Journal Tikrit Univ. For Agri. Sci. Vol. (16) No.(2) – 2016
ISSN-1813-1646

Some Histological Effects of Panadol Extra on Albino Mice Liver

Bassam Abdulhakeem Waheeb Hassan[1] * and Samira Abdulhussain Abdullah **
*dept. of biology , college of science, Tikrit university ** college of medicine Tikrit university .

Key Words:
Histological Effects, Panadol Extra, Albino Mice Liver.

Correspondence:
Bassam A.W. Hassan
E-mail:
bassamawh1991@gmail.com
Mobile No.:
07712265383

ABSTRACT

The present study was aimed to investigate the effect of panadol extra drug in induction of lesions on the liver tissues of male albino mice. Experiment was done in the laboratories of the state company for drugs industry and medical applications, Samarra-Iraq (SDI), and continued from march (2015) to July (2015), thirty male mice with age (8-10) weeks and (23-27) gm of weight were distributed into six groups, each group included five male mice.

The result showed high significant increase ($P < 0.01$) in the liver weight of animals treated with panadol extra drug compared with control group.

Microscopic examination showed a histological lesions present in the liver of treated groups represented by necrosis, degeneration and disorganization of the hepatocytes columns towards the central vein, wall thickening of central veins and hepatic arteries with congestion, bile duct surrounded by fibers and infiltration of lymphocytes and neutrophils compared with control group

.

بعض التأثيرات النسجية المستحدثة بواسطة عقار الـ بانادول إكسترا على الكبد في الفئران البيض

بسام عبدالحكيم وهيب حسن * وسميرة عبدالحسين عبدالله**
*قسم علوم الحياة – كلية العلوم – جامعة تكريت **كلية الطب – جامعة تكريت

الكلمات المفتاحية :
التاثيرات النسجية ، عقار بانادول اكسترا ، الكبد ، الفئران البيض .

للمراسلة :
بسام عبدالحكيم وهيب حسن
البريد الالكتروني:
bassamawh1991@gmail.com
رقم الهاتف المحمول:
07712265383

الخلاصــة

هدفت الدراسة الحالية إلى معرفة تأثير عقار بنادول اكسترا في استحداث آفات نسجية في نسيج الكبد في ذكور الفئران البيضاء، اجريت الدراسة في مختبرات مصنع أدوية سامراء للفترة من شهر آذار لعام 2015 وحتى شهر تموز من العام نفسه. تراوحت أعمار الحيوانات بين 8–10 أسابيع. و أوزانها تراوحت بين 23–27 غم. قسمت الحيوانات إلى ستة مجاميع وكل مجموعة تضمت خمسة حيوانات. أظهرت نتائج الدراسة حدوث زيادة معنوية عند مستوى احتمالية ($P < 0.01$) في وزن الكبد للحيوانات المعاملة بعقار البنادول اكسترا مقارنة مع مجموعة السيطرة.

كما أظهر الفحص المجهري حدوث آفات نسجية في نسيج الكبد في المجاميع المعاملة بعقار البنادول اكسترا تمثلت بوجود تنخرات، انحلال الخلايا الكبدية وعدم انتظامها باتجاه الوريد المركزي، تثخن جدار الوريد المركزي والشرايين الكبدية مع وجود احتقان فيها، إحاطة قناة الصفراء بألياف وحدوث ارتشاح الخلايا اللمفية الخلايا العدلة مقارنة مع مجموعة السيطرة.

[1] This paper is a part of M.Sc. thesis for the first author

INTRODUCTION :

Panadol extra is a capsule-shaped tablet (caplet) to help short-term pain relieve. (*Derry, et al., 2014*). Each caplet contains two active ingredients — paracetamol and caffeine. The "Extra" in panadol extra refers to the addition of caffeine (*www.nps.org.au/medicineupdate, 2010*).

Paracetamol is an analgesic commonly used worldwide and generally considered safe when consumed according to the maximum recommended dosage of 4g day*(Larson et al. 2005)*. The therapeutic dose of paracetamol is 10-15 mg/kg with a therapeutic index of approximately 10 *(Prescott 1983).*The adult oral dose of paracetamol for analgesic and antipyretic effects is 650-1000 mg every 4h, with a maximum daily dose of 4g. *(Bizovi & Smilkstein 2002*).

