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Effects of pre and post-treatments with dipyridamole in gentamicin-induced acute nephrotoxicity in the rat

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This study investigated the pretreatment and post-treatment effects of dipyridamole (20 mg/kg/day, *p.o.*) in gentamicin-induced acute nephrotoxicity in rats. Rats were administered gentamicin (100 mg/kg/day, *i.p.*) for 8 days. Gentamicin-administered rats exhibited renal structural and functional changes as assessed in terms of a significant increase in serum creatinine and urea and kidney weight to body weight ratio as compared to normal rats. Renal histopathological studies revealed a marked incidence of acute tubular necrosis in gentamicin-administered rats. These renal structural and functional abnormalities in gentamicin-administered rats were accompanied with elevated serum uric acid level, and renal inflammation as assessed in terms of decrease in interleukin-10 levels. Dipyridamole pretreatment in gentamicin-administered rats afforded a noticeable renoprotection by markedly preventing renal structural and functional abnormalities, renal inflammation and serum uric acid elevation. On the other hand, dipyridamole post-treatment did not significantly prevent uric acid elevation and renal inflammation, and resulted in comparatively less protection on renal function although it markedly reduced the incidence of tubular necrosis. In conclusion, uric acid elevation and renal inflammation could play key roles in gentamicin-nephrotoxicity. Dipyridamole pretreatment markedly prevented gentamicin-induced acute nephrotoxicity, while its post-treatment resulted in comparatively less renal functional protection.
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1. Introduction

Aminoglycosides are potent broad-spectrum antibiotics employed for the treatment of life-threatening infections. Aminoglycoside antibiotics kill bacteria through binding to the ribosomal decoding site and reduction in fidelity of bacterial protein synthesis (Hermann, 2007). Since their discovery several years back, aminoglycosides stand as a mainstay of antibacterial therapy against serious Gram-negative bacterial infections (Hermann, 2007). Aminoglycoside antibiotics have several advantages such as rapid concentration-dependent bactericidal effect, synergism with beta-lactam antibiotics, low rate of true resistance, clinical effectiveness and importantly low-cost therapy (Begg and Barclay, 1995).

Nephrotoxicity is one of the most important therapeutic limitations of aminoglycosides, especially gentamicin, whereas nephrotoxicity appears clinically in 10–25% of therapeutic courses (Lopez-Novoa et al., 2011). Aminoglycosides-induced nephrotoxicity is characterized in terms of slow rise in serum creatinine, tubular necrosis and decline in glomerular filtration rate (Martínez-Salgado et al., 2007). Gentamicin is effective against various Gram negative bacterial infections. However, the frequent clinical use of gentamicin is limited because of its nephrotoxic adverse action (Balakumar et al., 2010; Lopez-Novoa et al., 2011). Gentamicin-associated renal impairment occurs in up to 30% of treated patients (Ali et al., 2011).

Gentamicin-induced acute nephrotoxicity occurs because of its tubular effect while tubular cytotoxicity is triggered by drug accumulation in epithelial tubular cells. Studies in animal models and cultured cells demonstrated that gentamicin can enter tubular cells via endocytosis mediated by the megalin-cubilin complex (Quiros et al., 2011). The drug might accumulate in epithelial

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tubular cells causing loss of brush border in epithelial cells, overt tubular necrosis, reduced renal blood flow and oxidative stress (Ali et al., 2011; Sardana et al., 2015). In addition to renal oxidative stress, renal inflammation plays a key role in gentamicin-induced nephrotoxicity (Ali et al., 2011; El Gamal et al., 2014). Although several pharmacological interventions have been shown to prevent gentamicin-induced nephrotoxicity, it is a matter of great concern to identify a promising agent to blunt gentamicin-nephrotoxicity.

Dipyridamole is a platelet inhibitor, and it has been employed along with aspirin for the secondary stroke prevention (Chaturvedi, 2008). Dipyridamole is an adenosine reuptake inhibitor (Meester et al., 1998; Sharma et al., 2013). Dipyridamole possesses pleiotropic anti-inflammatory, anti-proliferative and anti-oxidant action (Vargas et al., 2003; Zhuplatov et al., 2006; Soliman and Arafah, 2012) and we have recently reviewed its pleiotropic benefits, including renoprotective action (Balakumar et al., 2014). Number of clinical and experimental studies highlights the renoprotective potentials of dipyridamole. For instance, dipyridamole and aspirin treatment either alone or in combination reduced proteinuria in diabetic patients with nephropathy (Hopper et al., 1989; Khajehdehi et al., 2002). Likewise, dipyridamole reduced the urinary albumin excretion in patients with diabetic microalbuminuria (Aizawa et al., 1990). Dipyridamole at high-dose is proischemic, and it could cause a '*coronary steal*' effect (Becker, 1978; Ando et al., 1982; Tommasi et al., 2000). On the other hand, dipyridamole at low-dose orally could have a minimal hemodynamic effect (Ye et al., 2007). Recently, we have shown that dipyridamole treatment has a pleiotropic renoprotective action in diabetic rats (Balakumar et al., 2014a). We further reported that treatment with dipyridamole had a therapeutic potential in partially preventing the diabetes mellitus-induced vascular endothelial and renal abnormalities in rats (Sharma et al., 2014). While considering its pleiotropic renoprotective effect, we investigated the effects of low-dose dipyridamole pretreatment and post-treatment in gentamicin-induced acute nephrotoxicity in rats.

