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The safety of prolong usage of diazepam on liver and renal functions in rats

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Abstract

In this study the effect of diazepam on some blood chemistry values was studied in male rats. Intraperitoneal administration of diazepam at a dose of 0.6mg/kg body weight for 60 days didn't induce significant changes in serum glucose, urea, cholesterol, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, creatinine and alkaline phosphatase levels. Findings of this study give further sound for the safety of benzodiazepines.

Keywords: Diazepam; Safety; Liver, Kidney; Blood chemical values

Introduction

Diazepam (a benzodiazepine) was widely used in medical practice as antiepileptic, hypnotic, centrally acting muscle relaxant, tranquilizer and in treatment of alcohol withdrawal reaction [1]. Many unwanted effects were associated with benzodiazepine therapy including drowsiness, ataxia, hypotension, blurred vision, incontinence and respiratory depression [2], and other unusual responses were also recorded with benzodiazepines therapy including, nightmares, paradoxical delirium, confusion, depression, aggression and hostile behavior [3]. Hegarty and Dundee reported a significant incidence of painless thrombosis at injection site 7 to 10 days after intravenous diazepam administration, hematological, renal and hepatic toxicity have seldom been reported for benzodiazepines [3-5], however, a case of acute hepatic necrosis in doubtful relation to diazepam in-combination with other drugs has been recorded [6].

1. Material and methods

Twenty mature albino male rats from the colony of scientific research council, 12-14 weeks old, with a body weight of 250-300g were used. The animals were housed in individual cages and kept in a temperature-controlled room (22±1°C) with photo period of 14 hr. light and 10 hr. darkness. Water and pelleted diet were provided *ad libitum*. After seven days of adaptation, rats were randomly divided into two equal groups. The first group was injected intraperitoneally with 0.6mg/kg body weight of diazepam (Gewacalm^{R}, Chemicalinz, AG-Austria) daily in a single dose for 60days. Control animals were treated with normal saline. On the morning of day 61 post-treatment, blood was collected by cardiac puncture (without anesthesia) and allowed to stand for 4hr. at refrigerator temperature (4°C) before centrifugation at 2500RPM for 30 minutes and the prepared sera were stored in deep freezer (-20 °C). Glucose, urea, total bilirubin, cholesterol, creatinine, alkaline phosphatase, AST, ALT was determined with the technicon SM A 12/60 system (Technicon Co., Domont, France). The difference between control and treated group was detected by student t-test [7].

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2. Results

The study showed that intraperitoneal injection of diazepam to male rats at a dose of 0.6mg/kg body weight daily for 60 days induced slight elevation in serum cholesterol, total bilirubin, creatinine and alkaline phosphatase levels, while the serum glucose, urea, ALT and AST levels were slightly decreased, however, all these effects were not significant (table 1).

Table 1 Blood chemistry values in male rats treated with0.6 mg/kg bw of diazepam daily for 60 days

Groups	Glucose mg/dl	Urea mg/dl	Total Cholesterol mg/dl	AST U/l	ALT U/l	Total bilirubin mg/dl	Creatinine mg/dl	Alkaline phosphatase mg/dl
Control	112±15	25±1.7	64±5.5	59.3±8.1	15±1.1	0.9±0.09	0.67±0.06	6.4±0.6
Diazepam treated	108±12	26.2.2	65±2.1	55.4±9.8	14±0.8	1.0±0.13	0.70±0.14	6.8±0.8

3. Discussion

The liver is the most important organ in which drugs are structurally altered into metabolites, while kidneys in which drugs excreted, liver and kidneys received 20 and 25% of the cardiac output respectively, thus it is not surprising that drugs can damage these organs [8].

Biochemical tests have been used as indicators for the toxic effect of drugs and foreign substances on the liver, kidneys and other tissues [9].

Hepatic and renal toxicity and alteration of liver and renal function tests have been recorded with many central nervous system depressants [10], but there was no sound that diazepam induce hepatic or renal damage [3, 5]. Therefore, short acting benzodiazepines, such as oxazepam and lorazepam, have been said to be drug of choice for elderly patient or those with liver diseases [11].

Also, there were no previous reports showing that benzodiazepines affected macromolecules formation [12]. Otherwise, antiepileptic and hypnotic drugs are usually prescribed for long period, often in high dosage, and often in combination. It is hardly surprising, therefore that patients treated with these drugs showed evidence of highest degree of hepatic enzymes induction [13-15].

These enzymes are responsible for metabolism of drugs and endogenous substances [1-2]. Thus, the results of this study, in part, give further evidence to previous studies which showed that this enzyme system wasn't induced by diazepam [5]. In conclusion, the findings presented here give further sound for the safety of benzodiazepines previously prescribed [1-2, 11].

4. Conclusion

The findings of the current study revealed that diazepam (a benzodiazepine) for 60 days in rats didn't affect blood chemistry values especially liver and kidney parameters. These results give further sound for the safety of benzodiazepines.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

The authors declare that there is no conflict of interest.

Statement of ethical approval

The study was approved by the ethical committee of Thi-Qar College of medicine. It performed on animals according to the regulations of the ethical committee of Thi-Qar University.

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