[***The Indian Practitioner*** (1977): (XXX), November, 479]

# Paracetamol-induced Hepatotoxicity and the Protective Effect of Liv.52

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Paracetamol is very commonly used antipyretic analgesic. Over-dosage of paracetamol has been reported to cause acute centrilobular hepatic necrosis and is now one of the common causes of hepatic failure in Britain. Liv.52, an indigenous preparation has been shown to have a protective effect against many hepatotoxic agents like carbon tetrachloride and allyl alcohol which are only of toxicological importance. The following study was undertaken to ascertain if Liv.52 has a protective effect against paracetamol-induced liver damage.

## MATERIALS AND METHODS

(A) Thirty six male albino rats weighing between 100 g and 140 g were divided into 3 equal groups. The animals in Group I received paracetamol orally once a day for 7 days. The animals in group II received paracetamol as in group I but received in addition Liv.52 orally, half an hour before every administration of paracetamol. The animals in group III received normal saline orally, once a day for 7 days. After seven days, half of the surviving animals were killed and in each case, the liver, both the kidneys and both the adrenal glands were removed and weighed and their weight expressed and weighed and their weight expressed as g/100 g body-weight in the case of liver and kidneys and as mg/100 g body weight in the case of adrenal glands. The remaining animals continued the treatments as before for another seven days and all surviving animals were killed and their liver, kidneys and adrenal glands were removed and weighed. The livers were also examined histologically.

(B) Eighteen rabbits of either sex weighing 2 kg to 3 kg were divided into 3 equal groups. All rabbits were acclimatized to rectal probes for recording their temperature by a thermocouple for a period of 6 hours. All rabbits received Typhoid para A and para B vaccine intravenously in the dose of 0.1 mg/kg on the day of the study. In addition group I received normal saline orally 45 minutes and 75 minutes after the intravenous injection, group II received normal saline at 45 minutes and paracetamol at 75 minutes and group III received Liv.52 at 45 minutes and paracetamol at 75 minutes. Temperatures were recorded every 15 minutes for four hours.

## DRUGS

*Paracetamol*: A commercially available syrup of paracetamol containing 25 mg per ml was used. The dose for rats was 1 g per kg of paracetamol and for rabbits, 150 mg per kg. Administration was orally by stomach tube in all cases.

*Liv.52*: A market sample of Liv.52 syrup was used. The dose was 1 ml per kg orally for both rats and rabbits.

## RESULTS

Table 1 shows the effect of paracetamol alone and in combination with Liv.52, on the body weight and mortality in rats. Seven days' treatment did not have any effect on weight of animals but one rat out of 12 died in the paracetamol group. After 15 days' treatment, mean weight in the paracetamol group was significantly lower and two out of 5 animals died in this group. There was no change in weight and no mortality in paracetamol + Liv.52 group.

**Table 1:** Effect of paracetamol and paracetamol + Liv.52 on body weight (g) and mortality in rats

| Group | Mean Initial b. wt. | Mean b. wt. at 7 days | Mean mortality between 7 days | Mean b. wt. at 15 days | Mean mortality between 7-14 days |
|---|---|---|---|---|---|
| Control | 129 ± 4.2 | 134 ± 4.05 | 0/12 | 190 ± 10.05 | 0/6 |
| Paracetamol (1 g/kg) | 126 ± 4.5 | 126 ± 6.05 | 1/12 | 128 ± 16.50* | 2/5 |
| Paracetamol (1 g/kg) + Liv.52 (1 ml/100 g) | 141 ± 4.05 | 145 ± 4.30 | 0.12 | 182 ± 6.50 | 0/6 |

*$p<0.001$

Table 2 shows the weights of liver, kidney and adrenals at 7 days and 14 days. Paracetamol caused a significant increase in the weights of liver and kidneys both at 7 days and 14 days. Adrenal weights showed a significant increase in this group at 7 days but adrenal weights were not significantly different from controls at 14 days. With Liv.52 and paracetamol, there was a smaller but significant increase in the liver weights at 7 days but at 14 days the liver weight was similar to controls. Kidney weights did not show any appreciable change from control at either 7 days or 14 days. Adrenal weights at day 7 and 14 were not different from the controls in the group treated with paracetamol and Liv.52.

**Table 2:** Showing mean weight in a g of liver, both kidneys and in mg of both adrenal glands, expressed per 100 g weight of the rat

| Group | Days 7 | | | Days 14 | | |
|---|---|---|---|---|---|---|
| | Liver | Kidneys | Adrenals | Liver | Kidneys | Adrenals |
| Control | 3.34 ± 0.16 | 30.76 ± 0.03 | 12.75 ± 0.02 | 3.95 ± 0.25 | 0.72 ± 0.10 | 9.4 ± 1.20 |
| Paracetamol (1 g/kg) | 5.70 ± 0.25* | 0.92 ± 0.05* | 18.59 ± 1.60$^{\#}$ | 4.96 ± 0.25$^{\$}$ | 0.91 ± 0.05$^{\#}$ | 11.45 ± 0.65 |
| Paracetamol (1 g/kg) + Liv.52 (1 ml/100 g) | 4.32 ± 0.15$^{\#}$ | 0.81 ± 0.018 | 11.65 ± 0.70 | 3.60 ± 0.26 | 0.74 ± 0.05 | 9.60 ± 0.85 |