2. Materials and methods

The experimental protocol of the present study has been approved by the 'Research & Ethics committee', AIMST University (Reference number: AUHAEC 1/FOP/2013). Male Sprague Dawley rats of weighing about 180–300 g were employed in this study. Rats were acclimatized in the 'AIMST University Central Animal House' and maintained on standard rat pellets and tap water while rats were given *ad libitum* access to food and water. Rats were exposed to normal day and night cycles.

2.1. Induction of experimental nephrotoxicity

Rats were administered gentamicin (100 mg/kg/day, *i.p.*) for 8 days to induce experimental acute nephrotoxicity.

2.2. Experimental protocol

Rats were randomly divided into 5 groups, and each group consists of six rats. Dipyridamole was suspended in 0.5% carboxymethylcellulose. Gentamicin sulfate was dissolved in distilled water.

Group 1 (*Normal Control*), rats were maintained on standard food and water, and no treatment was given. Group 2 (*Gentamicin Control*), rats were administered gentamicin (100 mg/kg/day, *i.p.*) for 8 days. Group 3 (*Dipyridamole per se*), normal rats were administered dipyridamole (20 mg/kg/day, *per os*) for 8 days. Group 4 (*Dipyridamole Pretreated*), rats administered gentamicin (100 mg/kg/day, *i.p.*, 8 days) were treated with dipyridamole (20 mg/kg/day, *per os*) while the treatment was started a day before the administration of gentamicin and it was continued for 8 days from the day of administration of gentamicin. Group 5 (*Dipyridamole Post-treated*), rats were administered gentamicin (100 mg/kg/day, *i.p.*) for 8 days. These rats were treated with dipyridamole (20 mg/kg/day, *per os*) for next 6 days after the completion of 8 days protocol of gentamicin administration.

2.3. Assessment of nephrotoxicity

At the end of the experimental protocol, rats were sacrificed at after 24 h of the last gentamicin administration (Gentamicin control and dipyridamole pretreated groups), and after 24 h of the last dipyridamole administration (Dipyridamole *per se* and dipyridamole post-treated groups). The blood samples were collected and renal samples were isolated immediately. Gentamicin-induced acute nephrotoxicity in rats with or without treatments was biochemically assessed by estimating serum creatinine, urea and uric acid levels using the commercially available Reflotron assay kits. In addition, the kidney weight to body weight ratio (KW/BW, mg/g) was calculated. Further, the concentration of interleukin 10 (IL-10) in renal tissue homogenate was measured using specific enzyme-linked immunosorbent assay (ELISA). Moreover, histopathological analysis was performed to assess glomerular and tubular architecture.

2.3.1. Estimation of serum creatinine

The serum creatinine concentration was estimated using commercially available Reflotron strips employing the Reflotron Plus Apparatus (Roche Diagnostics, Germany). After application to the test strip, the serum sample flows into the reaction zone. In a reaction catalysed by creatinine iminohydrolase, creatinine is hydrolyzed to N-methylhydantoin with release of ammonia. In further reaction steps, hydrogen peroxide is formed that reacts with an indicator to form a blue dye, which is directly proportional to the creatinine concentration present in the sample. At a temperature of 37 °C, the dye formed was measured at 642 nm, and the creatinine concentration was expressed in mg/dL.

2.3.2. Estimation of serum urea

The serum urea concentration was estimated using commercially available Reflotron strips employing the Reflotron Plus Apparatus (Roche Diagnostics, Germany). After application to the test strip, the serum sample flows into the reaction zone. The urea present in the sample is hydrolyzed to ammonium carbonate from which ammonia is expelled due to the alkaline buffering. This leads to the partial color change of buffered indicator to green/blue, the intensity of which is directly proportional to the urea concentration of the sample. At a temperature of 37 °C, the depth of color formed was measured at 642 nm and the urea concentration was expressed in mg/dL.

2.3.3. Estimation of serum uric acid

The serum uric acid concentration was estimated using commercially available Reflotron strips employing the Reflotron Plus Apparatus (Roche Diagnostics, Germany). The principle involved in the estimation of serum uric acid is shown below. After application to the test strip, the serum sample flows into the reaction zone. In the presence of uricase, the uric acid is oxidized by oxygen to allantoin and hydrogen peroxide. In a reaction catalysed by peroxidase (POD), the hydrogen peroxide then converts an indicator into its oxidized blue form. At a temperature of 37 °C, the dye formed was measured at 642 nm, and the uric acid concentration was expressed in mg/dL.

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