Toxicological study of Zaleplon (Anxiolytic drug) in experimental animals.

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ABSTRACT

Anxiety disorders are among the most prevalent mental disorders in the general population. Nearly 30 million persons are affected in the United States, with women affected nearly twice as frequently as men. These disorders are frequently treated using benzodiazepines (Diazepam) and non-benzodiazepines (Zaleplon). Non-benzodiazepines have replaced the benzodiazepines for anxiety treatment due to low risk of dependence and CNS effects encouraging drug abuse.

This work was designed to investigate the toxicological overdose effect of zaleplon and diazepam on behavior, blood pressure, heart rate, brain neurotransmitter content and liver & kidney functions in rats.

Rats were divided into five groups: 1% Tween 80, p.o. (control), diazepam (1 & 4 mg/kg, p.o.) and zaleplon (1 & 4 mg/kg, p.o.). All groups were injected daily for four weeks to perform the following: behavioral study (assessment of motor co-ordination and anxiety performance), measurement of blood pressure & heart rate, determination of the free amino acid and monoamine contents in the whole brain, determination of serum aminotransferases activity, total protein, total and direct billirubin, creatinine & blood urea nitrogen of experimental rats.

Zaleplon decreased motor co-ordination, blood pressure and heart rate with extent lesser than diazepam. However, it decreased anxiety performance and brain monoamine content with extent more than diazepam. While, diazepam increased brain amino acid content, serum aminotransferases activity, total protein, total & direct billirubin, creatinine and blood urea nitrogen by magnitude more than zaleplon.

These results suggest that: zaleplon is safer than diazepam in treatment of anxiety.

Keywords: Diazepam, zaleplon, anxiolytic, motor co-ordination & anxiety performance.

INTRODUCTION

Anxiety is a psychological and physiological state characterized by somatic, emotional, cognitive and behavioral components. It is the displeasing feeling of fear & concern, worry, uneasiness and dread. It may help an individual to deal with a stressor by prompting them to cope with it (Henig, 2009). It may include heart palpitations, tachycardia, muscle weakness & tension, fatigue, nausea, chest pain, shortness of breath, headache, stomach aches or tension headaches. As the body prepares to deal with a threat; blood pressure, heart rate, perspiration and blood flow to the major muscle groups are increased, while immune and digestive functions are inhibited. External signs of anxiety may include; pallor, sweating, trembling and pupillary dilatation (Davison and Gerald, 2008; Carlson and Donald, 2010).

When anxiety becomes excessive, it may fall under the classification of an anxiety disorders. These disorders have been widely reported throughout the world commonly in older adults. Where, anxiety is a subjective perception of dissatisfaction with the amount and/or

quality of sleep or early awakening with inability to fall asleep again (Sylvers *et al.,* 2011).

Anxiety disorders are among the most prevalent mental disorders in the general population. Nearly 30 million persons are affected in the United States, with women affected nearly twice as frequently as men. These disorders are associated with significant morbidity and often are chronic and resistant to treatment (Curran and Chalasani, 2012) and they can be viewed as a family of related but distinct mental disorders, which include the following: panic disorder with or without agoraphobia, agoraphobia with or without panic disorder, specific phobia, social phobia, obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), acute stress disorder and generalized anxiety disorder (Doyle and Pollack, 2003; Pigott, 2003; Henig, 2009).

Sleep disorders are frequently treated using benzodiazepine (ex. Diazepam) and non-benzodiazepine (ex. Zaleplon) anxiolytics (Morin *et al.,* 2004; Dolder *et al.,* 2007). Where, anxiolytics should be prescribed for short periods only with the frequency and duration of use customized to each patient's circumstances (Ramakrishnan and Scheid, 2007).

Benzodiazepine anxiolytics are most useful for short term treatment in promoting sleep. However, long term use may lead to adverse effects and withdrawal phenomena, such as; sleepiness and reduced alertness (Becker, 2006; Naghibi and Rayatnia, 2011). In contrast, the newer generation non-benzodiazepine anxiolytics have no significant adverse effects and withdrawal phenomena when taken as recommended, making them the best first line choice for long term treatment

of anxiety (Follesa et al., 2002; Pandi-Perumal *et al.,* 2006). Also, the non-benzodiazepines have largely replaced the benzodiazepines for anxiety treatment due to low risk of tolerance, dependence and residual central nervous system effects compared with benzodiazepine anxiolytics (Noguchi *et al.,* 2002; Ganzberg *et al.,* 2005; Foda and Bakhaidar, 2010). So, these benefits of non-benzodiazepine anxiolytics encourage the patients to take overdose of this type of anxiolytics leading to drug abuse.

The aim of this work was to investigate the toxicological overdose effect of some anxiolytic drugs (ex. Zaleplon and Diazepam) on behavior, blood pressure, heart rate, brain neurotransmitter content and liver & kidney functions in experimental animals by using several parameters as well as to study the probable mechanism(s) of action of these anxiolytic drugs.

MATERIALS AND METHODS
Animals

Male Sprague Dawley rats (120 – 130 gm) were purchased from the animal house of National research center (Dokki, Giza, Egypt). Animals were acclimatized in the animal house of pharmacology department – National research center of Egypt, for at least one week prior to experimentation. Animals were kept at 22 ± 3°c and 5% relative humidity during the whole experiment. Standard food pellets and water were supplied. Animals' treatment protocol was approved by National Research Center Animal Right Committee.

Drugs

In the current study, diazepam and zaleplon were used and obtained from Egyptian International Pharmaceutical Industries Co. (EIPICO), Egypt, and

Sigma company, Egypt, respectively. These drugs were suspended in sterile bidistilled water using 1% tween 80 immediately before administration.