The liver is the main organ for metabolism of paracetamol, eliminating 25% of the therapeutic dose. In adults the majority of paracetamol (approximately 90%) is conjugated with glucuronide (40-67%), sulphate (20-46%) and cysteine (3%), forming inactive and harmless metabolites *(Bertolini et al. 2006).* paracetamol is excreted by kidney (*Bertolini & Ferrari 2006*). Caffeine is the most commonly consumed psychostimulant in the world *(Fredholm 1999).* Its widespread use is related in part to its desirable acute effects *(Addicott & Laurienti 2009),* Whether the acute effects and withdrawal symptoms of caffeine occur independently of one another or in clusters representative of common underlying mechanisms also remains unknown. *(Hughes 1993 & Smith 2002).*

Caffeine is distributed rapidly to all body tissues and readily crosses the blood-brain barrier and placental barrier and is distributed into breast milk, it is roughly 36% bound to plasma proteins. In adults, caffeine is partially metabolized in the liver via demethylation reactions, dependent on the Cytochrome P450 isoenzymes; major metabolites include paraxanthine (80%), theobromine (10%), and theophylline (4%). The plasma half-life of caffeine is 3-7 hours in adults. Caffeine metabolism in neonates is limited due to their immature hepatic enzyme systems, therefore unchanged caffeine and its metabolites are excreted in the urine. Caffeine metabolism occurs in the liver. Metabolism of low doses of caffeine, 70 to 100 mg, exhibits linear pharmacokinetics *(Bonati et al. 1982).*

Liver is the largest organ of the body, constituting 2-5% of the adult body weight. (*Junqueira & Carneiro 2008*). The liver is surrounded by connective tissue, and composed of polygonal lobules separated by connective tissue. At the periphery of the lobule, are regions that consist of bile ducts, lymphatics, nerves and branches of the hepatic artery and the portal vein. At the center of the lobule is the central vein. Hepatocytes (parenchymal cells) are the basic structural component of the liver, representing 60% of the total cell number and 80% of the total liver volume (*Sasse 1992 & Arias et al. 1997*).

The aim of this study was designed to find the histopathological changes in the liver of mice after treatment with panadol extra . and determining the drug effect on the liver weights.

Materials and Methods :

In this study, thirty male albino mice (*Mus musculus)* weighted (23 – 27 gm), were divided to six groups, each group contains five male mice , the animals were fed by the special food of laboratory animal (pellets), that consist the following materials :Wheat, Crushed barley,Soya bean, Protein, Lime stone powder, Salt, and Mixing of vitamins and metals. were locally prepared according to National Research Council (N.R.C) and were given water and food ad Labium, the pellets were locally synthesized from the following materials.

The first group (control) was given water and diet only for 14 days, the second group was treated and given 0.2ml of panadol extra at concentration (0.40 mg/B.W.) orally every day for 14 days , the third group was treated with 0.2ml of panadol extra at concentration (0.60 mg/B.W.) orally every day for 14 days , the fourth group(control 2) was given water and diet only for 21 days, fifth group was treated with given 0.2ml of panadol extra at concentration (0.40 mg/B.W.) orally every day for 21 days , and sixth group was treated with 0.2ml of panadol extra at concentration (0.60 mg/B.W.) orally every day for 21 days. Then after, animals were killed and the organs, liver and kidney were

isolated, weighted and examined histologically, all histological steps were made according to John and Alan (1982). . The data were analyzed Statistical by Beth, at al. (2004). software.

Results and discussion :

The present study showed significant (P <0.01) in liver weight of mice compared with control group , Table (1) .

Table (1) : Means ± standard deviations of liver weight after 14 and 21 days of treatment .

Groups	Mean ±SD of liver after 14 days	Mean ±SD of liver after 21 days
Control	1.58 ± 0.08	1.59 ± 0.07
panadol extra (0.40 mg)	1.93 **± 0.1	1.96 **± 0.12
panadol extra (0.60 mg)	1.91 **± 0.07	2.01 **± 0.08

In a study conducted by *Girish et al. (2009)* to demonstrate the effect of paracetamol on liver weight of rat. They mentioned that the difference in weight of liver was statistically significant increase when compared between control group and other treated groups, this is in agreement with the present result.

