Open Access
Full Length Article

ORIGINAL ARTICLE

Effect of Time-Lapse Administration of Panadol (Paracetamol) on Spleen and Kidney Functions of Adult Albino Mice

Muddasir Hassan Abbasi[1,*], Komal David[2], Muhammad Idnan[2], Zaira Ahmad[3] and Asif Mahmood Qureshi[2]

[1]Centre for Applied Molecular Biology (CAMB), University of the Punjab, Lahore, Pakistan
[2]School of Zoology, Minjah University, Lahore, Pakistan
[3]Environmental Science Department, Lahore College for Women University, Lahore, Pakistan

ABSTRACT

Panadol is a remarkable pain and fever reducing non opioid drug. It is known to be completely safe and tolerant medicine throughout the globe among people of all age groups. The goal of this study was to elaborate the histopathological effects of reduced interrupted regime of panadol on spleen and kidney functions of mice (*Mus musculus*).

The animals were categorized into four groups, the control group (C), and rest of the three were labeled as 1, 2 and 3, made on the basis of time interval of pandol administration via gavage (n=7). Matched volume of panadol (15000 µg/0.1ml) and normal saline was given to mice. Tissue samples were collected after sacrifice of the mice and processed for assessment.

The findings of the current study reflected the histopathological damage of kidney and spleen caused by panadol in reduced interval of time. The kidney section illustrated clear distortion in glomeruli integrity, marked increase in interstitial spaces, damaged epithelia, and degeneration in tubules in all the groups. The spleen histology exhibited the degradation of white pulp, depopulation, activation of follicles, cellular disruption thereby overall disorganized stature. The raised values of serum creatinine and blood urea examinations also revealed the deleterious effects of panadol overconsumption.

It is inferred from the above mentioned outcomes that though panadol is considered to be a safe drug even then its intake prior to four hours can account for adverse effects on kidney and spleen.

Keywords
Creatinine, Kidney, Mice, Overdose, Panadol.

*Address of Correspondence
muddygcs@gmail.com

Article info.
Received: October 03, 2018
Accepted: November 14, 2018

Cite this article: *Abbasi MH, David K, Idnan M, Ahmed Z, Qureshi AM. Effect of Time-Lapse Administration of Panadol (Paracetamol) on Spleen and Kidney Functions of Adult Albino Mice. RADS J. Biol. Res. Appl. Sci. 2018; 9(2): 88-93.*

Funding Source: *Nil*
Conflict of Interest: *Nil*

INTRODUCTION

The analgesic effect of Panadol among painkilling remedies is quite well established but it won't be inappropriate to call it a mystery drug because even after a decade of research its exact mechanism of action is still to be elucidated[1]. Mazaleuskaya acquainted that paramount of Panadol efficacy in terms of its analgesic and antipyretic dimensions depend chiefly on the administration of its appropriate dose. Recent evidence expounds that Panadol, when used at a recommended dose of 4g/day in adults and 50-75mg/kg/day in young ones, is far more beneficial and tolerable as compared to other over the counter medication[2].

Overdosing of Panadol accounts for a major cause of drug-related toxicities including, acute liver damage and other complications throughout the world (Kanabar)[3]. The half-life of Panadol at standard dose is 1.5-2.5 hours, but in case of overdosing the metabolism retards thus extending the half-life to 4-8 hours. The fever and pain

ceasing properties of Panadol depend on its concentration reaching the brain cells requiring an exit of Panadol from the bloodstream to the nervous system tissues before it implies its effect[4].

Toxicity of Panadol gets explicit generally in three phases. In the first twenty-four hours' mild symptoms like nausea, vomiting, profuse sweating, malaise and diffused abdominal discomfort appears according to Thapa et al[5]. In the next seventy-two hours' liver malfunctioning initiates as it is the main site of metabolism of drugs, hepatic transaminase and aspartate aminotransferase AST level is enhanced and acute renal impairment occurs. The next phase about ninety-six hours after overdose is characterized by severe vomiting, jaundice, gastrointestinal disturbance, coagulation failure, low blood glucose, encephalopathy, acidosis of metabolic system and acute kidney failure. Later on, the high-level resolution of hepatic and renal complications and multi-organ damage and death occurs.

