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Could paracetamol induces acute renal impairment when used in therapeutic doses? A rat model study

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Abstract Paracetamol (PA) induced- acute and chronic renal failure has been studied extensively, but when used in toxic doses. However, the effect of PA on renal tissue when used within therapeutic doses is poorly investigated. The current study included 2 groups of 8 rats each. PA was dissolved in 1% Dimethyl sulfoxide (DMSO) as a vehicle. Group I (control group): was daily administrated 1% DMSO, group II (PA treated group, using therapeutic doses).Serum urea and creatinine were measured using colorimetric methods. The overall results showed that PA treated rats exhibited significant higher mean serum urea and creatinine levels (63.87 mg/dl ± 5.38, 2.6mg/dl ± 0.48 respectively) compared to the controls (49.48mg/dl ± 5.07, 1.93mg/dl ± 0.06 respectively), ($p<0.5$ for both), indicating acute renal impairment. So we conclude that PA when used within therapeutic dose range could lead to acute renal impairment in rats, so further researches regarding the possible combination of PA with other substances that could reverse these effects are recommended.

Keywords Paracetamol, Therapeutic dose, Renal toxicity, Rat model

1. Introduction

Toxic effects on the kidney related to medications are both common and expected, given the kidney's roles in plasma filtration and maintenance of metabolic homeostasis. The renal vascular bed is exposed to a quarter of resting cardiac output. As such, glomerular, tubular and renal interstitial cells frequently encounter significant concentrations of medications and their metabolites, which can induce changes in kidney function and structure [1].

Paracetamol (acetaminophen, N-acetyl-p-aminophenol, PA) first described in 1878 as the analgesic and antipyretic drug and it was little used clinically until the withdrawal of Phenacetin from the market on account of observed renal toxicity. At the time of writing, PA is probably the most widely available and commonly used drug worldwide and represents a very important analgesic; indeed it is included in the 20th World Health Organization Model List of Essential Medicines as updated in March 2017 [2].

PA was considered one of the most nephrotoxic analgesics and has now been withdrawn from the market in most countries. These findings have led to the recommendation that paracetamol be used only in limited amounts and for limited time periods. Research into the biologic basis of paracetamol nephrotoxicity has been recently encouraged by a National Kidney Foundation Ad Hoc Committee [2,3].

In overdoses, acetaminophen can induce interrelated biochemical reactions in hepatocytes including the formation of reactive oxygen species, deregulation of Ca^{+2} homeostasis, covalent modification and oxidation of proteins, lipid peroxidation, and DNA fragmentation [4], which result in hepatic necrosis and depletion of glutathione stores, nephrotoxic effect and renal insufficiency in humans and experimental animals and in severe cases to death [5-8].
So the present study has been conducted to investigate weather PA could induces nephrotoxicity when used within therapeutic dose ranges, which were investigated seldom.

2. Materials and methods

2.1. Chemicals

All chemicals obtained from Sigma Chemical Company, Egypt and from Egyptian Company for Biotechnology (S.A.E), Egypt.

2.2. Experimental animals design and treatment

Sixteen male Wister albino rats, 8 weeks, 120-140 g body weight, obtained from the Animal House of the Faculty of Medicine, Assiut University, Egypt. All the experiment with animals were carried out according to the guideline of the Institutional Animal Ethical Committee. Rats were housed in polyethylene cages (8 rats/cage), with normal relative humidity normal dark cycle; they fed standard commercial diet & water ad libitum during the experimental period. Rats were divided randomly into 2 groups of 8 rats each. Rats were given pure water with the following treatments orally by intra gastric tube. For these experiments, PA was dissolved in 1% DMSO as a vehicle: Group I (control group): was daily administrated 1% Di methyl sulfoxide orally [9], for 2 weeks. Group II: receive 42.84 mg/kg PA daily for 2 weeks [10].

2.3. Preparation of the samples for biological determination

After the end of experimental period, rats were anesthetized and the blood samples were collected from the retroorbital veins into plain tubes. Tubes of blood were centrifuged (cooling centrifuge Mikro 220R Germany) at 4000 rpm for 10 min. to separate the serum. Sera were collected in epindorffs and stored at -20 ºC till the time of biochemical analysis.

2.4. Biochemical assessments of serum specific markers related to renal dysfunction

Assessment of serum specific markers related to renal damage in the form of creatinine, blood urea nitrogen (BUN) levels in the serum, were performed using standard kits from Lab. Essentials Inc., Egypt.

