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Ameliorative effect of selenium in cisplatin-induced testicular damage in rats

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ABSTRACT

In this study, we investigated the protective effect of selenium (Se) on cisplatin (Cis) induced testicular damage using histopathological, immunohistochemical and biochemical approaches. Twenty-one male Wistar rats were equally divided into three groups of seven rats each: control (C), Cis, and Cis + Se. Cis and Cis + Se group rats received Cis at a dose of 12 mg/kg b.w./day, intraperitoneally for 3 consecutive days. Cis + Se group rats received selenium via oral gavage 3 mg/kg/day (twice-a day as 1.5 mg/kg) until 11th consecutive days starting at 5 days before cisplatin injection. C group received only 0.9% NaCl intraperitoneally and orally at same time and at equal volume. After the treatment, the histopathological, immunohistochemical and biochemical examinations were performed. In seminiferous tubules of Cis treated rats were observed the most consistent findings characterized with vacuolization, desquamation, disorganization, and also was a considerable reduction in elongated spermatids, however the Cis + Se group exhibited improved histopathologic changes. In the immunohistochemical examinations, caspase-3 immunopositive cells displayed higher in the Cis group according to C and Cis + Se groups. Bcl-2 and NF-κB staining revealed a moderate number in the C group and significantly fewer in the Cis group compared to the Cis + Se groups. Additionally, MDA levels were also significantly increased in the Cis group in comparison to Control group, but pretreatment with selenium prevented elevation of MDA levels significantly in Cis + Se group rats. This study indicates that Cis-treatment induced testicular apoptosis and lipid peroxidation, and combined treatment with selenium prevented severity of the toxicity in rats.

1. Introduction

Cisplatin (cis-diamminedichloroplatinum II) (Cis) is a platinum-based chemotherapeutic agent that was introduced into the clinical using clinic in 1972 by Rosenberg and Vancamp (1969). It is used as a cytotoxic agent in the treatment of many types of cancers, including genitourinary cancer and breast cancer, and it is one of the drugs of choice in the management of germ cell tumours (Quinn et al., 2005). Cis causes inhibition of DNA replication and repair and disturbance of the cell cycle, also encourages the effects of the apoptotic process by interacting with DNA in the cells (Wang et al., 2004). The mechanism of cisplatin in the treatment of cancer is induction of apoptosis due to altered apoptosis-related signals and the activation of signalling pathways (Siddik, 2003).

Many proteins are involved in Cis-mediated apoptosis regulation through the altered expression of proteins, such as caspase and Bcl-2 family members (Venkatraman et al., 2005; Oruc et al., 2012). Apoptosis is a programmed cell death that initiates through one of extrinsic (other cell signals) or intrinsic (senses cell stress) pathways. Cell death process can initiated by apoptosis promoting factors such as caspases, p53, Fas and other, or stopped by apoptosis inhibiting factors such as Bcl-2, Bcl-xL, NF-κB, survivin and others. Apoptosis also serves as an important defence strategy against cell damage, which is modulated by the caspase (cysteinyl aspartate-specific proteases) enzyme system. If the activity of

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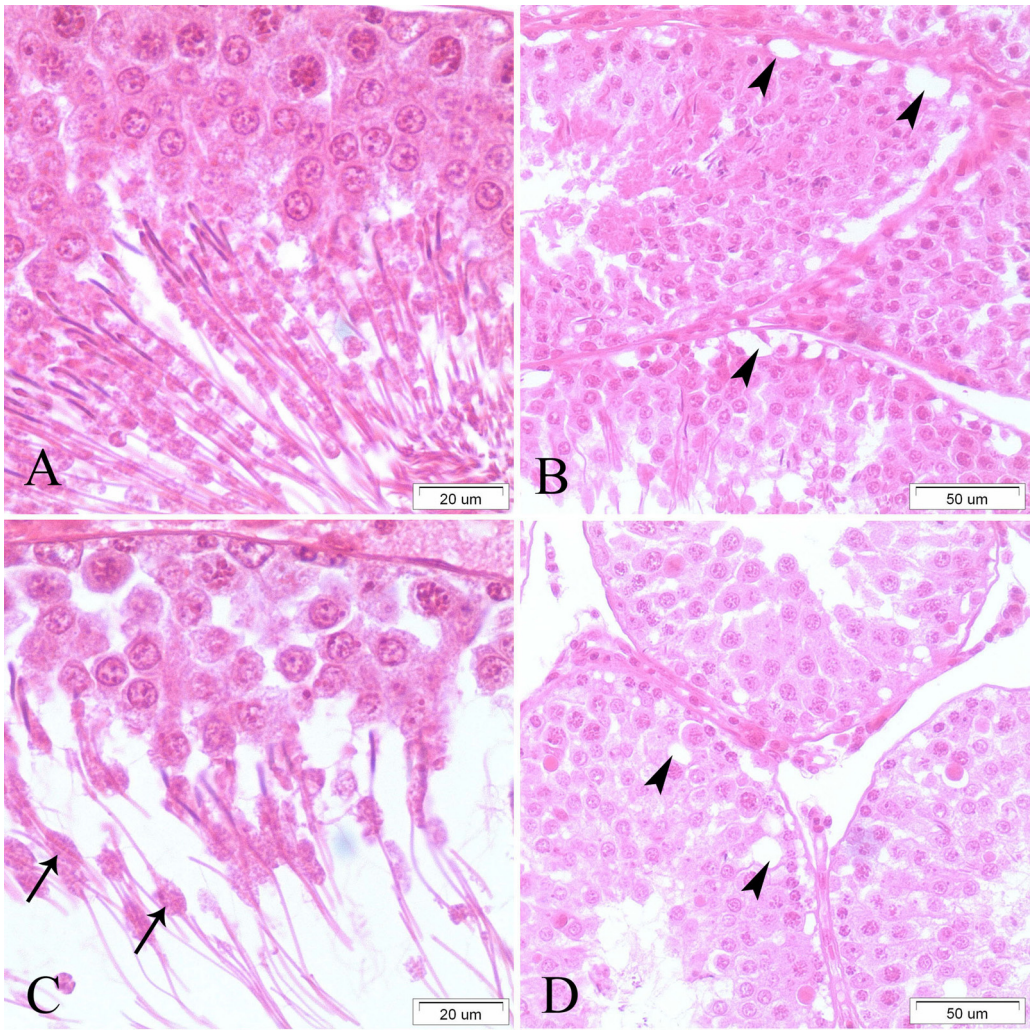