Steps involved in liver damage evoked by Panadol overdose are associated with increased formation of free radicals leading to heavy oxidative stress. The putative metabolite of Panadol, NAPQI gets accumulated leading to consumption of glutathione (GSH) thereby GSH stores in liver reduce. Excess NAPQI interact with cellular protein mercapto groups. A result is an overgrowing number of reactive oxygen species (ROS) thereby increase peroxidation of lipids. Nitration of tyrosine, a chief biomarker in peroxynitrite formation finally causes liver necrosis as stated by El Morsey *et al*[6].

Kidneys are the major homeostatic organs as they regulate not only blood pressure but also the blood composition and fluid volume of the blood. Therefore, drug overdose not only affects the liver but also put kidneys under irretrievable stress. Panadol causes acute and chronic kidney failure. The mechanism, which leads to liver injury has been well studied however the molecular level of Panadol-induced nephrotoxicity is poorly encompassed as mentioned by Lorz *et al*[7]. Abraham et al[8] found out that there is no special treatment for Panadol- induced kidney damage. Vitamin C is a good chain-breaking antioxidant and a free radical absorber. Super-dose of vitamin C may prove beneficial in the treatment of Panadol induced nephrotoxicity. The basic mechanism for protection by vitamin C apparently seems to be the rejuvenation of non- protein thiol.

Panadol is an extensively used remarkable drug, however, the main point is to use it according to the recommended dosage to avoid any kind of damage or toxicity to the body. In this regard time delay between repeated doses is the hallmark to achieve steady state plasma levels in due time. The major emphasis of the current study is to elucidate the histopathological effects of a reduced interrupted regime of Panadol on spleen and kidney function of mice and correlate the changes with that of a human. This study will be important in the prognostic evaluation of dose interval of panadol in humans.

MATERIAL AND METHOD

Materials

All the materials/chemicals were obtained from commercial sources as indicated: Panadol 500mg tablets, (GlaxoSmithKline consumer healthcare) were taken from a local market. Chemicals including formalin, ethanol, and chloroform were from Sigma-Aldrich Chemie (Munich, Germany) or Merck (Darmstadt, Germany).

Colonies of Female Mice (*Mus musculus*)

Female albino mice were nurtured for two weeks in the well-maintained animal house of School of Zoology in Minhaj University Lahore (MUL). The mice were scrutinized for their weight thrice a week and experimental work was initiated when the animals attained the weight of 30g. The availability of fresh water and food (the chow i.e., 20% unrefined protein in its composition) was made possible all the time until the onset of the experimental procedure.

Methodology

Dose Calculation and Preparation

The standard human dose of Panadol (500mg/kg) was converted and prepared for mice (30g). Three standard tablets of 500 mg/kg were powdered and mixed with 10 ml of distilled water to prepare the required dose.

Experimental Design

The animals were categorized into four groups (n=7), the control group (C), and rest of the three were experimental groups labelled as 1, 2 and 3, made on the basis of the time interval of 1 hour, 2 hours and 3 hours respective of the initial dose administration. The control group was provided with normal saline of the matched volume of Panadol (15000 µg/0.1ml) which was given to the experimental group at a time lapse of 1, 2 and 3 hours respective of the initial dose. All of the doses were given to each of the adult female mice via gavage.

Tissue Sampling and Processing

The blood samples were extracted from the heart right after dissection, and all the viscera were placed in a petri dish with 0.9 % saline. Kidneys & spleen from each animal were collected in separate glass vials. All the organs were rinsed with physiological sodium saline and portion was fixed in 10% formalin. Paraffin-embedded sections were prepared, processed followed by microscopic imaging as described by Abbasi *et al* [9].

RESULTS

Renal Profile

In the current study Blood Urea, Nitrogen (BUN) and serum creatinine level were measured. The rationale behind the measurement of urea and creatinine to check the kidney functioning is that glomerular filtration rate (GFR) is reflected both by plasma as well as serum levels, the key parameters that characterize renal function. BUN shows a comparative rise in group 1 and 3 while group 2 exhibits a mild decrease. An opposite trend can be noted in the case of serum creatinine level for all the comparable groups (Table **1**).

Table 1: Comparison of Blood Urea Nitrogen (BUN) and Creatinine levels between control(C) and experimental groups of Panadol administrated mice.