Vakiloddin et al. (2015) referred that the paracetamol caused high significant increase in weight of liver. Where, liver weight was statistically significant when compared between control group and other treated groups, this is in agreement with the present result.

Ghimire et al. (2012) also found high significant increase in weight of liver.

The microscope examination showed the normal liver structure in control group, whereas the central vein appeared normal and the hepatocytes were arranged in radical form and its normal in the shape and size, also the sinusoids appeared normal in the size , as well as kupffer cells appeared normal fig. (1) and fig. (2).

The histological study of the liver under the light microscope demonstrated the liver different changes as necrosis, degeneration and disorganization of the hepatocytes toward the central vein and disappearance of the hexagonal pattern of the individual liver cells, thickening wall of central veins and hepatic arteries with congestion. Sclerosing cholangitis, bile duct surrounded by fibers.. Hyperemia of blood vessels was prominently associated with infiltration of lymphocytes and neutrophils infiltration around the blood vessels and even inside the blood vessels. fig. (3) , fig. (4) , fig. (5), fig. (6)

In a study conducted by *Lim et al. (2010),* they mentioned that the paracetamol induce many liver lesions in mice. Paracetamol lead to a significant increase AST serum concentration and significant increase in ALT serum concentration in the group administered paracetamol. Also, paracetamol induced congestion and moderate inflammatory changes with congested sinusoids, nuclear changes, and centrilobular necrosis, this is in agreement with the present result.

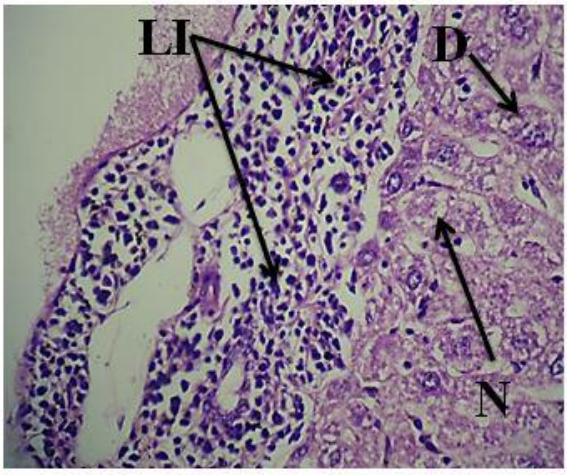

Figure (5): Liver of mice administrated with (panadol extra (0.40 mg/B.W.)for 21days, showed degeneration (D) and necrosis (N) of hepatocytes with severing lymphocytes infiltration (LI) (H&E 400 X).

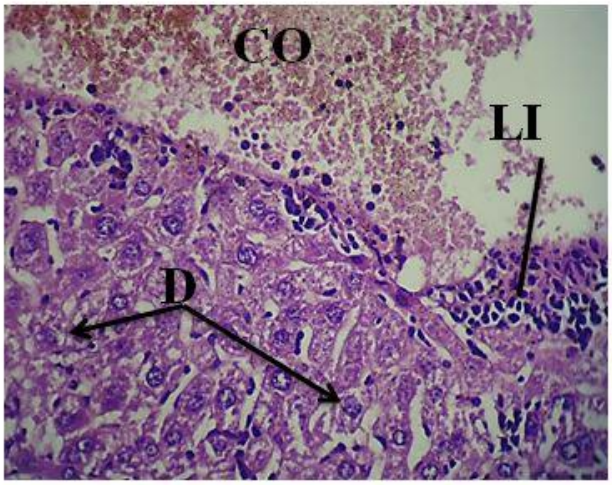

Figure (6): Liver of mice administrated with (panadol extra (0.60 mg/B.W.)for 21days, showed degeneration (D) of hepatocytes with lymphocytes infiltration (LI) and congestion (CON) (H&E 400 X).

