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The Effects of Methionine on Paracetamol Induce Live Injury – Hepatomegaly- (Animal Study)

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Abstract
This study which was done for a total (45) mice, over a time of 30 days, reflects that paracetamol overdoses causing hepatic enlargement with high significant results (P<0.0001), although combined together with Methionine and by the same intra-gastric route of administration, with no any hepatoprotective effectiveness of Methionine, that there is no significant results (P=0.1566).Also this study reflects; that there were no any effect of Methionine on the ratio of the liver wt. / body wt. of the mice, in which the (P=0.1668 "no significant results), against paracetamol over-doses induce hepatomegaly, while paracetamol was highly significant (P=0.0001) on this ratio, when compared with control group.
Key words: Paracetamol, Methionine, Over-dose, Hepatomegaly (enlargement of the liver).

Introduction

Acetaminophen, also known as paracetamol, is a widely used over the counter analgesic and antipyretic agent (1). It is commonly used for the relief of fever, headache and other minor aches and pains. It is a major ingredient in numerous cold and flu remedies (2). Although, it is generally safe for human use at recommended doses, acute overdoses are often seen when acetaminophen is consumed above 1000 mg per single dose and above 4000 mg per day for adults (3), potentially fatal liver damage, and in rare cases, a normal dose can do the same damage in normal individuals. The risk is however heightened by alcohol consumption (2). Paracetamol toxicity is the foremost cause of acute liver failure in the Western world, and accounts for most drug overdoses in the United States, the United Kingdom, Australia and New Zealand (4).

Paracetamol is derived from coal tar, and is part of the class of drugs known as “aniline analgesics”; it is the only one of such drugs still in use today (5). It is the active metabolite of phenacetin. It is not considered to be carcinogenic at therapeutic doses (6). The words acetaminophen and paracetamol both come from the chemical names for the compound: para acetylaminophenol and N-acetyl-para-aminophenol. In some contexts, it is simply abbreviated as APAP, for *N*-acetyl-para-aminophenol (1).

In the late 1960s, clinicians recognized that acute acetaminophen overdose caused a dose-related liver injury and that without treatment many patients die(7). Studies in animals described the metabolism of acetaminophen to NAPQI and showed that as long as hepatic glutathione was present, toxic effects could be prevented(8). Soon there were reports that methionine18 and cysteamine19 (two medications known to restore hepatic glutathione) could prevent acetaminophen-induced hepatic injury. Use of these agents resulted in dramatic increases in survival, but the side effects (flushing, vomiting, and “misery” associated with these therapies led researchers to seek alternative treatment(7).

Methionine is a protein-based amino acid and lipotropic compound that helps with metabolism and breaks down fat. It can also help with chelation, which is the removal of heavy metals from the body to ensure that the liver, kidneys, and bladder remain healthy. This amino acid preserves artery function and maintains healthy nails, hair, and skin. Additionally, it is essential for muscle growth and energy (5).

The most common medical use of this amino acid is as a preventative treatment for liver damage caused by acetaminophen poisoning. Acetaminophen is typically found in prescription and over-the-counter pain relievers. Taking too much can cause serious liver damage. Medical care staff usually administer Methionine orally or intravenously within 10 hours of an overdose in order to help prevent liver damage(8).

A single high per oral dose of N-acetyl-DL-Methionine (359.5 mg/kg) was administered to Bom:NMRI male mice using methylcellulose as a drug vehicle. The administration of a single high per oral dose of N-acetyl-DL-Methionine (359.5 mg/kg) to Bom:NMRI male mice caused an inhibition of the hepatic glutathione decrease compared to a control group treated with methylcellulose only. N-acetyl-DL-Methionine caused a reduction and time delay of the hepatic glutathione decrease found in the group treated with methylcellulose only. There was no observed cellular damage of the liver or kidneys assessed histologically or by plasma ALAT after dosing with a mixture of N-acetyl-DL-Methionine(8).

Larger trials, or trials in other clinical settings, have not been performed. For example, there are no systematic studies evaluating the usefulness of Methionine and/or acetylcysteine for patients who have hepatic injury but not hepatic failure. Nonetheless, the efficacy and apparent safety of this agent, as demonstrated in the two small studies(9,10) have lead to widespread use of Methionine and/or acetylcysteine therapy in almost all cases of acetaminophen-induced liver injury. A Harrison PM 1991 review of the available data concluded that acetylcysteine “should be given to patients with overdose” but acknowledged that the quality of the evidence is limited and may be superior than Methionine(12).

