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Protective role of caffeic acid phenethyl ester (cape) on gentamicin-induced acute renal toxicity in rats

H. Parlakpinar[a,*], S. Tasdemir[a], A. Polat[b], A. Bay-Karabulut[c], N. Vardi[d], M. Ucar[d], A. Acet[a]

[a] *Department of Pharmacology, Faculty of Medicine, Inonu University, 44280 Malatya, Turkey*
[b] *Department of Physiology, Faculty of Medicine, Inonu University, 44280 Malatya, Turkey*
[c] *Department of Biochemistry, Faculty of Medicine, Inonu University, 44280 Malatya, Turkey*
[d] *Department of Histology, Faculty of Medicine, Inonu University, 44280 Malatya, Turkey*

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Abstract

The toxicity of gentamicin (GEN) in the kidney seems to relate to the generation of reactive oxygen species (ROS). Caffeic acid phenethyl ester (CAPE) has been demonstrated to have antioxidant, free radical scavenger and anti-inflammatory effects. It has been proposed that antioxidant maintain the concentration of reduced glutathione (GSH) may restore the cellular defense mechanisms and block lipid peroxidation thus protect against the toxicity of wide variety of nephrotoxic chemicals. We investigated the effects of CAPE on GEN-induced changes in renal malondialdehyde (MDA), a lipid peroxidation product, nitric oxide (NO) generation, superoxide dismutase (SOD), catalase (CAT) activities, GSH content, blood urea nitrogen (BUN) and serum creatinine (Cr) levels. Morphological changes in the kidney were also examined.

A total of 32 rats were equally divided into four groups which were: (1) control, (2) injected with intraperitoneally (i.p.) GEN, (3) injected with i.p. GEN + CAPE and (4) injected with i.p. CAPE.

GEN administration to control rats increased renal MDA and NO generation but decreased SOD and CAT activities, and GSH content. CAPE administration with GEN injections caused significantly decreased MDA, NO generation and increased SOD, CAT activities and GSH content when compared with GEN alone. Serum level of BUN and Cr significantly increased as a result of nephrotoxicity. CAPE also, significantly decreased serum BUN and Cr levels. Morphological changes in the kidney due to GEN, including tubular necrosis, were evaluated qualitatively. In addition, CAPE reduced the degree of kidney tissue damage induced by GEN. Both biochemical findings and histopathological evidence showed that administration of CAPE reduced the GEN-induced kidney damage.

* Corresponding author. Tel.: +90 422 341 0660 1309; fax: +90 422 341 0036.
E-mail address: hparlakpinar@hotmail.com (H. Parlakpinar).

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Our results indicated that CAPE acts in the kidney as a potent scavenger of free radicals to prevent the toxic effects of GEN both at the biochemical and histological level. Thus, CAPE could be effectively combined with GEN treatment.

Keywords: Caffeic acid phenethyl ester; Gentamicin; Reactive oxygen radicals; Renal toxicity; Rat

1. Introduction

Aminoglycoside antibiotics are commonly used for the treatment of severe gram negative bacterial infections. Despite their beneficial effects, aminoglycosides have considerable nephrotoxic side effects (Parlakpinar et al., 2003). The most widely used drug in this category is gentamicin (GEN) (Reiter et al., 2002). A major complication of GEN treatment is nephrotoxicity, accounting for 10–20% of all cases of acute renal failure (ARF) according to experimental results (Erdem et al., 2000). Also, 30% of the patients treated with GEN for more 7 days show some signs of nephrotoxicity that markedly limits its use (Pedraza-Chaverri et al., 2000). So, GEN nephrotoxicity promotes both increased morbidity and health-care costs. Although the change in GEN dosing from multiple-daily to once-daily dose has reduced the risk of nephrotoxicity, the incidence of GEN-induced ARF still remains high (Kopple et al., 2002).

Neprotoxicity induced by GEN is a complex phenomenon characterised by an increase in blood urea nitrogen (BUN) and serum creatinine (Cr) concentration, and severe proximal renal tubular necrosis followed by deterioration and renal failure (Smetana et al., 1988; Al-Majed et al., 2002). Although the pathogenesis is still not well understood, the toxicity of GEN in the kidney seems to relate to the generation of destructive reactive oxygen species (ROS) in these cells (Reiter et al., 2002; Al-Majed et al., 2002). ROS have been implicated in a wide range of biological functions, but they can express both beneficial and highly toxic effects on cellular homeostasis (Mates, 2000). A large body of in vivo and in vitro evidence indicates that ROS are important mediators of GEN-induced nephrotoxicity (Pedraza-Chaverri et al., 2000; Kopple et al., 2002; Al-Majed et al., 2002; Abdel-Naim et al., 1999). ROS have been proposed as a causative agent of cell death in many different pathological states as well as, in glomerular disease (Smetana et al., 1988), in renal ischemia and reperfusion injury (Longoni et al., 2002), and in various models of toxic renal failure (Piotrowski et al., 1996).

Several studies have demonstrated that various agents including melatonin (Ozbek et al., 2000), vitamin E, superoxide dismutase (SOD) (Pedraza-Chaverri et al., 2000), lipoic acid (Al-Majed et al., 2002; Sandhya and Varalakshmi, 1997), zinc (Kumar et al., 2000), ginkgo biloba extract (Maldonado et al., 2003), diallyl disulfide (Pedraza-Chaverrý et al., 2003) and etc. can prevent GEN-induced renal damage. To date there is no study the protective effect of caffeic acid phenethyl ester (CAPE), a known potent antioxidant, free radical scavenger and anti-inflammatory (Martins et al., 2002) on aminoglycoside antibiotics including GEN.

CAPE is an active component of honeybee propolis extracts and has been used as a folk medicine for many years. At a concentration of 10 μmol, it completely blocks production of ROS in human neutrophils and in the xanthine/xanthine oxidase system (Ozyurt et al., 2001). Therefore, this experimental study was designed to investigate the possible protective effects of CAPE on nephrotoxicity induced by GEN in a rat model, and to clarify the association between renal malondialdehyde (MDA), nitric oxide (NO) production, SOD, catalase (CAT) activities, glutathione (GSH) content, Cr, BUN levels and GEN-induced nephrotoxicity.

2. Materials and methods

2.1. Experimental conditions

Female Wistar rats (aged 8–12 weeks) weighing 200–250 g were placed in a temperature ($21 \pm 2\,^{\circ}C$) and humidity ($60 \pm 5\%$) controlled room in which a 12 h:12 h light: dark cycle was maintained. Thirty-two rats were randomly assigned to four groups equally: (1) control group; injected intraperitoneal (i.p.) diluted 1% ethanol with saline (vehicle) for 12 days, (2) GEN-treated group; firstly injected i.p. with vehicle for 2