Evaluation of the Subacute Toxic Effects of an Isotonic D-ribose Solution Administered intravenously to Fischer Rats

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ABSTRACT

To evaluate the potential toxic effects associated with the intravenous administration of an isotonic solution (4.2%) of d-ribose once per day for 14 days in Fischer rats (F-244), thirty rats were randomly divided into 3 groups (5 males and 5 females each). Rats in group 1 received 10 ml/kg of a 4.2% d-ribose solution intravenously once per day for 14 days. Rats in group 2 (control) received the same volume of 0.9% saline intravenously once per day for 14 days. Rats in group 3 (satellite) received 10 ml/kg of a 4.2% d-ribose solution intravenously once per day for 14 days and were observed for a further 14 days after the last d-ribose injection. Rats were monitored for any clinical or behavioral alterations. Body weight, feed and water intake were measured. A complete post-mortems and histopathological examinations were performed on all animals and blood samples were obtained for hematological and plasma biochemical analyses. There were no statistically significant clinical, behavioral, hematological, biochemical, gross or histological toxic effects induced by the daily intravenous administration of the drug for 14 days in the male and female rats. Results of this study show that the repeated intravenous administration of an isotonic solution of d-ribose is well tolerated in rats.

Keywords: D-ribose; , Fischer rats; , side effects; , subacute toxicity; , intravenous administration; , myocardial ischemia; , hypoxia.

INTRODUCTION

The development of an effective therapeutic regimen utilizing alternative metabolic pathways for cellular metabolism and energy restoration is a novel approach in the emergency treatment of ischemic conditions, especially those involving the cardiac muscle. In addition to its importance in forming the structural subunits for riboflavin (vitamin B2), ribonucleic acid (RNA), adenosine triphosphate (ATP), nicotinamide adenine dinucleotide (NADH), and coenzyme-A, d-ribose, a naturally occurring monosaccharide aldopentose, plays an important role in cellular energy metabolism through the pentose phosphate pathway[1-4]. Studies have shown a potential cardioprotective effect in patients with congestive heart failure and coronary ischemic disorders due to d-ribose supplementation [5-13]. Beneficial effects of d-ribose were also evaluated in patients with renal ischemic disease, chronic fatigue syndrome and fibromyalgia after oral supplementation with positive

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outcomes [14-16]. Therefore, d-ribose can be proposed as a metabolic treatment in hypoxic disorders that require fast restoration of cellular energy levels or medical conditions characterized by low energy reserves in tissues. The development of an effective and clinically safe therapeutic regimen using the intravenous route to minimize tissue damages resulted from hypoxic disorders requires a comprehensive assessment of any potential toxic effects of the drug in laboratory animals. The study reported here was designed to evaluate the potential clinical, behavioral, hematological, biochemical, gross pathological and histological toxic effects associated with the intravenous administration of d-ribose daily for 14 days in Fischer rats.

MATERIALS and METHODS

Animals

This study was performed in accordance with the regulations of good laboratory practices (GLP) and the Organization for Economic Cooperation and Development (OECD) guidelines [17-19]. All experimental protocols were approved by the Animal Care and Use Committee of Jordan University of Science and Technology (JUST-ACUC).

Five-week old, healthy Fischer Rats (F-244) were obtained from the Product Safety Research Laboratories, Royal Scientific Society, Amman/Jordan. Rats were housed in temperature (21-23^{o}C) and humidity (35%-70%) controlled rooms with 12 hour light-12 hour dark cycles. Rats were placed individually in clear-sided cages for ease of observation without disturbing their behavior. Wood shavings were used as bedding. Rats were fed a commercially available diet (Local Supplier, Jordan). Fresh water was offered *ad libitum*.