Materials and methods:

A-Establishment of mice model:

We were able to visualized a model in "Albino white mice", for induction of liver injury by oral administration of the drugs (paracetamol or Methionine) by using special gastric needle tube, in which the dose of paracetamol which are used is 225mg/kg/body weight/24hrs and 225.5mg /kg/body weight for 24hrs for Methionine(8.9.11), as a solution for 30 days. These doses was selected because Paracetamol can produce liver injury without moribund state, or result in any mortalities that are observed with larger or lesser doses of paracetamol(9). While the doses of Methionine are selected according to safety of this agent when used together with Paracetamol(8,9,11).

B. Preparation of laboratory animals for in vivo studies:-

Experiment was carried on "45 Albino white mice". The of their body weights around "13.14-22.18gm, in which these mice maintained on special diet.

These animals divided into "3 groups" of "15 mouse" for each group.

The first group were treated with225mg/kg body weight/24hrs of Paracetamol(11).

The second group were treated with 225 mg/kg body weight/24hrs of Paracetamol, together with 225.5mg/kg/body weight for 24hrs Methionine in alternative dosing(8).

The third group was the control group, were on tap water(control group).

C. Preparation of the liver:-

After 30 days, all animals were killed by the way of decapitation, after weighting each mouse before killing. The total livers together with their gall bladders were exposed and then excised from each animal, and weighed by electronic device "Mettler, H.K. 160 Switzerland". Matching were written for each animal, for compare(13).

Results:

1- ***The effects of Paracetamol over doses together with Methionine on the weight of the animal.***

The mean ± SD of the weight of the animals were presented in table(1&2 also),in which the weight of the animals which were treated by both high doses of paracetamol and 225.5mg/kg/body wt of Methionine were high in some animals (mean 18.539 ± SD 1.079) (no=15).

This means that the alteration in weight of the animals which were treated by both drugs was not significant (P=0.9393) These data were presented in table(3) and in graph (No.1).

2- - ***The effects of Paracetamol over doses together with Methionine on the weight of the livers of the mice:***

It was found that the weight of the livers of the mice which were treated with both high doses of paracetamol, with Methionine were not affected (P=0.1566), that the doses which were selected and given to the animals , which do not exceeded the fatal doses of Paracetamol with at least the suitable doses of Methionine were not affected. These are visualized in graphic pathways (Side–by–side histograms No 2),

3- ***The effects of Paracetamol over doses together with Methionine*** **on ratio (the weight of the liver/weight of the animal×100):**

The mean and the SD of these ratios were tabulated in(table 1,2 and 3) and in graph 3, in which there was no affected results for Methionine to avoid liver enlargement due to Paracetamol overdoses P=0.1668 for Methionine, while P value for Paracetamol over doses in this ratios <0.0001.

Discussion:

Paracetamol (acetaminophen), is one of the most using drug for relief mild-moderate pain with some injuries to different organs of the body when given in high doses(14).In which Paracetamol can cause hepatomegaly in overdoses(15).

In this study, we found that there was no significant results between Paracetamol and Methionine on the body weight when they were given together to mice, that P=0.9398 for Methionine which is not significant result, this is discussed by" Prescott LF, Sutherland GR, Park J" and also by "Prescott LF, Newton RW, Swainson CP et al", that there is some degrees of effectiveness of Methionine on Paracetamol over dose on liver, with no any other benefit on other parts of body(18,19), while P=0.5332 for Paracetamol on body mice, which is not significant, this result is excepted, that over dose of Paracetamol can cause potentially fatal kidney damage brain and liver damage, and in rare individuals may affect the total body health and weight(16,17).

This study also reflect that the combination of Methionine in selective dose with Paracetamol overdose, do not prevent hepatomegaly induced by Paracetamol overdose, which were not significant P=1566.

So Paracetamol overdose caused hepatomegaly although it had been combined with Methionine with high significant results P<0.000I, which is in agreement with "Prescott LF, Matthew H" that Oral administration of paracetamol in graded doses (250, 500 and 1000 mg/kg, once orally) damaged the liver of rats after 48 hrs, and the severity and extent of liver damage appeared to be dose dependent, in which Methionine may not act in some of these overdoses as antidote for hepatotoxic induced by paracetamol overdoses, that hepatomegaly developed in more than 95% of rates treated by Methionine and gradual doses of paracetamol(20).

