Research Article

Gentamicin Nephrotoxicity: Mechanisms and Renoprotective

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Abstract. Gentamicin is one of the most used aminoglycosides especially in the treatment of life-threatening Gram-negative bacteria, however its use is limited due to associated nephrotoxicity. Despite the huge number of studies about gentamicin nephropathy, the exact mechanisms underlying the nephrotoxic effect of gentamicin remain indeterminate. Several studies have highlighted the role of oxidative stress, inflammatory and apoptotic pathways in gentamicin induced renal damage. Naturally occurring antioxidants, different antihyperglycemic drugs and antihypertensive agents have been experimentally used to prevent renal injury induced by gentamicin in different animal models. In this review, we will discuss the proposed mechanisms and renoprotective strategies regarding gentamicin-induced nephrotoxicity.

Keywords: Gentamicin, Nephrotoxicity, Antioxidant, Antidiabetic, Antihypertensive, Oxidative stress, Inflammation.

1. Introduction

Gentamicin (GM) is an aminoglycoside antibiotic in the form of freely water-soluble amorphous white powder derived from Micromonospora purpurea [1] with molecular weight of 477.6, molecular formula C21H43N5O7 and IUPAC name 2-[4,6-diamino-3-[3-amino-6-[1-(methylamino)ethyl]oxan-2-yl]oxy-2-hydroxycyclohexyl]oxy-5-methyl-4-(methylamino)oxane-3,5-diol [2]. Gentamicin is one of the most widely used aminoglycosides owing to its effectiveness, low cost, broad spectrum of activity and low rates of resistance. Gentamicin use is not limited to adults as it is also approved for use in infants and even premature neonates [3]. Gentamicin possesses concentration-dependent bactericidal effect through inhibition of protein synthesis. It binds to the 30s ribosomal subunit leading to codon misreading and mistranslation [4]. It also possesses dose-dependent post antibiotic effect [4].

2. Pharmacokinetics of Gentamicin

Gentamicin is poorly absorbed from gastrointestinal tract (GIT) as it is a highly polar compound. As a result, it’s usually administered by parenteral routes. GM is distributed in the extracellular water; it doesn’t cross blood brain barrier but crosses the placenta. GM is excreted by the kidney through glomerular filtration with half-life about 2-3 hours [4].
3. Indications of Gentamicin

Indications for parenteral GM include; surgical prophylaxis (single dose GM used alone or in combination), empirical treatment for less than 48 hours (GM is used in combination in intra-abdominal infections, surgical site infection, urinary tract infection, genital infections, respiratory tract infection including both hospital and community acquired pneumonia, infective endocarditis, central nervous system (CNS) infections, and sepsis), and directed treatment that may last for weeks as in brucellosis, tularemia, pneumonic plague and pseudomonal infections [5]. Oral GM is also used as a prophylactic agent in gastrointestinal surgery as a part of decolonization regimens [6]. GM is also available in ophthalmic preparations for conjunctivitis and keratitis [7]. GM has also shown antifungal activity; combination with azoles resulted in synergistic effect [8, 9].

4. Adverse Effects of Gentamicin

The main adverse effects associated with GM use are nephrotoxicity and otootoxicity (both vestibular and cochlear) while neuromuscular paralysis is a rare adverse effect that was reported in patients with myasthenia gravis and those receiving neuromuscular blockers. This paralysis can be reversed by the administration of calcium gluconate [10].

5. Gentamicin Nephrotoxicity

Nephropathy represents a major clinical complication of GM use that was not only reported in patients receiving therapeutic doses of gentamicin but also in patients receiving prophylactic doses, it was even reported despite careful monitoring by the antibiotic stewardship program [11, 12]. GM use was responsible for around 15% of acute kidney injury reported cases [13].

Administration of clinical doses of GM to humans or 10-20 mg/kg to rats for few days was enough to induce some tubular changes that may progress to renal failure but to induce extended cortical necrosis rapidly higher doses of gentamicin (40 mg/kg or more) are needed [14]. It has been reported that 30% of patients treated with gentamicin for more than 7 days show signs of nephrotoxicity [15]. Many factors increase the risk of nephrotoxicity including older age, preexisting renal impairment, dehydration, hypothyroidism, pregnancy, hepatic dysfunction, hyponatremia, metabolic acidosis, long treatment duration as well as higher doses and multiple daily dosing regimen. Further, coadministration of other nephrotoxic drugs such as non-steroidal anti-inflammatory drugs (NSAIDs), cisplatin, amphotericin B, vancomycin, cyclosporin, cephalosporins, iodide-based contrast media and diuretics, can increase the incidence of GM induced kidney damage [16-19]. Nephrotoxicity was observed with serum trough levels higher than 2 µg/ml [20].