After a 1-week period of acclimatization, 30 rats (15 males and 15 females) were randomly divided into 3 groups (5 males and 5 females each). This is the minimal number of rats recommended by most guidelines. Rats in group 1 received 420 mg/kg (10 ml/kg) of 4.2% d-ribose solution intravenously once per day for 14 days. Rats in group 2 (control) received the same volume of 0.9% saline intravenously once per day for 14 days. Rats in group 3 (satellite) received 420 mg/kg (10 ml/kg) of 4.2% d-ribose solution intravenously once per day for 14 days and were observed for a further 14 days after the last d-ribose injection. In order for the rats to have the same age at sacrifice, injection of either d-ribose or saline to the first two groups was begun 14-15 days after starting administration with the third group. For calculation of growth rate in satellite groups, monitored weight was considered on days 1 and 13 as well as on the sacrifice day.

Test substance:

D-ribose ($C_5H_{10}O_5$; Molecular weight: 150.13) was obtained from Chengzhi Co., Beijing, China. The test substance (Batch No.: 80032101) was supplied as a spherical white powder. The composition, purity and stability tests of the raw material of the test substance were performed by the sponsor (Heartland Biosciences, Minnesota, USA). A certificate of composition, purity and stability along with specific recommendations for appropriate handling, storage and preparation was also provided by the sponsor.

Preparation of the test substance as isotonic solution which is suggested for intravenous administration was carried out in sterile conditions. The test substance was dissolved in sterile water for injection, USP (4.2%, PH 6.9, > 98% pure, 270 mOsm/L) approximately 30 minutes prior to injection. The solution was then filtered using syringe driving membrane filters (0.22µm pore size) (PVDF; Jet Biofil, Shanghai, China) to ensure sterility. The ready for use solution was tested to confirm its sterility and absence of endotoxins (LAL, Clongen Laboratories, California, USA). The stability of the solution was not performed; therefore a freshly prepared solution was used for injection each time.

Sterile 0.9% saline was also prepared and used for injection in control groups. The volume of the test substance administered to each animal was calculated based on the individual body weight at a dose rate of 10 ml/kg. The test substance was administered intravenously, once a day, seven days a week for 14 days,

at approximately the same time each day.

Intravenous injection technique:

Rats were held off-feed for 12 hours before injection. The lateral tail vein was used for intravenous injection of d-ribose and saline. The rat was placed in a specially designed restrainer with the tail extended out. The tail was sanitized using alcohol swabs before injection. A 27-gauge butterfly needle was used to catheterize the vein. Once the vein was catheterized and blood was observed at the end of the needle, the solution was then injected slowly over 5-10 minutes. A 2-ml sterile syringe was used to inject the solution. Animals were offered food and water 3 hours after the completion of each injection.

Clinical and behavioral observation:

Animals were monitored immediately after injection every 30 minutes during the first 4 hours post administration and twice daily after that for the entire length of the study. Animals in the satellite group were further observed for 14 days after the last injection to allow for detection of any late-occurring clinical signs. Rats were monitored for any abnormal clinical signs or changes in behavior. The body weight was measured using a digital scale with an accuracy of up to 1 g. Food was offered once per day 3 hours after the completion of administration. To measure feed consumption, feed left-over was collected and its weight was obtained before a fresh amount was offered. Water was offered in clean bottles and was changed every 12 hours and the amount consumed was calculated. Both feed and water consumed were reported as amount consumed per animal and computed per Kg of body weight per day.

Hematology and plasma biochemistry analyses:

Hematology and plasma biochemistry evaluation was performed on day 15 in groups 1 and 2 and on day 29 in group 3. Approximately 2 ml of whole blood was collected at the time of euthanasia. Blood was placed in tubes containing 3.8% sodium citrate. To prevent dilution effects, the amount of anti-coagulant in the tubes was reduced according to the amount of blood obtained. Blood samples were transported immediately after collection to the laboratory on ice for analysis. The following hematology parameters were determined using an electronic cell counter (ABC Vet hematology analyzer, ABX Diagnostics, France): total white blood cell (WBC) and differential cell counts including percentages of segmented neutrophils, lymphocytes, monocytes, eosinophils, and basophils, red blood cell count (RBC), hemoglobin concentration (Hb), hematocrit (Ht), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC) and platelets count.