Experimental design

Animals (Adult male Sprague Dawley rats) were randomly divided into five groups; each consists of ten animals according to the following scheme:

Group (1): 1% Tween 80, p.o. and served as control.

Group (2): Diazepam (1 mg/kg, p.o.).

Group (3): Diazepam (4 mg/kg, p.o.).

Group (4): Zaleplon (1 mg/kg, p.o.).

Group (5): Zaleplon (4 mg/kg, p.o.).

All groups were administered daily for four successive weeks.

Biochemical measurement

Blood samples were obtained from retro-orbital plexus of veins of each animal under light anaesthesia by diethyl ether, 24 hours after last treatment, and collected in non-heparinized tubes. The non-heparinized blood was allowed to coagulate and then centrifuged to separate the serum. Serum was obtained by blood centrifugation at 2500 rpm for 10 minutes, liquated and stored at -20°C for biochemical analysis (Cocchetto and Bjornsson, 1983).

METHODS

The present study was done by the following: a) Behavioral study including assessment of motor co-ordination by using the rotarod test (Kauppila et al., 1991; Lundblad et al., 2003) and anxiety performance by using the elevated plus maze test (Salum et al., 2003; Braun et al., 2011). b) Measurement of blood pressure and heart rate by using tail-cuff technique (Irvine et al., 1997). c) Determination of the free amino acid and monoamine contents in the whole brain by using HPLC (Heinrikson and Meredith, 1984; Pagel et al., 2000). d) Determination of serum aminotransferases activity (Reitman and Frankel, 1957), total protein (Henry et al., 1974), total & direct billirubin (Walter and Stucki, 1970), creatinine (Degiorgio, 1974) and blood urea nitrogen (Tabacco et al., 1979).

Statistical analysis

Data were presented as mean ± Standard error. Comparisons between means were carried out using two way ANOVA test. When a significant F value was obtained, Bonferroni post hoc analysis was performed to determine specific differences.

A probability level of less than 0.05 was accepted as being significant in all types of statistical tests. SPSS software program (version 14) was used to carry out all statistical tests.

RESULTS

Behavioral study

Effect of diazepam and zaleplon on rats' motor co-ordination

Diazepam (1 mg/kg, p.o.) and zaleplon (4 mg/kg, p.o.) decreased rotarod performance significantly by 16.5% and 17.5% after four weeks respectively, while diazepam (4 mg/kg, p.o.) decreased rotarod performance significantly by 18.7% after 30 minutes, 19.2% after two weeks and 21.8% after four weeks as compared with corresponding control group values as shown in Figure (1).

Effect of diazepam and zaleplon on rats' anxiety performance

Diazepam (1 and 4 mg/kg, p.o.) showed significant increase in anxiety performance by 52.2% & 99.3% after 30 minutes, 61.6% & 107.4% after two weeks and 109.7% & 140.7% after four weeks respectively. In addition, for

zaleplon (1 and 4 mg/kg, p.o), anxiety performance was increased significantly by 85.5% & 105.7% after 30 minutes, 58.7% & 103.7% after two weeks and

53.8% & 86.7% after four weeks respectively comparing to corresponding control group values as shown in Figure (2).
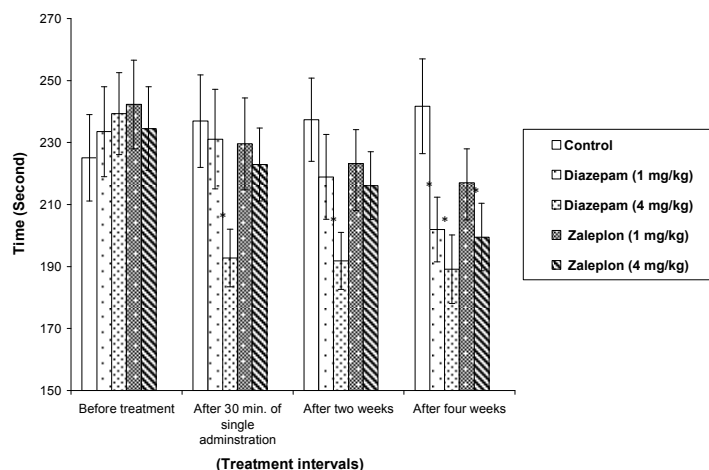

Figure 1. Effect of diazepam and zaleplon on rats' motor co-ordination.
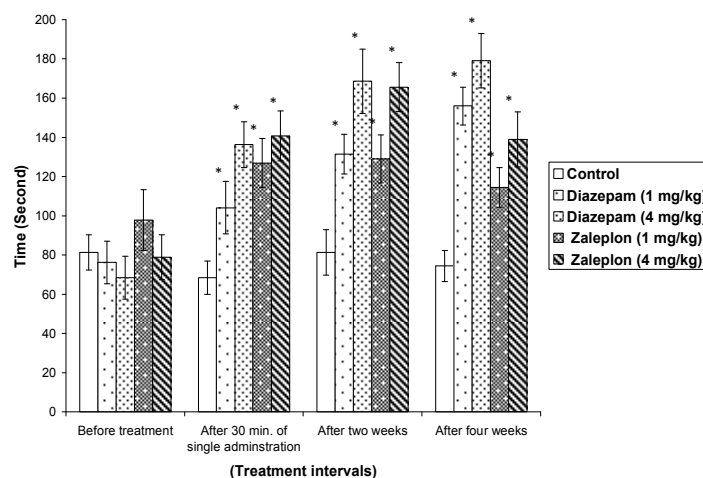* Significantly different from corresponding control group values at (p < 0.05).