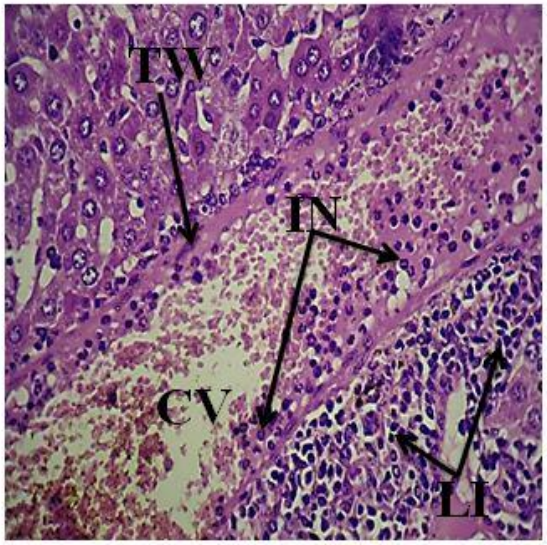

Figure (3): Liver of mice administrated with (panadol extra (0.40 mg/B.W) for 14 days, showed central vein (CV) with thickening wall (TW), with lymphocytes infiltration (LI) and neutrophils infiltration (IN) (H&E 400X).

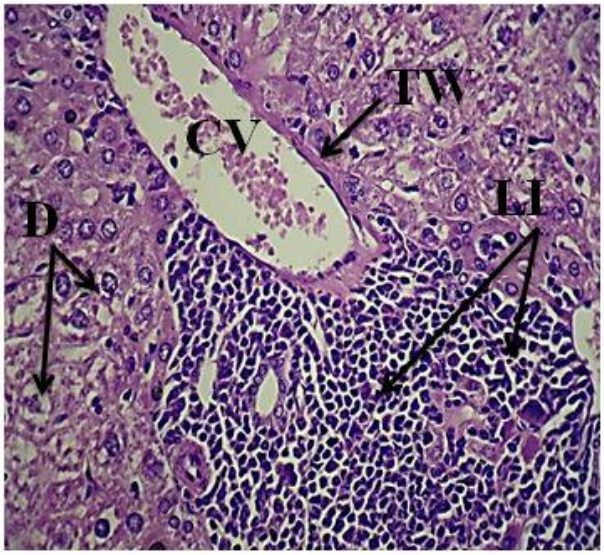

Figure (4): Liver of mice administrated with (panadol extra (0.60 mg/B.W.)for 14 day, showed central vein (CV) with Thickening wall (TW), degeneration of hepatocytes (D) with lymphocytes infiltration (LI) (H&E 400 X).

In other study, *Sharma & Rathore (2010)* demonstrated the effect of paracetamol on liver tissue of mice. Physiologically, they mentioned that Paracetamol injection caused sharp rise in the serum levels of all AST, ALT, ALP and Bilirubin. Histologically, Paracetamol injection caused damaged hepatocytes and Severe infiltration from damaged blood vessel, this is in agreement with the present result.

*Galal et al. (*2012*)* stated that the paracetamol lead to central veins congestion and hepatocytes necrosis and degenerative changes in the rat liver, this is also in agreement with the present result. Degenerative changes of hepatocytes and lymphocytes infiltration were observed by *Kumar et al. (2014)*.

Abd El-Ghany et al. (2012) founded congestion of central veins in the rat liver, this is in agreement with the present result.

Also, *Hussain et al. (2014)* referred in their study that the paracetamol lead to congestion of blood vessels along with hepatic cell necrosis, , eosinophils, macrophages, plasma cells infiltration, degeneration of hepatocytes nuclei, and fibrosis in the rat liver, this is in agreement with the present result.

In other studies founded similar results with paracetamol increased serum levels of AST, ALT, ALP and Bilirubin as well as degenerative damages of hepatocytes , *Girish et al. (2009);* changes with fibroctyes and fibers, this is in agreement with the present result.

References:

Abd El-Ghany, M.A., Rasha, M. and Hagar, M.; (2012). Hypolipidemic effect of caffeine beverages in fatty liver injured rats. J. Scien.Res., 8(3): 1502-1509.

Addicott, M.A. and P.J. Laurienti, (2009). A comparison of the effects of caffeine following abstinence and normal caffeine use. Psychopharmacology,. 207(3): p. 423-431.

Arias IM, jakoby WB, Popper H, Scachter D, Schafritz DA: (1997). Section 4 the organ: The hepatic microvascular system. The liver: Biology and Pathobiology, 3rd Ed. Lippincott Williams & Wilkins,. Available from: URL: http://liver.med. tufts.edu/.

Bertolini A, Ferrari A, Ottani A, Guerzoni S, Tacchi R, Leone S. (2006). Paracetamol: new vistas of an old drug. CNS.Drug Rev.; 12:250- 275.