The exact mechanisms pertaining to GM nephrotoxicity are obscure. The main observed change was apoptosis of tubular epithelial cells mainly those of proximal tubules as a result of accumulation of GM in these cells [19]. Two main pathways of GM uptake into cells have been identified: endocytosis and diffusion. Diffusion occurs via non-selective cation channels [21, 22]. Endocytosis occurs via the megalin and cubulin complex which is a transport molecules for cations and proteins [21]. After reaching a certain threshold, the GM in endosomes is released into cytosol [23]. On releasing into cytoplasm, GM causes mitochondrial dysfunction, oxidative stress through overproduction of hydroxyl radical and superoxide anion with consequent activation of apoptotic pathways [24, 25].

The damaged cells can obstruct the lumen leading to increased hydrostatic pressure in the tubules and the capsule as well, thus decreasing the glomerular filtration [26]. GM interferes with reabsorption of cations resulting in activation of tubuloglomerular feedback loop and thus a decline in glomerular filtration to prevent excessive loss of solutes and fluids [27, 28]. Gentamicin causes mesangial cell contraction, which decreases glomerular filtration rate (GFR), followed by proliferation then apoptosis of these cells [29]. The mesangial contraction maybe mediated by secretion of platelet activating factor and vasoconstrictors such as endothelin-1, angiotensin-II and thromboxane A2 and overproduction of reactive oxygen species [30-32]. Oxidative stress is also responsible for mesangial cells apoptosis [33].

GM causes interstitial nephritis as well [34]. Gentamicin administration is followed by a decrease in renal perfusion as a result of increased vascular resistance [35].

Gentamicin induced renal damage is associated with increased serum creatinine and urea concentrations as well as increased serum cystatin C level and a decline in GFR [37]. Histopathological changes observed in GM induced renal damage include apoptosis and necrosis of tubular epithelial cells, casts formation, glomerular damage, and infiltration of inflammatory cells [38].

6. Experimental Approaches to Mitigate Gentamicin Nephrotoxicity

6.1. Role of natural antioxidants. Mitochondrial dysfunction and overproduction of reactive oxygen species (ROS) have been hypothesized as a pivotal contributor to GM nephrotoxicity [39, 40]. Thus, many experimental studies were conducted to evaluate the possible protective effect of different antioxidants against gentamicin induced nephrotoxicity. For example; berberine, a naturally occurring alkaloid with antioxidant properties, has been shown to possess renoprotective effect against gentamicin nephrotoxicity [41]. Similar effects were observed using curcumin, a phenolic compound of the curcuminoi group, where curcumin ameliorated gentamicin induced oxidative stress and renal injury [42]. In addition, resveratrol, a naturally occurring
Figure 1: mechanisms involved in GM nephrotoxicity [36].

6.2. Role of antidiabetic drugs. Sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, protects glucagon-like peptide-1 (GLP-1) from degradation and has antioxidant properties as described in previous studies by Chen et al. and Gault et al. [51, 52]. Thus, Abuelezz et al. [53] hypothesized that sitagliptin may have a protective role against renal injury induced by GM administration. Their work established the protective effect of sitagliptin against gentamicin nephrotoxicity via their antioxidant activity as sitagliptin administration prevented the GM induced depletion of antioxidants such as catalase (CAT), superoxide dismutase (SOD), reduced glutathione (GSH), and glutathione peroxidase (GPx) and prevented the increase in malondialdehyde (MDA) level. They proved that the nephroprotective effect of sitagliptin is partially mediated by protecting the mitochondria. Administration of sitagliptin (30mg/kg/day) successfully prevented the GM induced decrease in activity of mitochondrial respiratory enzymes (NADH dehydrogenase, succinate dehydrogenase, and cytochrome c oxidase) [53]. Sitagliptin also possessed mitochondrial protective activity in cardiac and brain cells [54, 55]. Sitagliptin also showed nephroprotective effect in other models including ischemia/reperfusion injury and diabetic nephropathy through mitigating oxidative stress and preventing apoptosis of renal cells [51, 56]. Similar protective effect was observed using sitagliptin (10mg/kg/day for 10 days) in gentamicin induced nephropathy in mice [57].

Saxagliptin, another DPP-4 inhibitor with previously described renoprotective effect [58, 59], showed similar protective effect against gentamicin nephropathy via modulation of oxidative stress, inflammation and apoptosis [60].