Figure 2. Effect of diazepam and zaleplon on rats' anxiety performance.
* Significantly different from corresponding control group values at (p < 0.05).

Effect of diazepam and zaleplon on rats' blood pressure

Diazepam (1 mg/kg, p.o.) and zaleplon (4 mg/kg, p.o.) caused significant decrease on blood pressure by 13.8% and 15.4% after four weeks respectively. While, diazepam (4 mg/kg, p.o.) caused significant decrease on blood pressure by 15.6% after 30

minutes, 11.7% after two weeks and 23% after four weeks in comparison with that of corresponding control group values as shown in Figure (3).

Effect of diazepam and zaleplon on rats' heart rate

Diazepam (1 mg/kg, p.o.) and zaleplon (4 mg/kg, p.o.) caused significant decrease on heart rate by

6.3% and 7.5% after four weeks respectively. While, diazepam (4 mg/kg, p.o.) caused significant decrease on blood pressure by 8.2% after 30 minutes,

8.7% after two weeks and 11.7% after four weeks comparing to corresponding control group values as shown in Figure (4).
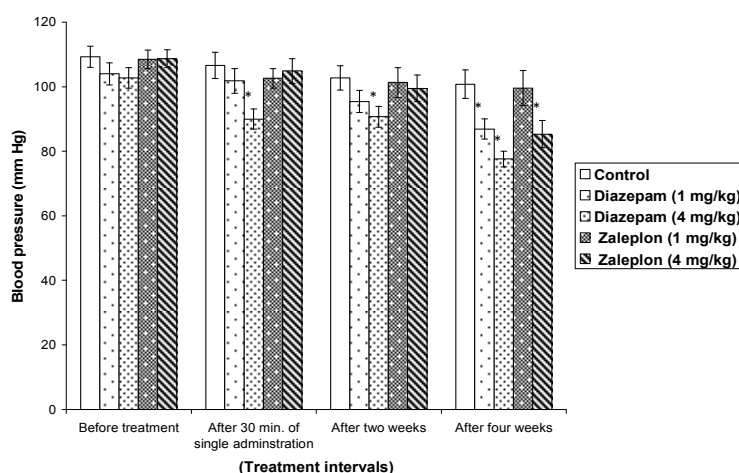

Figure 3. Effect of diazepam and zaleplon on rats' blood pressure.
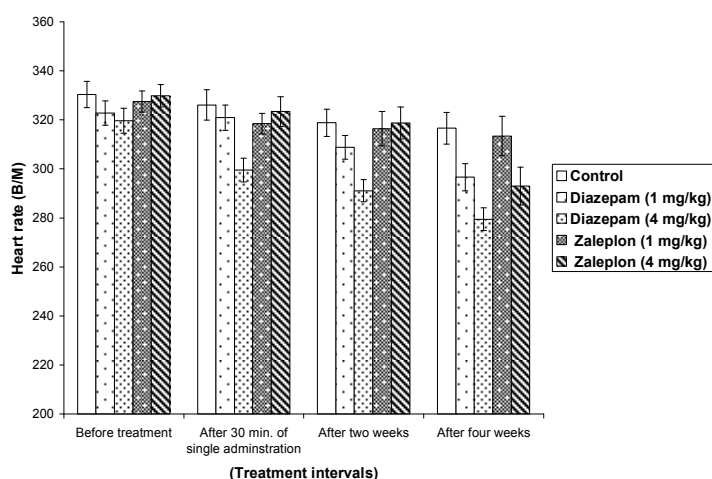* Significantly different from corresponding control group values at ($p < 0.05$).

Figure 4. Effect of diazepam and zaleplon on rats' heart rate.
* Significantly different from corresponding control group values at ($p < 0.05$).

Effect of diazepam and zaleplon on rats' free amino acid contents in the whole brain

Diazepam (1 mg/kg, p.o.) caused significant decrease on aspartic acid by 18.2% and significant increase on GABA by 18%. While, diazepam (4 mg/kg, p.o.) induced significant decrease on aspartic and glutamic acids by 20% and 20.9% respectively, however it

caused significant increase on GABA by 26.4%. But for zaleplon (4 mg/kg, p.o.); GABA was increased significantly by 18.2% as compared with corresponding control group values (Figure 5).

Effect of diazepam and zaleplon on rats' monoamine contents in the whole brain

Diazepam (1 mg/kg, p.o.) caused significant increase on dopamine and

serotonin by 32% and 28% respectively. While, diazepam (4 mg/kg, p.o.) induced significant decrease on nor-epinephrine by 22.8%, significant increase on dopamine and serotonin by 54% and

50% respectively. However for zaleplon (4 mg/kg, p.o.); serotonin was raised significantly by 30% in comparison with that of corresponding control group values as shown in Figure (6).
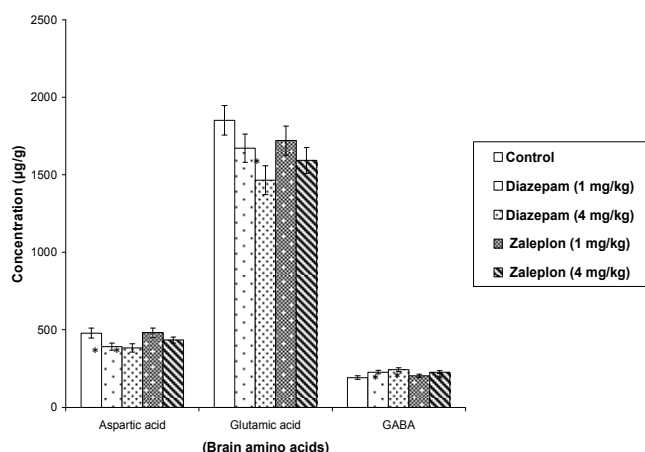