Fig. 1. Histopathological examinations of testicular sections in the control and experimental groups. (A): Control group, (B and C): Cis group, and (D): Cis + Se group. Seminiferous tubules were seen normal histo-architecture in the control group. In the experimental groups showed irregularities in germinal cell configuration, vacuolization (arrow heads) in basal compartment, unmetamorphosed germ cells (arrows) and decreased mature sperms count in seminiferous tubule lumen. H&E staining.

antiapoptotic factors is inhibited, both tumor cells and normal cells can undergo apoptosis and retard proliferating. The expression of apoptosis promoting factors are inhibited by nuclear factor-κB (NF-kB); the abnormal expression of NF-κB has been reported in many cancer cells (Dolcet et al., 2005). Furthermore, it has been suggested that abnormal expression of NF-κB can increases the expression of Bcl-2 and Bcl-xL and prevent the death receptor apoptotic pathway (Dolcet et al., 2005; Venkatraman and Anto, 2005; Yang et al., 2004).

Gonadal dysfunction is the one of the most common side effects of Cis treatment in cancer therapy (Ateşşahin et al., 2006). Previous studies on acute toxicity and the long-term effects of chemotherapy have shown that immediate gonadal dysfunction is induced by Cis-based chemotherapy in testicular germ cell tumour patients and that fertility is reduced after polychemotherapy (Schrader et al., 2002). Many studies have been conducted regarding the toxic effects of Cis treatment in healthy testes (Sawhney et al., 2005; Seaman et al., 2003; Zhang et al., 2001). The cellular/biochemical mechanism of testicular injury induced by Cis is poorly understood; however, numerous studies have shown that cisplatin treatment is associated with initiation of oxidative stress by generation of free radicals and reactive oxygen species (ROS) (Cayır et al., 2011; Karadeniz et al., 2011). When produced in excessive amounts, the ROS stimulate DNA disintegration and a loss of sperm function associated with peroxidative damage to the mitochondria and sperm membrane. Further, testis is more susceptible to oxidative damage because of a high content of polyunsaturated membrane lipids and low antioxidant capacity (Vernet et al., 2004). Thus testis is highly affected by many oxidative agents such as Cis. In addition, the preventive and corrective effects of many substances against Cis-induced testicular toxicity have been studied by many researchers (Aminsharifi et al., 2010; Ilbey et al., 2009a,b).

Selenium (Se), a potential chemoprotective agent, is an essential trace element with biological functions in the human body, and it plays a role in cancer prevention and treatment (Sanmartín et al., 2012). The most important metabolic role of selenium in mammalian tissues is its function in the active site of the selenoenzyme glutathion peroxidase and this enzyme, together with other antioxidant enzymes such as superoxide dismutase and catalase, protects cells against oxidative stress damaged by excess reactive oxygen and nitrogen species, hydrogen peroxides and lipid peroxides (Tinggi, 2008; Yazici et al., 2014). However, there are a few studies regarding the protective effects of Se on Cis-induced testicular toxicity, neither of which investigated histopathological changes in testes (Rezvanfar et al., 2013; Salem et al., 2012). Therefore, we aimed to investigate the ameliorative effect of Se on Cis-induced testicular damage in terms of apoptosis and histopathological damage and lipid peroxidation alone.