Groups	BUN (mg/dl)	Creatinine level (mg/dl)
C	10.14	0.43
1	13.29	0.36
2	12.29	0.39
3	15.14	0.37

Values represent a mean of 7 replicates

Histopathology

Kidney

Kidney histology of the control group depicted normal sized renal capsule with fuzzy proximal as well as clear distal tubules (Fig. **1a**). Repeating the dose after one hour of the administration of initial dose the renal tissues elucidated widening of interstitial spaces, and some darkly stained areas demonstrating damage to the tissues, moreover the glomerulus stays no more intact (Fig. **1b**). Dose repetition after two hours of initial dose the histological findings demonstrated much widened interstitial spaces, the glomerular space markedly enhanced and the renal capsules not only got reshaped but a great variation arose among the size of renal capsules (Fig. **1c**). Likewise, the third experimental group exhorts much deterioration in renal structure when it was given the repeat dose of Panadol after three hours of the first dose (Fig. **1d**).

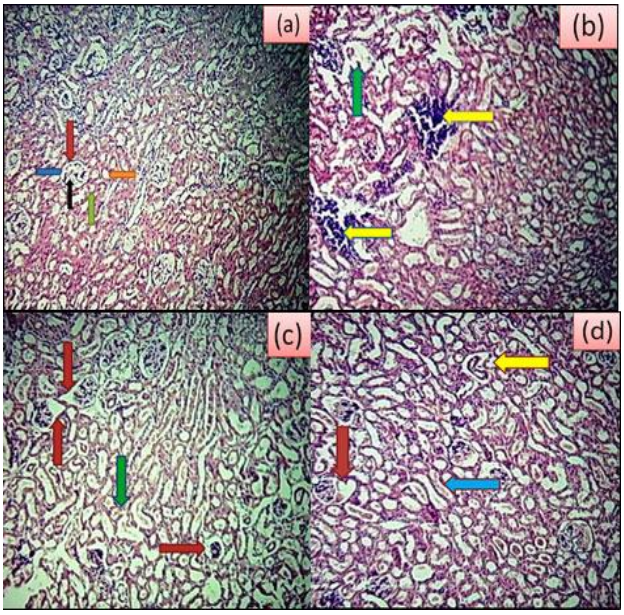

Fig. 1: Haematoxylin-eosin staining of kidney sections of Panadol administered mice after 1 (b), 2 (c), and 3h time interval compared with control (a). Renal corpuscles indicated by red arrow, intact glomeruli (black arrow), normal glomerular space (blue arrow), proximal tubules (green arrow) and distal tubules (orange arrow). Enlarged Bowman's space (red arrows), architectural deterioration (yellow and blue arrows) can be evident in treated mice after 1, 2 and 3hrs (Magnification: 160×).

Spleen

Morphologically prominent red pulp (RP) and the white pulp (WP) were obvious in the control section of the spleen (Fig. **2a**). The spleen section of the first experimental group elaborated deterioration of splenic follicles (Fig. **2b**). While second and third group manifest not only necrosis but also depopulation and distortion of follicles (Fig. **2c-d**).

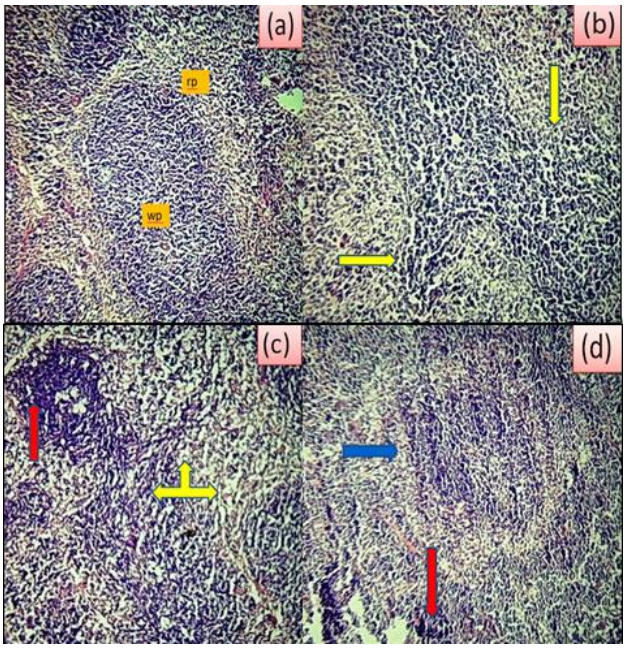

Fig. 2: Haematoxylin-eosin staining of spleen sections of Panadol administrated female mice after 1 (b), 2 (c) and 3h time interval compared with control (a). White pulp (wp) & red pulp (rp) can be marked in (a). In Panadol induced mice after 1, 2, 3 hours' distortion of follicles (yellow arrows), depopulation (blue arrow), darkly stained areas (red arrows) elucidate structural damages (Magnification: 160×).