Figure 5. Effect of diazepam and zaleplon on rats' free amino acid contents in the whole brain.
* Significantly different from corresponding control group values at (p < 0.05).
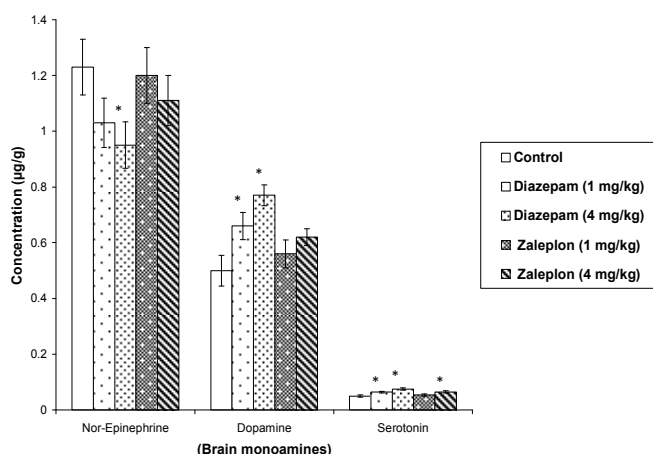

Figure 6. Effect of diazepam and zaleplon on rats' monoamine contents in the whole brain.
* Significantly different from corresponding control group values at (p < 0.05).

Biochemical measurement
Effect of diazepam and zaleplon on rats' serum aspartate aminotransferase activity
Diazepam (1 mg/kg, p .o.) and zaleplon (1 mg/kg, p.o.) induced significant increase on AST activity by 24.9% and 30% after four weeks respectively.

While, diazepam (4 mg/kg, p.o.) and zaleplon (4 mg/kg, p.o.) caused significant increase on AST activity by 43.4% & 38% after two weeks and 46.2% & 28.6% after four weeks respectively as compared with corresponding control group values as shown in Figure (7).

Effect of diazepam and zaleplon on rats' serum alanine aminotransferase activity

Diazepam (1 mg/kg, p.o.) induced significant increase on ALT activity by 45.4% after four weeks. However, diazepam (4 mg/kg, p.o.) and zaleplon (4

mg/kg, p.o.) caused significant increase on ALT activity by 68.5% & 30.8% after two weeks and 87.7% & 41.1% after four weeks respectively comparing to corresponding control group values as shown in Figure (8).
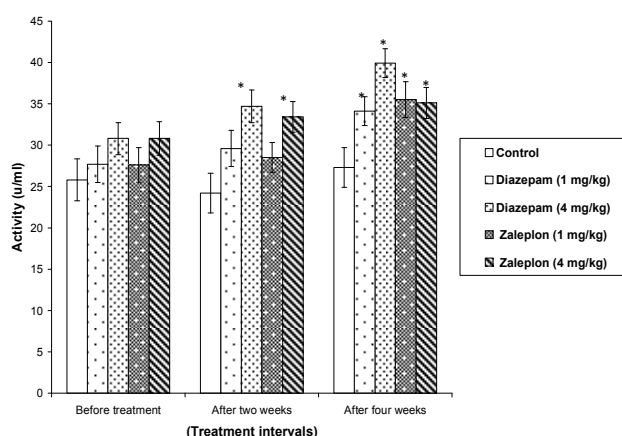

Figure 7. Effect of diazepam and zaleplon on rats' serum aspartate aminotransferase activity.
* Significantly different from corresponding control group values at ($p < 0.05$).
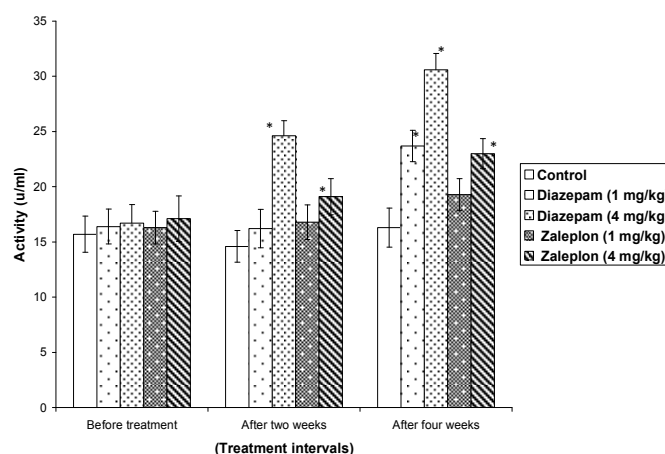

Figure 8. Effect of diazepam and zaleplon on rats' serum alanine aminotransferase activity.
* Significantly different from corresponding control group values at ($p < 0.05$).

Effect of diazepam and zaleplon on rats' serum total protein

Diazepam (1 and 4 mg/kg, p.o.) and zaleplon (4 mg/kg, p.o.) caused significant decrease on serum total protein by 8.3%, 10.5% and 6.3% after four weeks respectively comparing to

corresponding control group values as shown in Figure (9).