Bertolini, A. and A. Ferrari. (2006). "Paracetamol: new vistas of an old drug." CNS Drug Rev 12(3-4): 250-275.

Beth, D.; Robert G. and Trapp. (2004). Basic and clinical biostatistics, 4th ed. Lange Medical Books/ Mc Graw-Hill Medical Publishing Division. New York. pp: 83-154.

Bizovi K, Smilkstein M. (2002). Acetaminophen.In: Goldfrank's Toxicologic Emergencies, 7 Edition, eds Goldfra, Flomenbaum NE, Lewin NA, How, Hoffman RS, Nelson RS, New York: McGraw-Hill,: 480-501.

Bonati, M., R.; Latini, and F. Galletti, (1982). Caffeine disposition after oral doses. Clinical Pharmacology and Therapeutics, .32(1): 98-106.

Derry, C. J. ; Derry, S.and Moore, R A. (2014). "Caffeine as an analgesic adjuvant for acute pain in adults". Cochrane database of systematic reviews. doi:10.1002/14651858.CD009281.pub3. PMID 25502052.

Fredholm, B.B. (1999).Actions of caffeine in the brain with special reference to factors that contribute to its widespread use. Pharmacological Reviews, . 51(1): 83-133.

Galal, R.M, Hala F. Z., Mona M. S., Azza M. A. (2012).Potential protective effect of honey against paracetamol-induced hepatotoxicity. Arch Iran Med. 15(11): 674 –680.

Ghimire, S. C.; Carl C. and Leonard R. (2012).Toxicological evaluation of certain veterinary drug residues in food. WHO Library Cataloguing-in-Publication. pp: 1-175.

Girish, C.; Koner, B.C.; Jayanthi, S. and Pradhan, S.C. (2009). Hepatoprotective activity of six polyherbal formulations in paracetamol induced liver toxicity in mice. J. Med. Res. 129: 569-578.

Hughes, J.R. (1993). Caffeine self-administration and withdrawal: Incidence, individual differences and interrelationships. Drug and Alcohol Dependence, 32(3): 239- 246.

Hussain, L.; Javaria I.; Kanwal R.; Muhammad T.; Muhammad I.; Muhammad S. and Hamid A. (2014). Hepatoprotective effects of Malva sylvestris L. against paracetamol-induced hepatotoxicity. Turk. J. Biol. 38: 396-402.

John, D.B. and Alan, S. (1982). Theory and Practice of Histological Techniques.churchil, Livingstone. London and New York.

Junqueira LC, Carneiro J. (2008). Basic Histology, 10th edition Lange international edition. pp: 332-343.

Kumar, C. H., Ramesh, A. and Mohan, G. K. (2014). Hepatoprotective effect ethanolic extractof ficus mollis on paracetamol induce liver damage in albino rats. Res. J. Pharm. 5(6): 485-488.

Larson AM, Polson J, Fontana RJ, Davern TJ, Lalani E, Hynan LS, et al. (2005). Acetaminopheninduced acute liver failure: Results of a United States multicenter, prospective study. Hepatology. ;42(6):1364-72.

Lim, A. Y., Ignacio S., Srikumar C., Sufyan A. and John P J. (2010).Histopathology and biochemistry analysis of the interaction between sunitinib and paracetamol in mice. J. BMC Pharm. 10 (14): 1-17.

Prescott, LF. (1983) . Paracetamol overdosage. Pharmacological considerations and clinical management. Drugs ; 25:290-314.

Sasse D, Spronitz UM, Mally IP, (1992). Liver architecture. Enzyme ; 46: 8-32

Sharma A. and Rathore H.S. (2010). Prevention of acetaminophen induced hepatorenal toxicity in mice with fruits of terminalia chebula (myrobalan). Thai J Toxicology. 25(2): 144 -153

Smith, A. (2002). Effects of caffeine on human behavior. Food Chem Toxicol, . 40(9): 1243-55.

Vakiloddin, S.; Neeraj F.; Shivkanya F.; Sokkalingam A. D.; Kaveti B. and Sundram K. (2015). Evidences of hepatoprotective and antioxidant effect of *Citrullus colocynthis* fruits in paracetamol induced hepatotoxicity. Pak. J. Pharm. Sci. 28 (3): 951-957.

www.nps.org.au/medicineupdate, 2010.