosis, sodium depletion, high doses, administration in multidose, prolonged treatment and concomitant use of other drugs (NSAIDs, diuretics, amphotericin, cisplatin, cyclosporine, iodinated contrasts, vancomycin and cephalosporins) increase the risk of nephrotoxicity.

Most of the studies available in veterinary medicine in which nephrotoxicity of aminoglycosides has been studied are based on experimental models of acute renal injury caused by the administration of high doses of gentamicin.

The study by Sasaki et al. (2014) found that, in canine patients who were induced renal injury by administration of gentamicin 40 mg/kg/day/7 days SC, both the decrease in GFR and the increase in urine levels of cystatin C (UCCR, which means urine cystatin:creatinine ratio) were more early markers of kidney damage (day 4) than BUN, creatinine and other urine markers (NAG, NGAL, Cl-, Alb, L-FABP) that showed changes on day 8.

In patients with acute renal injury induced by administration of gentamicin (8-10 mg/kg/8h SC for 7 days), the determination of UNCR (urine NGAL:creatinine ratio) predicted 8 days earlier than creatinine the development of kidney injury (day 8 vs day 16). In addition, UNCR preceded the decrease in creatinine in two days (Palm et al., 2016).

Gautier et al. (2016) carried out a study in monkeys, which found that doses of gentamicin close to the therapeutic doses (10 mg/kg/24h IM) caused tubular lesions of minimal to mild severity. Some markers such as microalbuminuria or NAG were more sensitive than creatinine or BUN to detect this injury.

References