Effect of diazepam and zaleplon on rats' serum direct billirubin

Diazepam (4 mg/kg, p.o.) showed significant increase on serum direct billirubin by 25% after two weeks and

52.9% after four weeks. In addition, zaleplon (4 mg/kg, p.o) led to significant increase on serum direct billirubin by

17.7% after four weeks as compared with corresponding control group values as shown in Figure (10).
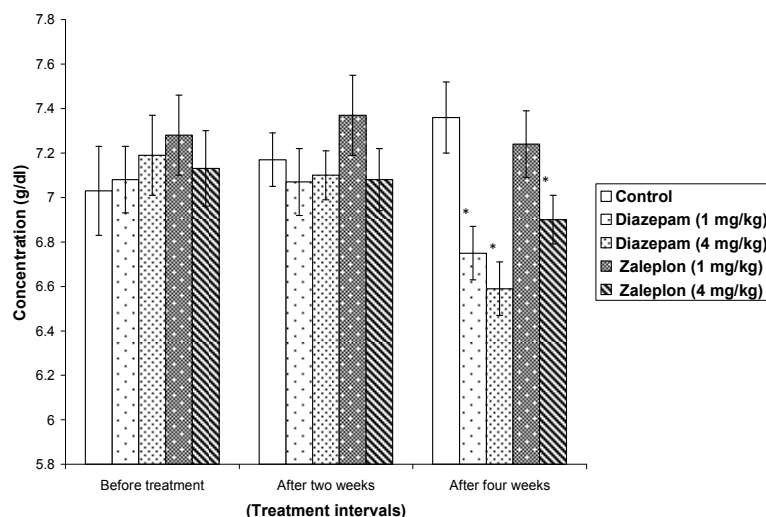

Figure 9. Effect of diazepam and zaleplon on rats' serum total protein.
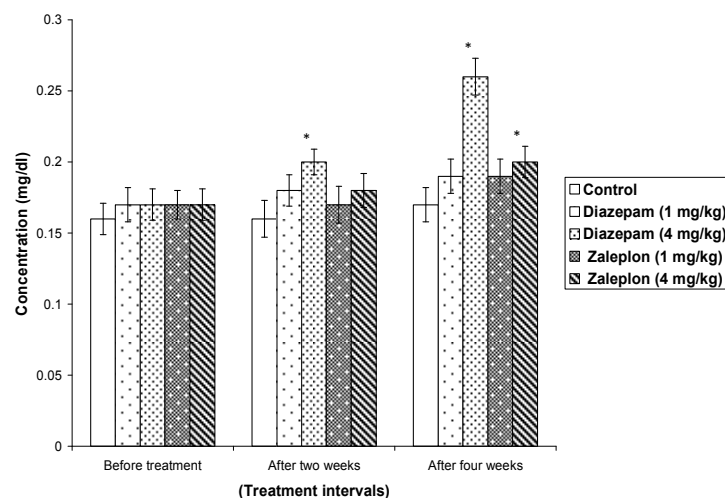* Significantly different from corresponding control group values at (p < 0.05).

Figure 10. Effect of diazepam and zaleplon on rats' serum direct billirubin.
* Significantly different from corresponding control group values at (p < 0.05).

Effect of diazepam and zaleplon on rats' serum total billirubin

Diazepam (1 mg/kg, p.o.) and zaleplon (4 mg/kg, p.o.) induced significant increase on serum total billirubin by 13.9% and 20% respectively after four weeks. Also, diazepam (4 mg/kg, p.o.) led to significant increase on serum total

billirubin by 11.1% after two weeks and 30.4% after four weeks in comparison with that of corresponding control group values as shown in Figure (11).

Effect of diazepam and zaleplon on rats' serum creatinine:

Diazepam (1 mg/kg, p.o.) and zaleplon (4 mg/kg, p.o.) showed significant increase on serum creatinine

by 18.8% and 16.7% after four weeks respectively. As well as, diazepam (4 mg/kg, p.o.) led to significant increase on serum creatinine by 20.9% after two

weeks and 25% after four weeks comparing to corresponding control group values as shown in Figure (12).

Figure 11. Effect of diazepam and zaleplon on rats' serum total billirubin.
* Significantly different from corresponding control group values at ($p < 0.05$).

Figure 12. Effect of diazepam and zaleplon on rats' serum creatinine.
* Significantly different from corresponding control group values at ($p < 0.05$).

Effect of diazepam and zaleplon on rats' blood urea nitrogen:

Diazepam (4 mg/kg, p.o.) performed significant increase on blood

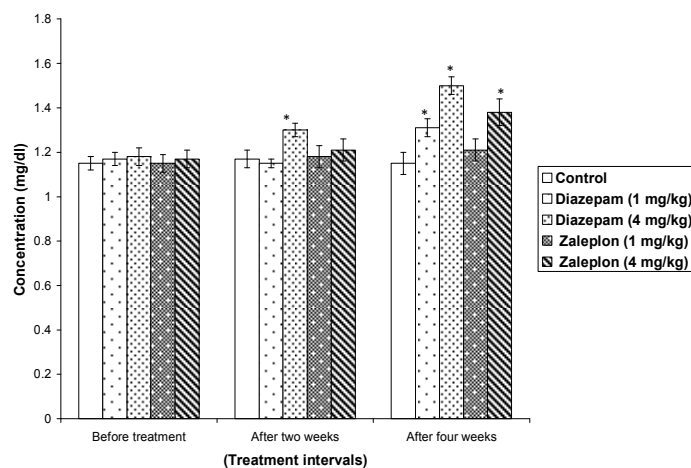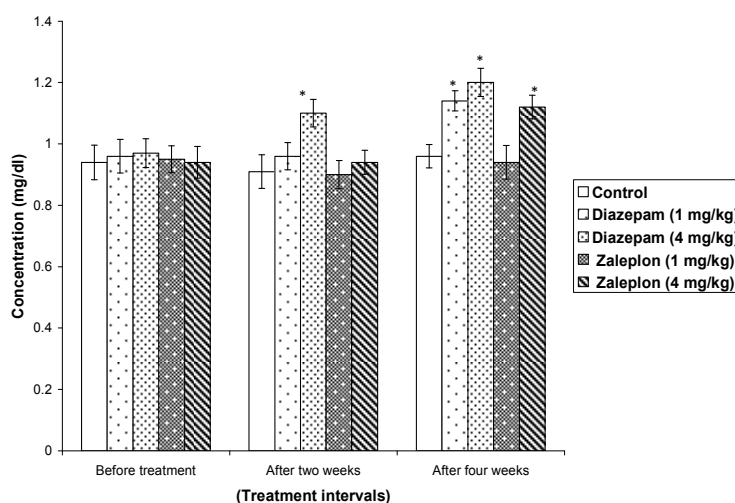urea nitrogen by 8% after four weeks as compared with corresponding control group values as shown in Figure (13).
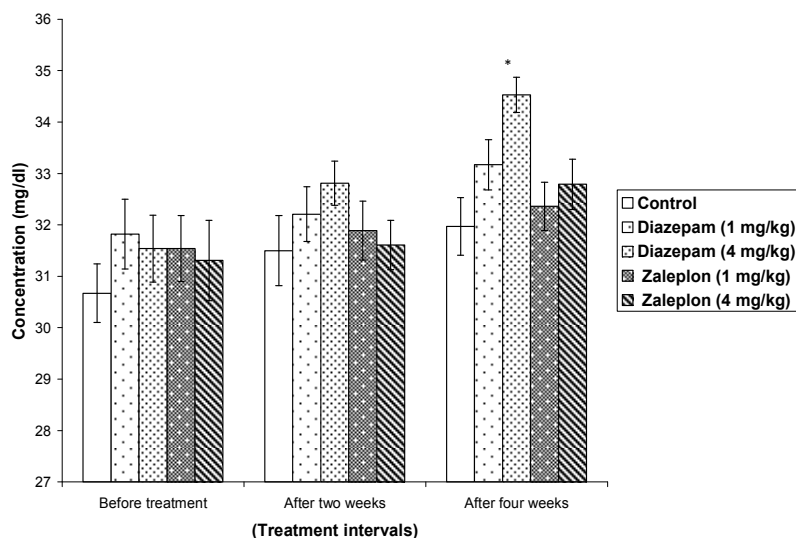
Figure 13. Effect of diazepam and zaleplon on rats' blood urea nitrogen.
* Significantly different from corresponding control group values at (p < 0.05).

DISCUSSION

Anxiety disorders are frequently treated using benzodiazepine and non-benzodiazepine anxiolytics (Morin et al., 2004; Dolder et al., 2007). Where, they should be prescribed for short periods only with the frequency and duration of use customized to each patient's circumstances (Ramakrishnan and Scheid, 2007).

For the motor co-ordination assay, the results of the current work for zaleplon (1 and 4 mg/kg, p.o.) were supported by Sanger et al., (1996), who reported that; in general, zaleplon had no effect on rotarod performance when taken as recommended dose (1 mg/kg) for short term of administration (15 days). However, it obtained a decrease in rotarod performance (muscle incoordinaion) incase of high dose (3 mg/kg) for long term of administration (30 days). In addition, Foster et al., (2004) reported that; zaleplon affected on rotarod performance in a dose-dependant manner. So, high dose of zaleplon administration (5 mg/kg)

produced rotarod performance deficits, which attributed to muscle relaxation.

Also, the results of the present work for diazepam (1 & 4 mg/kg, p.o.) were in agreement with Sarris (2007); Bodkin et al., (2012), who reported that, diazepam had no effect on performance of rats on the rotarod for short term of administration. However, for long term of diazepam administration, there was a clear effect on performance of rats on the rotarod by decreasing the ability of rats to balance on the rotarod, deducing that: diazepam may exert its anxiolytic action by direct action on the central nervous system giving muscle relaxation and not through sedation.

For the anxiety performance assay, the results of the present study for zaleplon (1 and 4 mg/kg, p.o.) were clarified by Foda and Bakhaidar (2010), who stated that, zaleplon produced hypnotic properties and decrease in anxiety performance due to binding selectively with high efficacy to the benzodiazepine site (ω_1) on the (α_1) containing GABA$_A$ receptors, which explained the decrease of anxiety

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performance in the present work. Moreover the current result was in line with Paparrigopoulos et al., (2008), who reported that; zaleplon induced anxiolytic, sedative-hypnotic, anticonvulsant and anti-conflict effects by a decrease in anxiety performance via its binding to the central nervous system (CNS)-type benzodiazepine receptors.

Also, the results of the present work for diazepam (1 & 4 mg/kg, p.o.) were explained by Mandrioli et al., (2010), who mentioned that; diazepam led to CNS depression and lowered the anxiety performance by potentiating the action of the inhibitory neurotransmitter (GABA) through binding directly to a site on GABA receptor that is distinct from the binding site of the endogenous GABA molecule, recognized as the α-subunit of the $GABA_A$ receptor, leading to an alteration in the functional response when the receptor is activated by GABA. This binding leads to activation of GABA receptor, then increasing the frequency of chloride channel opening leading to more Cl^- ions influx. In addition, Rex et al., (2002); Himmel (2008) reported that; diazepam resulted in CNS depression and decrease in anxiety performance, where it acts as a positive allosteric agonist of the post- and pre-synaptic $GABA_A$ receptor – chloride channel complex leading to potentiating the activity of brain's major inhibitory neurotransmitter (GABA) and lowering the activity of brain's major excitatory neurotransmitters (Glutamate and Aspartate) of rats.