In general the ratio of the liver weight of these mice/body weight reflects that the administration of both

Methionine in selective suitable dose together with high dose of paracetamol did not affected by this combination, in which paracetamol over doses was highly significant on live damage (hepatomegaly), p<0.0001, while Methionine had no any affect on the ratio, which is not significant P=0.1668, this means that this study reflects that there were no role (no affect) of Methionine on paracetamol over dosages induced hepatomegaly which is in agreement with" Prescott LF, Park J, Ballantyne A et al" and "Prescott LF, Illingworth RN et al", in which that administration of intravenous N-acetylcysteine can prevent hepatotoxicity more than Methionine, and also in agreement with that acetylcysteine can be used safely in oral rout to avoid liver damage due to Acetaminophen over doses in multiple cases in comparison with Methionine and other hepato-protective agents(21&22).

Tables

Table (1): Weight of the animals and the livers (in grams) for control groups:

No.	Weight of animal in (grams)	Weight of the liver in (grams)	Ratio*
1	21.47	1.24	5.775
2	21.35	0.81	3.792
3	19.65	0.78	3.969
4	18.27	0.83	4.448
5	18.66	0.68	3.644
6	21.30	0.90	4.225
7	13.14	0.87	5.910
8	14.72	0.72	4.736
9	15.20	0.74	4.868
10	20.17	0.86	4.263
11	17.17	0.17	0.463
12	22.18	0.63	2.840
13	20.40	0.80	3.919
14	18.28	0.61	3.336
15	15.23	0.72	4.727
ẍ±SD	18.48±2.739	0.824±0.170	0.795±0.795

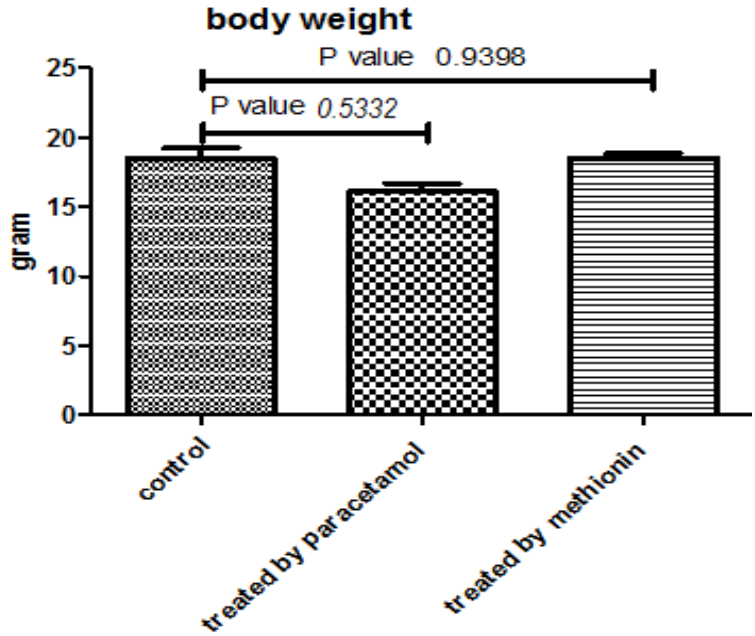
***Ratio = The weight of the liver/ the weight of the animal ×100**

Table (2) the weight of the animal and the weight of their livers in (grams) for those which were treated by high doses of Paracetamol:

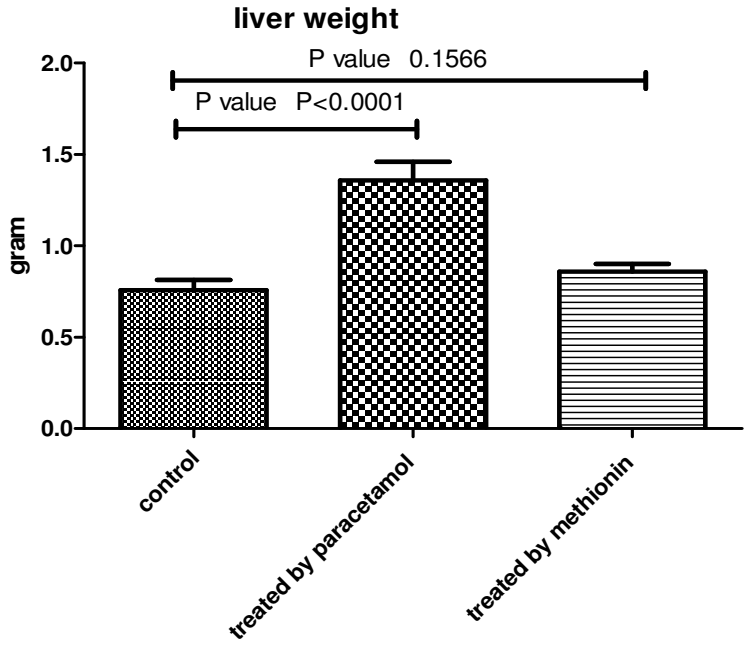
No.	Weight of animal in (grams)	Weight the liver in (gms)	Ratio
1	**13.80**	**1.16**	**8.405**
2	**17.70**	**1.72**	**9.717**
3	**19.42**	**1.73**	**8.908**
4	**13.17**	**1.13**	**8.580**
5	**17.28**	**0.86**	**4.976**
6	**14.17**	**1.71**	**8.256**
7	**14.26**	**1.13**	**7.924**
8	**19.30**	**0.90**	**4.663**
9	**14.17**	**0.72**	**5.081**
10	**16.50**	**1.15**	**6.969**
11	**19.00**	**1.92**	**10.105**
12	**15.17**	**1.84**	**12.121**
13	**13.80**	**1.17**	**8.883**
14	**14.68**	**1.54**	**10.490**
15	**19.11**	**1.70**	**8.895**
ẍ±SD	**16.596±2.4.409**	**1.358±0.381**	**8.321±2.253**

Table (3) the weight of the animals and their livers (in grams), for those which were treated with both Paracetamol and Methionine:

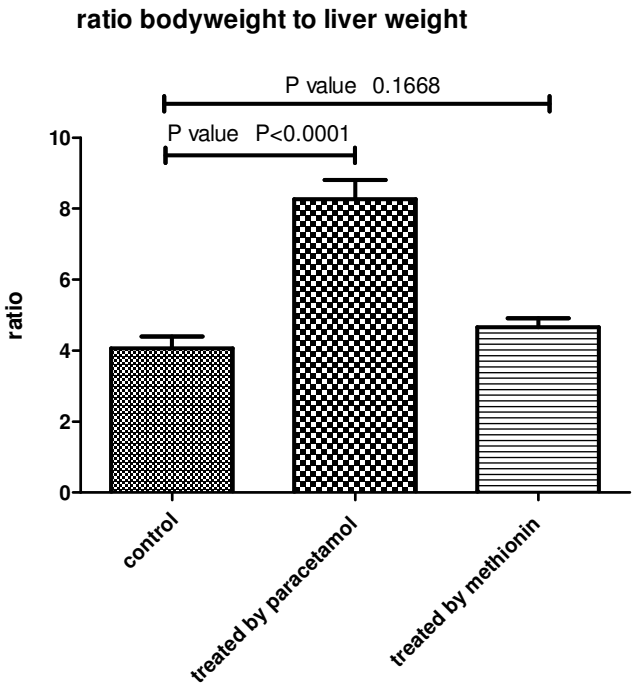
No.	Weight of the mice in(gms)	Weight the liver in (gms)	Ratio
1	17.3	0.85	4.911
2	18.8	0.79	4.212
3	20.6	0.73	3.522
4	17.8	0.90	5.019
5	19.3	0.89	4.681
6	19.5	O.73	3.741
7	18	0.90	5.071
8	17.29	0.90	5.228
9	17.25	1.25	7.238
10	20.5	0.95	4.616
11	18.85	1.11	5.878
12	18.2	0.72	3.824
13	17.8	0.80	4.471
14	17.6	0.67	3.811
15	19.3	0.70	3.6332
ẍ±SD	18.539±1.079	0.859±0.1553	4.622±1.476



No1: Side by side histogram of the affect of Paracetamol overdoses with Methionine on the weight of the mice.



No2: Side by side histogram shows the effect of both Paracetamol over doses and Methionine on the weight of livers.



No3: Side by side histogram shows the ratio body weight to weigh of the liver

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