Plasma was obtained by centrifugation of blood samples at 500 g for 10 minutes. The following parameters were determined using a Sp-2100 spectrophotometer (Hinotek Technology Co., Ltd., Ningbo, China): glucose, cholesterol, blood urea nitrogen, creatinine, total protein, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST). Blood urea nitrogen/creatinine ratios were calculated manually. Plasma sodium and potassium concentrations were determined using Easyvet (Medica Co., Massachusetts,USA). Prothrombin time was determined using thrombotest reagent (Axis-Shield, Shanghai, China).

Gross and histopathological examination:

Rats were euthanized using halothane overdose in a designated chamber on day 15 for the first two groups and on day 29 in the satellite group (group 3). A complete post-mortem examination was performed immediately after euthanasia. In addition, the following organs were collected and their weights were recorded immediately: brain, seminal vesicles, heart, spleen, kidneys, testes and epididymis, liver, thymus, lungs, ovaries, and uterus.

Tissue samples were also collected and placed in 10% neutral buffered formalin for histopathology examination. Tissue samples were further processed for histopathological (light microscopy) analysis after sectioning at 5 μm thickness and staining with hematoxylin and eosin (H&E) stain. Three slides from each organ per animal were examined by a pathologist. Tissues examined were from the adrenals, brain, prostate and seminal vesicles, heart, spleen, kidneys, testes and

epididymis, liver, thymus, lungs, thyroids, ovaries, uterus, aorta, sternum, cecum, colon, eyes and optic nerves, femur, injection site, lymph nodes, pancreas, rectum, salivary glands, sciatic nerves, skeletal muscle, small intestine, spinal cord, stomach, tongue, trachea, urinary bladder, and vagina.

Statistical analysis

Parameters entered in the analysis included initial body weight, weight gain, organ weights, food and water consumption and various parameters in the hematology and biochemistry analyses.

Statistical analysis was performed using the Student *t*-test "two samples assuming unequal variances" from the Analysis Tool Pak of Microsoft-Excel 2003, using Windows XP Professional. Data were expressed in means ± standard error of means (SEM). Two tail $p<0.05$ was considered significant.

RESULTS

Clinical signs, behavior and survivability

One male rat died during the first week of d-ribose administration. Extensive post-mortem gross examination and histopathology of the dead rat did not identify any possible cause of death. To complete its group, this rat was replaced by another rat that survived to the end of the study. All other rats survived to the scheduled sacrifice day without any major clinical signs at any time during the observation period. Generally, it appears that 420 mg/kg (10 ml/kg) of 4.2% d-ribose administered intravenously was well tolerated by both genders of rats.

Body and organ weights

The mean body weight of rats for each week is presented in Table 1. There were no significant differences in body weight between the control groups and the d-ribose treated groups. There were also no differences in rate of weight gain between the control groups and the d-ribose treated groups. However, in the satellite group, a higher rate of weight gain was observed during the two weeks after completion of d-ribose administration compared to the values obtained for the same rats during the administration period (Fig. 1). The means of organ weight in different groups of rats are presented in Table 2. There were no significant differences in organ weight between the d-ribose treated groups and the control groups.

Feed and water consumption

The means of feed and water consumption per rat and per kg of body weight are presented in Table 1. There were no significant differences in feed consumption between the control groups and the d-ribose treated groups either as amount of feed per rat or as amount per kg of body weight. However, a slight decrease in feed consumption when calculated as per kg of body weight was observed in the satellite group during the 2 weeks after completion of d-ribose administration in comparison to their feed consumption during the treatment period. The amount of water consumed per rat was almost the same for all groups. However, much variation in water consumption was noticed when the amount of water consumed was computed as consumption in ml per kg of body weight. These variations appeared from the differences in body weight between the satellite and the other groups (Table 1).

Hematology and plasma biochemistry analyses

The results of the hematology, total and differential white blood cell counts are presented in Tables 3 and 4. There were no significant differences in red blood cell and white blood cell counts between d-ribose treated male and female rats and their controls. The mean of platelet counts was higher than normal in all rats of all groups. No significant difference was observed between the d-ribose treated groups and the control groups; however, in the satellite groups, higher platelet counts were observed than in other groups. The differential white blood cell count showed no significant differences in percentages of neutrophils, lymphocytes, monocytes, basophils and eosinophils between d-ribose and saline-treated groups. Other hematological parameters also showed no significant differences between d-ribose

treated groups and their controls. All data were within normal ranges for Fischer Rats.