DISCUSSION

The current study is focused on renal and spleen impairment due to Panadol overdose in terms of the reduced interrupted regime. The kidney is the second targeted entity of any metabolite formed. Overdosing of drugs like Panadol can malfunction kidney even in the normal appearing subjects. However, nephrotoxicity pertaining to Panadol after a supra-therapeutic dose may occur even in the absence of hepatotoxicity.

In the present work, histological deterioration in the renal tubules along with cellular distortion was evident at each time point during the course of study. The histopathological assessment of experimental groups revealed not only glomerular shrinkage and enhanced space in Bowman's capsule but also desquamation of epithelial layer, vacuolar distortion of tubules and increase in interstitial spaces these results correlate with those explained by Zhou [10]. Our results are in accordance with those reported by Gulnaz[11] that overdosing of Panadol leads to the small size of the glomerulus, vacuoles and cellular desquamation in distal and proximal convoluted tubules. Severe necrosis in tubules, degeneration of epithelium and distortion of the glomerular structure was elucidated in another study reported by Fouad [12] that is in relevance with the current study. Excessive glomerular damage evident by bleeding along with epithelial rupture, deterioration of cell boundary and damage in brush border in proximal tubules as a result of Panadol overdose was explained by Khorsandi[13]. These changes might have occurred due to the interaction of toxic metabolites with the architectural integrity of renal tubules and glomeruli leading to release of lysosomal enzymes thereby causing damage. The results of the current study also stand in agreement with those of Ucheya[14] that elaborated hypoplasia, wider capsule space some even without glomeruli, vascular congestion and tubular necrosis due to Panadol overdose. In another study by Odigie[15] the histopathological results revealed tubular expansion and enlargement of glomerular space due to prolonged over-consumption of Panadol.

Panadol induced renal toxicity has been attributed chiefly to cytochrome P-450 oxidase isoenzymes found in kidney however other mechanisms like the role of prostaglandin synthetase and N-deacetylase enzymes must not be ignored. Paradoxically, the major element in detoxification of Panadol and its metabolites is glutathione but its conjugates are involved in the synthesis of nephrotoxic molecules as mentioned by Mazer[16].

Regarding splenic sections, the experimental groups elucidate not only shrinkage but also a cellular distortion of white pulp at each time point as compared to the control sections. Moreover, depopulation of lymphocytes was notable in white pulp these changes might be due to the interference of toxic metabolites of Panadol overdose.

The current results are in line with another investigation conducted by Gomaa[17] that explains Nonsteroidal anti-inflammatory drugs (NSAID) and Panadol induced disastrous effects on immunity related organs i.e. bone marrow, spleen, and lymph nodes. Moreover, the toxic metabolites of Panadol overdose damage hepatocytes thereby triggering an innate response of the immune system, the over activity of cells and activation of leucocytes may be in relation with tissue damage induced by an overdose of the drug.

In addition to histopathological assessment, the extent of renal damage is also characterized by the rise in urea and creatinine level, whose concentration in serum helps in an overview of Glomerular Filtration Rate (GFR) and ultimately renal function. The normal wear and tear of muscles of the body synthesize a chemical waste product creatinine that goes into the bloodstream. In the current study increase in blood, urea was observed in group 1 and 3, while group 2 showed a slight decrease in value this might be the reason of the self-corrective mechanism of the body. The serum creatinine values, however, showed a decrease in values within a narrow range, these results were quite similar with those elaborated by Sener[18] thus ratify the idea that some minimum time is required to take next dose otherwise an irreparable loss of integrity of kidney and spleen can be observed.

CONCLUSION

In this study, detrimental histopathological effects of a reduced interrupted regime of Panadol conjure with the notion of a completely safe drug and it is highly recommended that the correct dose within time frame must be taken. It is further recommended that the second dose must not be administered before four hours to avoid any substantial damaging effect of this drug and still more detailed studies are required to crack the mystery of this drug in biological medium.