As regard for the heart rate and blood pressure measurement, the results of the present work for zaleplon (1 and 4 mg/kg, p.o.) were explained by Mandrioli et al., (2010), who reported that; zaleplon has no effect on blood pressure or

heart rate at recommended doses (1 mg/kg). However at high doses (3 and 5 mg/kg) especially with long term of administration (one month), it decreased significantly the heart rate and blood pressure, where the adverse effects associated with zaleplon seem to be more rapidly resolved and less severe than those associated with benzodiazepine and other non-benzodiazepine hypnotics with a longer duration of action. Also, Weitzel et al., (2000) reported that; zaleplon decreased heart rate and blood pressure at high dose only (4 mg/kg) with a lesser extent than benzodiazepine hypnotics. But at therapeutic dose (1 mg/kg), there is no effect on heart rate or blood pressure. Moreover, Sanchez et al., (2000) stated that; zaleplon has no effect on blood pressure or heart rate, when administered at recommended dose (1 mg/kg) either alone or in combination with digoxin.

Also, the results of the current study for diazepam (1 & 4 mg/kg, p.o.) were in line with Kitajima et al., (2004); Grossman et al., (2005); Zahner et al., (2007), who reported that; systolic and mean blood pressure and heart rate decreased significantly after diazepam administration (1 mg/kg) attributing to central action of diazepam not peripheral one. Where, the nucleus of the solitary tract in the medulla plays an important role in controlling blood pressure and contains GABA receptors. Also, hypothalamus plays an important role in controlling blood pressure. As, diazepam acted directly on GABA receptors in medulla as an agonist and on hypothalamus.

As regard for brain neurotransmitters (Free amino acids and

monoamines) assay, the results of the present work for zaleplon (1 and 4 mg/kg, p.o.) were in agreement with Foda and Bakhaidar (2010); Mandrioli et al., (2010) who mentioned that; zaleplon led to CNS depression and produced its therapeutic hypnotic properties especially at high dose (5 mg/kg), where it selectively binds with high efficacy to the benzodiazepine site (ω_1) on the (α_1) containing GABA$_A$ receptors. This binding leads to activation of GABA receptor, then increasing the frequency of chloride channel opening leading to more Cl$^-$ ions influx. Also, Sullivan et al., (2004); Monti (2011) reported that; non-benzodiazepine drugs (eg. Zaleplon) had no effect on most of brain neurotransmitters except for GABA and serotonin, which increased significantly by using non-benzodiazepine drugs exerting their sedative and hypnotic action.

Also, the results of the present work for diazepam (1 & 4 mg/kg, p.o.) were explained by Riss et al., (2008); Mandrioli et al., (2010), who mentioned that; diazepam elevated GABA level by potentiating the action of the inhibitory neurotransmitter (GABA) through binding directly to a site on GABA receptor that is distinct from the binding site of the endogenous GABA molecule, recognized as the α-subunit of the GABA$_A$ receptor. Moreover, Rex et al., (2002); Himmel (2008) reported that; diazepam resulted in CNS depression, where it acts as a positive allosteric agonistic of the post- and pre-synaptic GABA$_A$ receptor – chloride channel complex leading to potentiating the activity of brain's major inhibitory neurotransmitter (GABA) and lowering the activity of brain's major excitatory neurotransmitters (glutamate and aspartate). Which explain our present

result for GABA, glutamate and aspartate. Furthermore, the increase in brain dopamine and serotonin levels in current result is clarified by Straub et al., (2010) who reported that, diazepam elevated dopamine and serotonin content in the brain of mice due to its dopaminergic and serotonergic activity. Oppositely, it lowered nor-epinephrine content in the brain of mice resulting in calming down and anxiolytic effect.

As regard for the hepatotoxiciy assay, the results of the present work for zaleplon (1 and 4 mg/kg, p.o.) were in line with Curran and Musa (2001); Clint et al., (2008), who mentioned that; zaleplon is the most widely anxiolytic drug used due to its high safety margin, but its long term use (40 days) for treatment of anxiety and insomnia produced mild hepatotoxicity, where liver enzymes (ALT & AST) activity, serum billirubin (total & direct) and alkaline phosphatase activity were elevated and serum protein (eg. albumin) was decreased. Moreover the current work was in agreement with Moore et al., (2003); Zientek et al., (2010), who reported that; zaleplon induced mild hepatotoxicity, so it was taken with caution for hepatic patients, where prolonged use of zaleplon (30 days) causes impairment of rat liver function, generation of free radicals in different regions of rat brain alleviating lipid peroxidation in various tissues, where lipid peroxidation plays an important role in hepatotoxicity of zaleplon.

Also, the results of the present work for diazepam (1 & 4 mg/kg, p.o.) were in agreement with Musavi and Kakkar (2003); Nandhini and Anuradha (2003), who reported that; long term use (30 days) of diazepam for treatment of anxiety and insomnia produced hepatotoxicity, whereas it attributed to

elevation in liver enzymes (ALT & AST) activity, serum billirubin (total & direct), alkaline phosphatase activity and malondialdehyde formation and decrease in reduced glutathione content and serum protein (eg. albumin). Also the current result was in compatibility with Seckin et al., (2007), who mentioned that; prolonged use of diazepam causes hepatotoxicity by impairment of rat liver function, generation of free radicals in different regions of rat brain alleviating lipid peroxidation in various tissues and inhibiting the activity of Ca^{+2} – ATPase leading to the calcium accumulation, where calcium accumulation together with increased lipid peroxidation may play an important role in diazepam induced hepatotoxicity. Furthermore, Chatterjee et al., (2009) reported that; diazepam treatment induced hepatotoxicity due to increase significantly in diene conjugate formation levels with parallel marked increase in malondialdehyde formation levels and decrease in reduced glutathione content. The above explanations supported current work for diazepam induced hepatotoxicity.