Results of the plasma biochemical analysis are presented in Table 5. Our data indicated no major alterations in any of the evaluated parameters after d-ribose administration. Glucose levels in treated animals were within normal ranges for plasma glucose concentration in rats. Cholesterol level in satellite male group was significantly higher than in control. There were no significant variations between groups in plasma levels of total protein, blood urea nitrogen, creatinine, and alanine aminotransferase (ALT). There was an increase of approximately 33-35% in the plasma levels of aspartate aminotransferase (AST) in the d-ribose treated male and female groups. There were no significant differences in plasma concentrations of sodium and potassium between d-ribose treated and control rats.

Gross and histopathological examination

There were no significant gross pathological changes observed in any of the rats during post mortem examination. Extensive histopathological examination of all body organs revealed no significant abnormal changes in any of the studied organs.

DISCUSSION

Although beneficial effects of d-ribose after oral supplementation in patients with congestive heart failure, coronary arterial disease, renal ischemic diseases, chronic fatigue syndrome and fibromyalgia have been illustrated [1, 3, 4, 14, 15]. Faster administration of d-ribose using an intravenous route may prove superior in patients suffering from these conditions. The development of an intravenous regimen of d-ribose for the treatment of such conditions is novel. The implementation of such regimen however, requires comprehensive safety and efficacy studies. Therefore, this study was designed to evaluate the potential toxicity of intravenous infusion of isotonic d-ribose (4.2%) solution in Fischer Rats. In order to eliminate any possible toxic effects resulting from fluid overload, the volume of 10 ml/kg of fluid administered intravenously was not exceeded [18-21].

Previous studies evaluating toxic or clinical effects of d-ribose have focused mainly on oral administration protocols. Several preclinical studies have evaluated the potential effects of prolonged and high dose of d-ribose on hematological, biochemical and histopathological parameters in non-pregnant Wistar rats as well as the potential embryotoxic effects in pregnant rats [22, 23]. Studies conducted on humans have mainly focused on the beneficial effects of d-ribose on certain health conditions. Some safety studies have also been conducted on healthy volunteers after oral administration [7, 24]. One study has shown that d-ribose administered once by intravenous infusion to healthy volunteers was well tolerated at a dose rate of 222 mg/kg/hour [25]. Minor side effects including diarrhea, gastrointestinal discomfort, nausea, and headache have been reported after oral administration to patients with stable coronary disease [7]. Similar symptoms have not been observed when lower concentrations of d-ribose were administered orally [24] or after intravenous administration of 222 mg/kg /hour [25]. These symptoms were more likely attributed to local physiological changes in the gastrointestinal tract and were not considered as serious adverse effects due to d-ribose administration. In our study, no changes in stool consistency or other signs related to gastrointestinal dysfunction have been detected in rats receiving an isotonic solution (4.2%) of d-ribose at 420 mg/kg intravenously, once per day for 14 days.

Our results showed no significant differences in body weight between d-ribose treated rats and control rats during the 14 days of d-ribose administration period. There were no significant differences in weight gain between the d-ribose treated groups and the control groups; however, in both the satellite male and female groups, a significantly higher rate of weight gain was observed during the two weeks after completion of d-ribose administration as compared to the values obtained for the same rats during the administration period. This increase was not associated with more consumption of feed or water. Since the rats in the satellite groups were younger than the rats in group one when d-ribose was introduced, it is likely that d-ribose affected the growth

rate of the younger rats more than the older ones during the administration period. This possible effect suggests that additional research to identify exact effect of d-ribose on growing bodies should be conducted. Previous reports published by Griffiths et al. [22] showed no significant differences in body weight or weight gain between the controls and those receiving 5% d-ribose orally by the end of his study (13 weeks). Griffiths and his colleagues, however, found a significant decrease in weight gain in rats receiving 10% and 20% d-ribose compared to controls [22]. The decrease in weight gain in groups receiving higher d-ribose in Griffiths study was not related to differences in feed consumption along the study period [22]. In the contrary, another study found that the decrease in weight gain was associated with a significant decrease in feed consumption when high doses of d-ribose (10 and 20%) were used in pregnant rats during the first week of the study [23]. Higher water consumption was reported in the Griffiths study after 6 and 12 weeks in non-pregnant rats receiving high doses of d-ribose (10% and 20%) but not in the first 4 weeks [22]. Similarly, in our study, feed and water consumption was almost the same for all groups over the study period and during the two weeks thereafter in the satellite groups.