Funding Disclosure Statement

There is no research grant for this particular research.

Acknowledgement

The authors are thankful to Ms. Sana Fatima, for her valuable comments on histological sections.

Disclosure Statement

The authors declare no potential conflict of interest.

Contributors' Statement

Muddasir Hassan Abbasi & Komal David contributed equally to this study. Muhammad Idnan is involved in the troubleshooting. Zaira Ahmad & Asif Mahmood Qureshi are involved in manuscript drafting. Muddasir Hassan Abbasi supervised the research project and approved the final draft.

REFERENCES

1. Borst P, de Wolf C, van de Wetering K. Multidrug resistance-associated proteins 3, 4, and 5. Pflug Arch Eur J Phy 2007;453(5):661-73.
2. Mazaleuskaya LL, Sangkuhl K, Thorn CF, FitzGerald GA, Altman RB, Klein TE. PharmGKB summary: pathways of acetaminophen metabolism at the therapeutic versus toxic doses. Pharmacogenet Genomics 2015;25(8):416.
3. Kanabar D. A practical approach to the treatment of low-risk childhood fever. Drugs R D 2014;14(2):45-55.
4. Hodgman MJ, Garrard AR. A review of acetaminophen poisoning. Crit Care Clin 2012;28(4):499-516.
5. Thapa B, Walia A. Liver function tests and their interpretation. Indian J Pediatr 2007;74(7):663-71.
6. El Morsy EM, Kamel R. Protective effect of artichoke leaf extract against paracetamol-induced hepatotoxicity in rats. Pharm. Biol. 2015;53(2):167-73.
7. Lorz C, Justo P, Sanz A, Subirá D, Egido J, Ortiz A. Paracetamol-induced renal tubular injury: a role for ER stress. J Am Soc Nephrol 2004;15(2):380-89.
8. Abraham P. Vitamin C may be beneficial in the prevention of paracetamol-induced renal damage. Clin Exp Nephrol 2005;9(1):24-30.
9. Abbasi MH, Fatima S, Khawar MB, Jahan S, Sheikh N. An In Vivo Study on Intoxicating Effects of Nerium oleander Water Based Extract on Multiorgan of Wistar Rat. Can. J. Gastroenterol. Hepatol 2018;2018.
10. Zhou Y-d, Hou J-g, Liu W, Ren S, Wang Y-p, Zhang R et al. 20 (R)-ginsenoside Rg3, a rare saponin from red ginseng, ameliorates acetaminophen-induced hepatotoxicity by suppressing PI3K/AKT pathway-mediated inflammation and apoptosis. Int Immunopharmacol 2018;59:21-30.
11. Gulnaz H, Tahir M, Munir B, Sami W. Protective effects of garlic oil on acetaminophen-induced

nephrotoxicity in male albino rats. Biomedica 2010;26(7):9-15.

12. Fouad AA, Yacoubi MT, El-Bidawy MH. Therapeutic potential of hemin in acetaminophen nephrotoxicity in rats. Environ Toxicol Pharmacol 2009;27(2):277-82.
13. Khorsandi L, Orazizadeh M. Protective effect of Curcuma longa extract on acetaminophen induced nephrotoxicity in mice. DARU 2008;16(3):155-59.
14. Ucheya R, Igweh J. Histological changes in kidney structure following a long–term administration of paracetamol (acetaminophen) in pregnant sprague dawley rats. Niger. J. Physiol. Sci. 2006;21(1-2).
15. Odigie EB, Achukwu PU. Histopathological effects of acetaminophen abuse in male Wistar rats, and prevalence in human subjects: An experimental and cross-sectional study. J Exp Clin Anat 2015;14(2):81.
16. Mazer M, Perrone J. Acetaminophen-induced nephrotoxicity: pathophysiology, clinical manifestations, and management. J. Med. Toxicol. 2008; 4(1):2-6.
17. Gomaa S. Adverse effects induced by diclofenac, ibuprofen, and paracetamol toxicity on immunological and biochemical parameters in Swiss albino mice. J Basic Appl Zool 2018;79(1):5.
18. Şener G, Şehirli AÖ, Ayanoğlu-Dülger G. Protective effects of melatonin, vitamin E and N-acetylcysteine against acetaminophen toxicity in mice: a comparative study. J. Pineal Res.2003; 35(1):61-68.