As regard for the nephrotoxicity assay, the results of the present work for zaleplon (1 and 4 mg/kg, p.o.) were in line with Moore et al., (2003), who reported that; zaleplon is used widely as an anxiolytic drug due to its high safety margin on vital organs, but its long term use (6 weeks) especially with high dose (4 mg/kg) for treatment of anxiety and insomnia induced mild nephrotoxicity, where serum creatinine and urea nitrogen were elevated but urea nitrogen elevation was with a lesser extent than serum creatinine elevation. Also, Petroski et al., (2006) mentioned that: zaleplon was taken safely for renal impairment patients, where prolonged use (30 days) of zaleplon at recommended dose (1 mg/kg) did not induce any alteration in kidney functions. However, prolonged use (30 days) of zaleplon at high dose (4 mg/kg) induced slight changes in kidney functions, as an increase in serum creatinine level.

As well as, the results of the present work for diazepam (1 & 4 mg/kg, p.o.) were in compatibility with Kim et al., (2010), who reported that; diazepam was considered as the most widely anxiolytic drug used from several decades. But, it has been found that; diazepam affects kidney functions leading to kidney impairment or nephrotoxicity, which mainly by elevating serum creatinine and blood urea nitrogen. Consequently, diazepam must be taken with great caution for renal patients especially incase of long term of administration (30 days). Also these results were in agreement with Mandrioli et al., (2010), who reported that; long term use (45 days) of benzodizepines (eg. diazepam) for treatment of anxiety and insomnia produced nephrotoxicity, which is attributed to elevation in serum creatinine and blood urea nitrogen, in contrast, reduction in urine output volume.

In conclusion: benzodiazepine anxiolytics (ex. Diazepam) should be used for short periods avoiding their adverse effects of long periods. Non-benzodiazepine anxiolytics (ex. Zaleplon) can be used for long periods instead of benzodiazepine anxiolytics (ex. Diazepam) due to their great safety margin. Overdoses of benzodiazepine and non-benzodiazepine anxiolytics produce great side effects, however zaleplon is with a lesser extent. So,

zaleplon is safer than diazepam in treatment of anxiety.

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دراسة سمية الزاليبلون (عقار مضاد للقلق) فى حيوانات التجارب

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إضطرابات القلق هي من بين الإضطرابات النفسية الأكثر إنتشاراً بين عامة الناس، بما يقرب من ٣٠ مليون شخص فى الولايات المتحدة الأمريكية، حيث تعانى النساء بما يقرب من ضعف ما يعانيه الرجال في كثير من الأحيان. وهذه الإضطرابات كثيراً ما يتم التعامل معها بإستخدام مضادات القلق من البنزوديازيبين و غير البنزوديازيبين. وقد حلت بعض مضادات القلق غير البنزوديازيبين إلى حد كبير محل مضادات القلق البنزوديازيبين فى علاج القلق بسبب المخاطر المنخفضة من قدرة الإحتمال والتبعية و الآثار المتبقية على النظام العصبى المركزى، مما قد يشجع المرضى على إدمان تلك الأدوية.

لقد صممت هذه الدراسة لبحث تأثير سمية الجرعة الزائدة من الديازيبام و الزاليبلون على السلوك و ضغط الدم و معدل نبض القلب و محتوى المخ من الناقلات العصبية و وظائف الكبد و الكلي في فئران التجارب.

قسمت الحيوانات في هذه الدراسة إلى خمسة مجموعات: (١٪) توين ٨٠ عن طريق الفم (المجموعة الضابطة)، و الديازيبام (١ و ٤ ملليجرام / كج، عن طريق الفم)، و الزاليبلون (١ و ٤ ملليجرام / كج، عن طريق الفم). و لقد تم حقن جميع المجموعات يومياً لمدة أربعة أسابيع لدراسة الآتى: الدراسة السلوكية (تقييم التوافق الحركى و أداء القلق)، و قياس ضغط الدم و معدل نبض القلب، و فحص الناقلات العصبية فى المخ (الأحماض الأمينية الحرة و أحاديات الأمينات)، و تقييم نشاط إنزيمى الكبد (ألانين أمينو ترانسفيريز و أسبارتات أمينو ترانسفيريز) و مستوى البروتينات الكلية و الصفراء (الكلية و المباشرة) و الكرياتينين و نيتروجين اليوريا فى مصل الدم، و فحص أنسجة الكبد و الكلى لفئران التجارب.

الزاليبلون أدى إلى إنخفاض فى التوافق الحركى و ضغط الدم و معدل نبض القلب بدرجة أقل من الديازيبام، و أيضاً أدى إلى إنخفاض فى أداء القلق و محتوى المخ من أحاديات الأمينات و لكن بدرجة أكثر من الديازيبام. بينما الديازيبام أدى إلى زيادة فى محتوى المخ من الأحماض الأمينية الحرة و نشاط إنزيمى الكبد و مستوى البروتينات الكلية و الصفراء (الكلية و المباشرة) و الكرياتينين و نيتروجين اليوريا فى مصل الدم بدرجة أكثر من الزاليبلون.

هذه النتائج تشير إلى أن عقار الزاليبلون أكثر أماناً من عقار الديازيبام فى إستخدامه كعلاج للقلق.