Our results indicate no significant changes in any hematology parameters in the d-ribose and saline treated groups in either sex. Previous studies have reported an increase in neutrophil and a decrease in lymphocyte numbers after oral supplementation of d-ribose for 13 weeks in Wistar rats [22]. Similar to our results, in human studies, there were no significant changes in neutrophil or lymphocyte differential counts after d-ribose administration [24]. Although platelet counts in rats in all groups in our study were higher than usual, these values were within the reference ranges found in the literature for Fischer rats F-244 [26]. Since there were no significant differences in platelet count between the d-ribose treated groups and their control groups, and the platelet counts observed in the satellite groups were within normal ranges for Fischer rats, these variations in platelet counts were not considered as due to d-ribose administration. All other hematology parameters in our study including prothrombin times, Hb, Ht, MCV, MCH, MCHC also showed no significant differences between d-ribose treated groups and the controls.

Few reports are available in recent literature concerning the effects of d-ribose on different plasma biochemical parameters. Oral supplementation of d-ribose in rats for 13 weeks has induced a slight increase in plasma concentrations of alkaline phosphatase, aspartate aminotransferase and albumin/globulin ratio without any detectable histopathological lesions in the liver [22]. In human studies, no alterations were reported in liver enzymes after d-ribose administration [24]. In our study, although AST was slightly increased (33-35%) in both female and male groups treated with d-ribose compared to controls, this increase was not statistically significant ($P > 0.05$). Plasma concentrations of ALT, albumin and total protein were not statistically different between groups. Other alterations in blood biochemistry parameters that have been reported previously in humans and animals after extended periods of oral supplementation with d-ribose include: decreased cholesterol, triglycerides and phospholipids in serum or plasma [7, 22, 23, 29]. In our study, significant increase in cholesterol level was observed in satellite male group compared to control. Since these changes were not detected in d-ribose treated male group or female groups and cholesterol levels were within normal ranges for Fischer rats, we have considered these as individual variations rather than late metabolic effects resulted by d-ribose administration.

Hypoglycemic effect after high dose d-ribose supplementation has been reported in early studies in humans and rats [27, 28]. Similar effects were obtained by Gross et al. [25, 29, 30] after intravenous and oral administration of d-ribose to healthy volunteers during the first two hours after d-ribose intake. This effect was associated with a transient increase in insulin levels [30]. In the present study, we did not observe such effects on plasma glucose levels.

Gross post-mortem morphological and histopathological examination of all rats involved in this study revealed no abnormal changes in any of the body

organs. Absolute and relative organ weights were also similar in all groups. Similarly, Griffiths et al. [22] found no indications of gross or histopathological alterations or organ weight changes after 13 weeks of oral d-ribose supplementation in Wistar rats.

CONCLUSION

Intravenous injection of an isotonic solution (4.2%) of d-ribose to Fischer F-244 rats at a dose of 420 mg/kg (10 ml/kg) once daily for 14 days did not induce any clinical, behavioral, hematological, biochemical, gross or histological adverse effects. More research regarding the effect of d-ribose on growing bodies is suggested.

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REFERENCES

(1) Zimmer H G, Ibel H. Ribose accelerates the repletion of the ATP pool during recovery from reversible ischemia of the rat myocardium. *J Mol Cell Cardiol* 1984; 16:863-866.

(2) Gallagher PM, Williamson DL, Godard MP, et al. Effects of ribose supplementation on adenine nucleotide concentration in skeletal muscle following high-intensity exercise. *Medicine & Science in Sports & Exercise (MSSE)* 2001; 33: S167.