Metformin, an insulin sensitizer of the biguanide group, is the first-line drug treatment for patients with type 2 DM especially obese patients [61]. Previous studies have reported the antioxidant activity of metformin [62, 63]. Despite the controversy regarding the effect of metformin on mitochondrial function, recent human studies revealed that metformin is capable of activating the mitochondrial respiratory chain in clinically used doses (daily dose: 1500-2200 mg) [64, 65]. Previous experimental studies claimed that GM administration inhibited oxidative phosphorylation and thus reduced ATP levels in the tubular cells [66]. The role of mitochondrial dysfunction was also reported in the pathogenesis of other forms of renal damage including diabetic nephropathy and ischemic injury [67, 68]. Based on these studies, Morales et al. hypothesized that metformin may protect against GM induced nephrotoxicity. Their work revealed that administration of metformin successfully protected against damage induced by GM and that this renoprotective effect of metformin is mediated by restoring the mitochondrial homeostasis and improving the oxidative status [25]. Interestingly, work by Alsharidah et al. [69]
showed that metformin administration diminished the oxidative stress induced by GM but failed to completely reverse the renal damage. This controversy could be explained by the difference in metformin doses used in both studies (100 mg/kg vs 60 mg/kg, respectively). Further, combining the antioxidant curcumin with metformin resulted in synergistic renoprotective effect via modulating oxidative stress, inflammation as well as apoptosis of renal cells [70].

Pioglitazone, a peroxisome proliferator-activated receptor-γ (PPAR-γ) agonist used for management of type 2 diabetes mellitus (T2DM), has shown beneficial effects on ischemic injury in multiple organs including the kidney via antioxidant and anti-inflammatory effect [71]. Further, pioglitazone showed inhibitory effect on the activation of the inflammatory mediator nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and inflammatory cells infiltration in the renal tissue [72]. NF-κB is a transcription factor that plays a vital role in GM induced renal damage by promoting synthesis of inflammatory cytokines and recruitment of inflammatory cells [73]. Surprisingly, in 2010 Al-Azzam et al. conducted a study to evaluate the nephroprotective effect of pioglitazone against GM nephrotoxicity but his work showed that administration of 10mg/kg/day pioglitazone failed to protect against gentamicin nephrotoxicity [74]. This ambiguity was later explained by the work of Medić et al. revealing a U-shaped effect of pioglitazone on gentamicin induced renal injury depending on the used dose of pioglitazone, when renoprotection was observed using 1mg/kg pioglitazone [37].

Glibenclamide, a sulfonylurea used for management of type 2 DM, showed nephroprotective effect through alleviating oxidative stress induced by GM administration [74]. It also possessed protective activity against renal ischemic injury [75, 76].

6.3. Role of antihypertensive drugs. Several studies have evaluated the possible protective role of different antihypertensive agents against gentamicin induced renal damage. For example, candesartan, an angiotensin II type I (AT1) receptor blocker with anti-inflammatory and antioxidant effect previously used to prevent against nephrotoxicity induced by cisplatin [77], was tested for a protective effect against gentamicin nephrotoxicity. This study was later explained by the work of Medić et al. revealing a U-shaped effect of pioglitazone on gentamicin induced renal injury depending on the used dose of pioglitazone, when renoprotection was observed using 1mg/kg pioglitazone [37].

It’s worth noting that modulating renin angiotensin aldosterone system by inhibiting angiotensin converting enzyme also confers protection against gentamicin induced nephropathy [81].

On the other hand, the cardio-selective β-blocker, nebivolol, with protective effect against contrast-induced renal injury, was evaluated for renoprotection against GM induced injury. It showed nephroprotective effect when it was administered either concomitantly with GM or 21 days prior to GM administration. This effect was mediated by the antioxidant effect of nebivolol as evidenced by increased renal activity of SOD, CAT, glutathione S-transferase (GST), higher renal level of GSH and decreased level of MDA and nitric oxide in renal tissue [82, 83].

Another class of the antihypertensive drugs, calcium channel blockers, has been evaluated for the possible renoprotective effect. Of them, nifedipine and amlodipine but not nitrendipine showed protection against nephrotoxicity induced by gentamicin. Their nephroprotection was mediated by antioxidant and antiapoptotic effect [84].

7. Conclusion

In conclusion, several natural antioxidants, oral hypoglycemic agents and antihypertensive drugs with antioxidant and anti-inflammatory activity have been used experimentally in animals to prevent GM associated renal damage. However, many studies are still needed to prove their clinical efficacy in protecting against GM nephropathy and the best doses to be used.

Competing Interests

The authors declare no competing interests.

References


B. D. Sahu, et al., Naringin ameliorates gentamicin-induced nephrotoxicity and associated mitochondrial dysfunction,