2.5. Statistical analysis

Statistical analysis was applied to the data to determine difference ($p<0.05$). Statistical data analysis was under taken using Graph Pad Prism version 7.0 b software (Graph Pad Software Inc., San Diego, CA, USA). All reported values were represented for quantitative data as the mean ± S.D. (n=8). Statistical significance was ascertained by unpaired T test to determine significant differences between means. Values of $p<0.05$ were considered significant.

3. Results and discussion

After administration of PA, serum urea and creatinine levels were significantly increased in PA group compared to control group ($P < 0.01$and $P < 0.01$ respectively) (Table 1, Fig. 1,2).

Table 1: Effect of PA on serum urea and creatinine concentration

Animal groups	N	Urea(mg/dl)	Creatinine (mg/dl)
Control	8	49.48 ± 5.07	0.06±1.93
PA	8	$63.87\pm5.38^{a**}$	$2.6 \pm 0.48^{a**}$

Data are expressed as mean ± SD; p values with an asterisk are significant.
$**p < 0.01$; PA: Paracetamol.

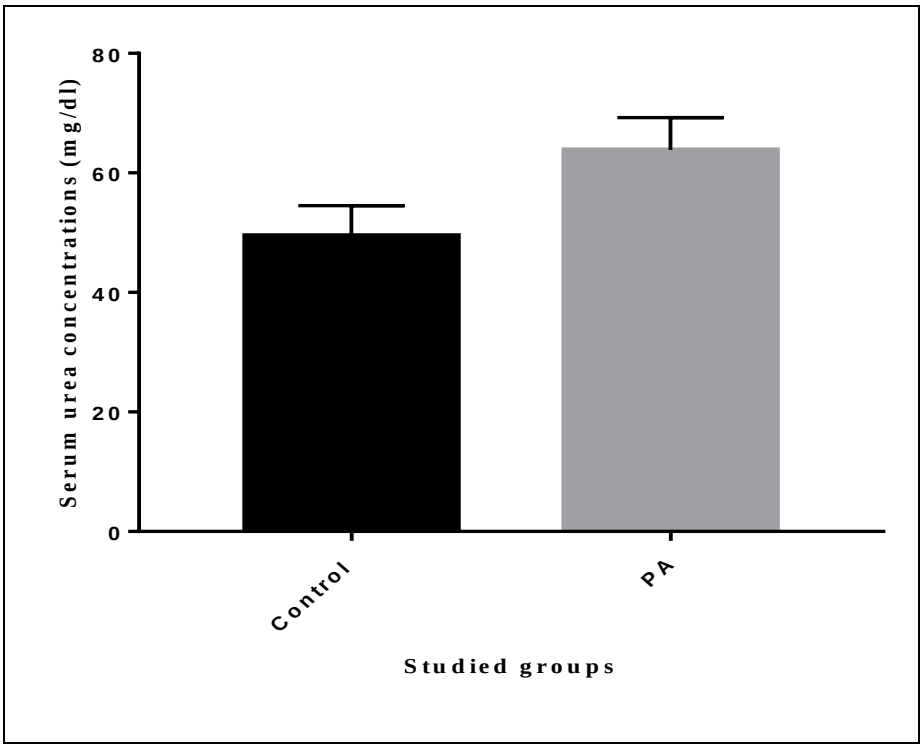

Figure 1: Effect of PA on serum urea concentration

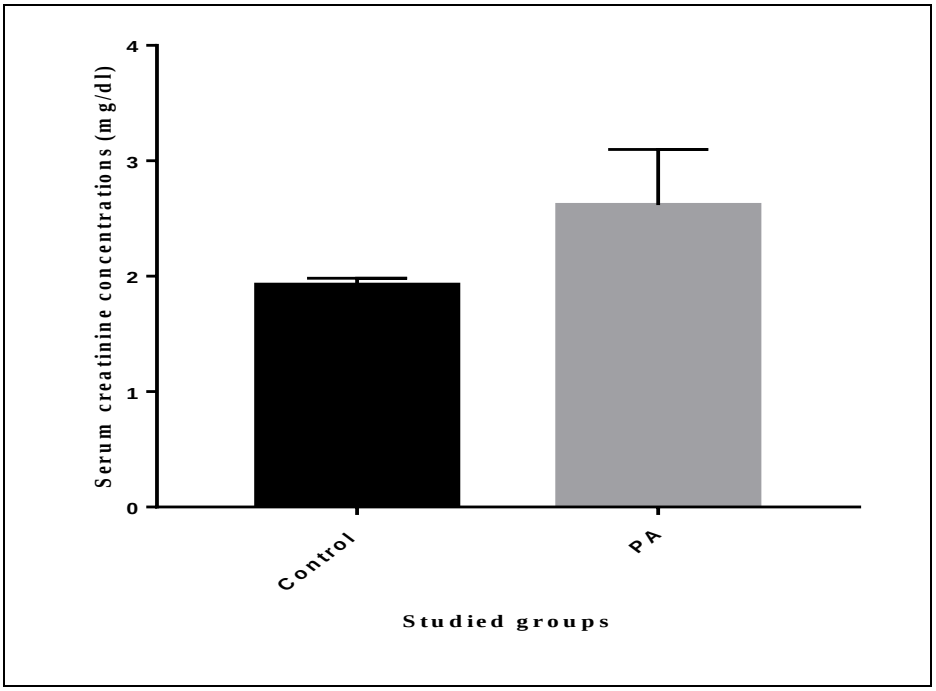

Figure 2: Effect of PA on serum creatinine concentration

The kidney is the second organ that affected by an PA overdose and nephrotoxicity has been reported in many studies [11,12]. Although nephrotoxicity is less common than hepatotoxicity with PA overdose, many reports have associated the renal effect with severe hepatotoxicity [13], and renal damage can occur, even in the absence of liver injury [14]. Nephrotoxicity occurs as a disturbance in renal function due to various drug interactions and chemicals [15].

PA causes acute and chronic renal failure. The mechanisms leading to hepatic injury have been extensively studied, but the molecular mechanisms regarding PA-induced nephrotoxicity are poorly defined [16] and renal damage can occur, even in the absence of liver injury [17].

In the assessment of kidney injury, levels of urea and creatinine in serum should be first determined. These are very sensitive markers employed in the diagnosis of kidney diseases. BUN and SCr levels may be indicators of acute tubular necrosis caused by PA toxicity [18]. In the current study, administration of 42.84 mg/kg PA orally caused a significant rise in BUN concentrations and SCr level. These results were in accordance with Dogukan Canayakina which reported that PA administration altered serum urea and creatinine levels, indicating nephrotoxicity [7].

