Beneficial effect of halofuginone on gentamicin - induced acute nephrotoxicity

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Gentamicin is widely used in clinical practices for the treatment of life-threatening gram negative infections. However, its clinical usefulness is limited by the development of nephrotoxicity [1, 2]. Halofuginone, is an analog of a low-molecular-weight quinazolinone alkaloid isolated from the plant *Dichroa febrifuga*. It is a potent inhibitor of collagen type 1 (I) gene expression and extracellular matrix deposition. [3]. The effect on extracellular matrix deposition has led to the demonstration that halofuginone has strong antifibrotic properties in several organs [4, 5]. In the light of the above mentioned findings, this study was designed to investigate the possible protective effect of halofuginone in a rat model of on gentamicin-induced nephrotoxicity. For this purpose, we assessed the effect of halofuginone on oxidant-antioxidant status and neutrophil infiltration to the inflamed organ and also evaluated its effectiveness on gentamicin-induced renal dysfunction using biochemical assays.

Sprague-Dawley rats (200-250 g; n=8-10) were treated with gentamicin sulphate (GEN; 80 mg/kg) or saline intraperitoneally for seven consecutive days. Halofuginone was administered (0.1 mg/kg/day) following GEN or saline injections. On the 8th day, all animals were decapitated. Trunk blood and 24 h urine were collected to measure the serum creatinine levels, blood urea nitrogen (BUN) levels and to calculate the creatinine clearance values. The kidneys were excised for histological evaluation and for the measurement of malondialdehyde (MDA) level, glutathione (GSH) content, myeloperoxidase (MPO) activity and chemiluminesce (CL). For histological evaluation of the renal tubular structure by light microscopy, the kidney samples were fixed in 10% formalin solution. Paraffin sections of 6 μm were stained with Periodic acid-Schiff (PAS) and hematoxylin and eosin. The renal injury based on tubular and glomerular degeneration, inflammatory cell infiltration, and vasocongestion was scored using a scale ranging from 0 to 3 (0: none, 1: mild, 2: moderate, and 3: severe).

Microscopic examination of the control and halofuginone groups showed a normal kidney morphology. In the GEN-induced renal injury group, light microscope investigations revealed an extreme degree of damage at glomeruli, proximal and distal tubules. A decrease in PAS reaction in the proximal tubules and basal membranes suggested a prominent kidney

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parenchymal injury. In addition, interstitial edema and leukocyte infiltration were noticed in tissue sections. The microscopic score of this group (8.00 ± 0.70) revealed leukocyte infiltration, tubular and glomerular degeneration and vasocongestion. In the halofuginone-treated renal injury group, the microscopic score was significantly lower than that of the saline-treated renal injury group (4.00 ± 0.82; $p<0.05$). Microscopic analysis demonstrated a reduction in the severity of kidney parenchymal damage. Tubular epithelial cells generally presented a normal morphology with few damaged tubular cells. A prominent PAS reaction was observed in both proximal tubules and basal membranes.

Halofuginone treatment to animals with GEN-induced renal injury caused a significant decrease in serum BUN ($p<0.05$) and reduced the elevated MDA ($p<0.05$), GSH content ($p<0.001$) and MPO activity ($p<0.001$), It was also effective to reverse the elevated CL values ($p<0.001$) of rats with GEN-induced nephrotoxicity and preserving renal morphology.

In conclusion, halofuginone has a beneficial effect on GEN-induced acute nephrotoxicity, as confirmed by histological evaluation and biochemical assays. The mechanism of the protective effect could be attributed, at least in part, to decreased tissue leukocyte infiltration and thus, to decreased oxygen-derived metabolite production.

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