(3) Zarzeczny R, Brault JJ, Abraham KA, et al. Influence of ribose on adenine salvage after intense muscle contractions. *J Appl Physiol* 2001; 91:1775-1781.

(4) Teitelbaum JE, St. Cyr JA, Johnson C. The use of D-Ribose in chronic fatigue syndrome and fibromyalgia: a pilot study. *J Alternative* Compl Med 2006; 12:857-862.

(5) Tveter K, St. Cyr, J., Schneider J, Bianco R, Foker J. Enhanced recovery of diastolic function after global myocardial function in the intact animal. *Pediat Res* 1988; 23, 226A.

(6) Perlmutter NS, Wilson RA, Angello DA, et al. Ribose facilitates thallium-201 redistribution in patients with coronary artery disease. *J Nucl Med* 1991; 32:193–200.

(7) Pliml W, Von Arnim T, Stablein A. et al. Effects of ribose on exercise-Induced ischaemia in stable coronary artery disease. *Lancet* 1992; 340:507-510.

(8) Pauly DF, Pepine CJ. D-Ribose as a supplement for cardiac energy metabolism. *J Cardiovasc Pharmacol Ther* 2000; 5:249–258.

(9) Omran H, Illien S, MacCarter D, et al. D-ribose improves diastolic function and quality of life in congestive heart failure patients: a prospective feasibility study. *Eur J Heart Fail* 2003; 5:615-619.

(10) Pauly DF, Johnson C, St. Cyr JA. The benefits of ribose in cardiovascular disease. *Med Hypotheses* 2003; 60:149–151.

(11) Carter O, MacCarter D, Mannebach S, et al. D-ribose supplementation improves peak exercise capacity and ventilatory efficiency in heart failure patients. *J Am Coll Cardiol* 2005; 45:185A.

(12) Vijay N, MacCarter D, Washam M, St. Cyr J. Ventilatory efficiency improves with D-ribose in congestive heart failure patients. *J Mol Cell Cardiol 2005;* 38, *820.*

(13) Perkowski D, Wagner S, Marcus A et al. D-Ribose improves cardiac indices in patients undergoing "off-pump" coronary arterial revascularization. *J Surg Res* 2007; 173:295.

(14) Sato H, Ueki M, Asaga T, et al. D-ribose attenuates ischemia/reperfusion-induced renal injury by reducing neutrophil activation in rats. *Tohoku Journal of*

Experimental Medicine **(***TJEM***)** 2009; 218: 35-40.

(15) Hudson T. D-ribose in chronic fatigue syndrome, fibromyalgia, and cardiac disease. *Nat Med J* 2010; 2, 1-3.

(16) Van Gammeren D, Falk D, Antonio J. The effects of four weeks of ribose supplementation on body composition and exercise performance in healthy, young, male recreational bodybuilders: A double-blind, placebo-controlled trial. *Curr Therap Res* 2002; 63, 486-495.

(17) *OECD* (1988) OECD principles of GLP (Directive 88/320/EEC). Organization for Economic Cooperation and Development. Paris, France.

(18) *OECD* (2002) *Guidance Notes for Analysis and Evaluation of Repeat-Dose Toxicity Studies, OECD Series on Testing and Assessment*, No. 32, OECD Publishing.

(19) *OECD* (2002) *Guidance Notes for Analysis and Evaluation of Chronic Toxicity and Carcinogenicity Studies, OECD Series on Testing and Assessment*, No. 35, OECD Publishing.

(20) Hull RM. Guideline limit volumes for dosing animals in the preclinical stage of safety evaluation. *Hum Exp Toxicol* 1995; 14: 305-307.

(21) Diehl KH, Hull R, Morton D, Pfister R, Rabemampianina Y, Smith D, Vidal J, Vorstenbosch C. A good practice guide to the administration of substances and removal of blood, including routes and volumes. *J Appl Toxicol.* 2001; 21: 15-23.

(22) Griffiths JC, Borzelleca JF, St. Cyr J. Sub-chronic (13-week) oral toxicity study with d-ribose in Wistar rats. *Food Chem Toxicol* 2007; 45: 144–152.