Also, it is consistent with other studies after oral or IP administration of PA which reported that BUN and creatinine levels of mice treated with PA was higher than the corresponding normal values [16, 19].

Von et al. also reported that renal insufficiency was defined as elevated SCr of more than double of the normal range and renal insufficiency is less common than liver failure in PA overdose but renal tubular damage occurs even in the absence of hepatotoxicity. Data published on this topic are rare consisting mostly of case reports or reports in a small number of patients. At present, a larger number of patients with renal insufficiency associated with acetaminophen overdose should be analyzed using a multicenter approach [20].

Elevation in the levels of urea and creatinine, noticed in our study could be explained by the presence of strong correlation between nephrotoxicity and oxidative stress. The elevated H_2O_2 and O_2- production alters the filtration surface area and modifies the filtration coefficient; both factors could decrease the glomerular filtration leading to accumulation of urea and creatinine in the blood [21,22].

In contrary, Ucar et al, reported that there is no difference in BUN level after treated with PA, PA-induced renal injury was not consistent with SCr and urea levels. These results may be due to lower doses of PA used [23].

Zyoud et al, demonstrate that serum acetaminophen concentration is associated with a reduction in serum potassium concentration and an elevation of SCr concentration. But it is reported that the mean SCr changes were significantly different between the patients who had PA concentrations above the possible toxicity treatment line versus patients who had PA concentrations below the possible toxicity treatment line, also they reported that a dose-dependent effect on BUN concentration after acetaminophen over-dose is absent [24].

Nandi et al, also reported that Percentage of plasma urea, creatinine levels were increased significantly in group that received paracetamol overdose compared to control groups and when received PA at therapeutic dose, the antioxidant enzymes GSH content in the kidney tissues were decreased significantly [25].

4. Conclusion

Paracetamol when used within therapeutic dose range could lead to acute renal impairment in rats, so further researches regarding the possible combination of PA with other substances that could reverse these effects are recommended.

Conflict of Interest

The authors declare that they have no conflict of interest.

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