(23) Griffiths JC, Borzelleca JF, St. Cyr J. Lack of oral embryotoxicity/teratogenicity with d-ribose in Wistar rats. *Food Chem Toxicol* 2007; 45: 388-395.

(24) Seifert J, Frelich A, Shecterle L, St. Cyr J. Assessment of hematological and biochemical parameters with extended D-Ribose ingestion. *Journal of the International Society of Sports and Nutrition (JISSN)* 2008; 5: 13.

(25) Gross M, Rieter S, Zollner N. Metabolism of D-ribose administered continuously to healthy persons and to patients with myoadenylate deaminase deficiency. *J Mol Med* 1989; 67:1205-13.

(26) Schultze EA, Sullivan JM. Screening a novel class of anticoagulants for multi-organ toxicity using Fischer 344 rats: Involvement of clinical and anatomical pathologists in the early drug development process. *Vet Clin Path* 2007; 36, 123-136.

(27) Segal S, Foley J, Wyngaarden JB. Hypoglycemic effect of D-ribose in man. *Proceed Soc Exp Biol* 1957; 95, 551-555.

(28) Segal S, Foley J. The metabolism of D-ribose in man. *J Clin Invest* 1958; 37, 719–735.

(29) Gross M, Kormann B, Zollner N. Ribose administration during exercise: Effects on substrates and products of energy metabolism in healthy subjects and a patient with myoadenylate deaminase deficiency. *Klin Wochenschr*. 1991; 69(4), 151-155.

(30) *Gross M, Zollner N. Serum levels of glucose, insulin, and C-peptide during long-term D-ribose administration in man.* Klin Wochenschr. *1991 69(1):31-6.*

تقييم التأثيرات السمية تحت الحادة لإعطاء محلول سكر الريبوز – د

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ملخص

يهدف هذا البحث إلى تقييم إمكانية التأثيرات السمية المصاحبة لإعطاء محلول مساوي التوتر (4.2%) من سكر الريبوز– د عن طريق الوريد مره يوميا لمدة 14 يوما للجرذان من نوع فيشر (F-244). وتم تقسيم ما مجموعه ثلاثون جرذاً عشوائيا إلى ثلاث مجموعات. **المجموعة الأولى:** تم إعطاؤها 10مل/ كغم محلول الريبوز– د(4.2%) وريديا مرة واحدة يوميا ولمدة 14 يوما. **المجموعة الثانية:** (المجموعة الإنضباطية) أعطيت محلولا مساوي التوتر من أملاح الصوديوم (0.9%) وريديا مرة واحدة يوميا ولمدة 14 يوماً. **المجموعة الثالثة:** أعطيت محلول الريبوز– د مساوي التوتر (4,2%) وريديا كما في المجموعة الأولى وتمت مراقبتها لمدة أسبوعين آخرين بعد آخر جرعة من الريبوز– د. تم مراقبة التأثيرات الإكلينيكية والسلوكية، وتم قياس الوزن، وكمية الغذاء والسوائل التي تأخذها الجرذان بالإضافة إلى دراسة تشريحية وفحوصات مجهريه لعينات الأنسجة من الأعضاء، وكذلك أخذ عينات من الدم لدراسة التأثيرات على الخلايا الدموية وكيمياء مصل الدم. نتيجة الدراسة تؤكد عدم وجود اختلافات إحصائية مميزة بين مجموعات الدراسة سواء كانت إكلينيكية، سلوكية، تحليلية لكيمياء وخلايا لدم، أو تغيرات نسيجية أو مجهريه ناتجة من التأثير السمي لإعطاء اليومي لمحلول الريبوز– د لمدة 14 يوما في كلا الجنسين. تؤكد النتائج أن عملية الإعطاء المتكرر لمحلول مساوي التوتر من مادة الريبوز– د وريدياً يتم تقبله بشكل جيد من قبل الجرذان.

الكلمات الدالة: ريبوز– د، جرذان فشر، الأعراض الجانبية، السمية تحت الحادة، الحقن الوريدي، الإحتشاء القلبي، نقص الأكسجه.

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