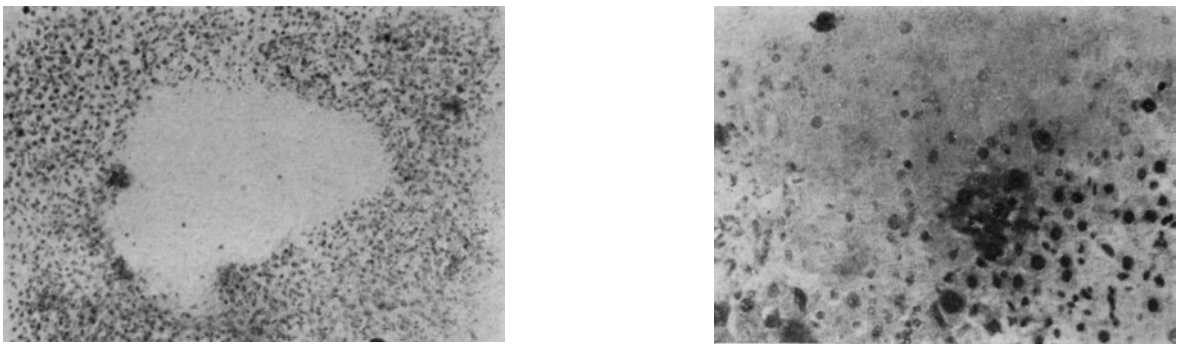
*$p<0.001$, $^{\#}p<0.01$ and $^{\$}p<0.05$ compared to control in the same column

Table 3 shows the effect of paracetamol and paracetamol + Liv.52 on T-AB vaccine induced pyrexia in rabbits. The mean initial temperatures were not significantly different in the groups. Also the mean maximum temperatures attained after the vaccine injection were not significantly different between the groups, and all groups showed a significant rise in temperature. The mean temperature at 2½ hours after vaccine injection, i.e. 75 minutes after paracetamol administration was significantly lower in the group treated with paracetamol as well as in the group treated with Liv.52 + paracetamol as compared to the control group, which received normal saline only. This indicates similar antipyretic activity of paracetamol in the two groups.

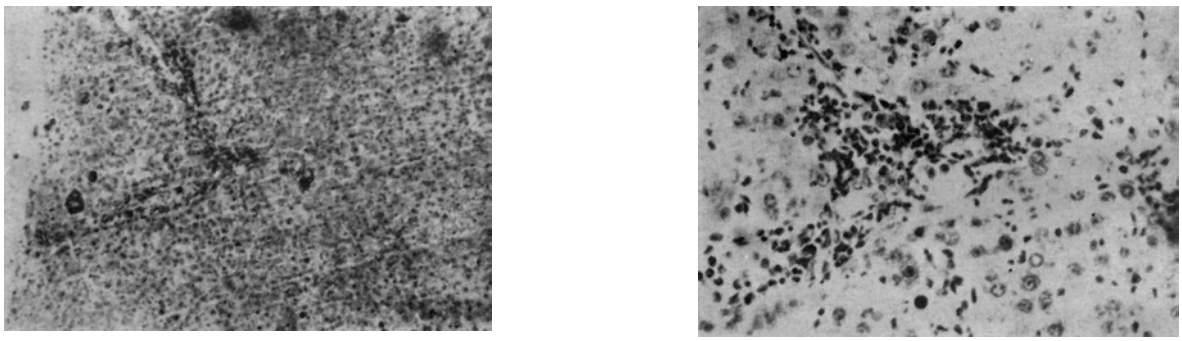
| **Table 3:** Pyrexia induced in rabbits by T.A.B. vaccine and the effect of paracetamol and paracetamol + Liv.52 | | | | |
|---|---|---|---|---|
| Group | Mean initial temperature | Mean maximum temperature attained upto 90 minutes after T.A.B. injection | Mean temperature at 2½ hours after T.A.B. injection | Mean fall of temperature by paracetamol |
| Control | 39.1 ± 0.035 | 40.4 ± 0.075 | 40.1 ± 0.11 | 0.3 ± 0.07 |
| Paracetamol (150 mg/kg) | 39.4 ± 0.06 | 40.3 ± 0.14 | 39.6 ± 0.08$^{\$}$ | 0.7 ± 0.11* |
| Paracetamol (150 mg/kg) + Liv.52 (1 ml/100 g) | 39.4 ± 0.96 | 40.7 ± 0.09 | 39.9 ± 0.08$^{\$}$ | 0.7 ± 0.09$^{\#}$ |
| *$p$<0.5, $^{\#}p$<0.01 and $^{\$}p$<0.001 compared to control in the same column | | | | |

Table 4 shows the histological changes in livers in the three groups. The paracetamol group showed large increase in weight and signs of central necrosis and bile stasis.

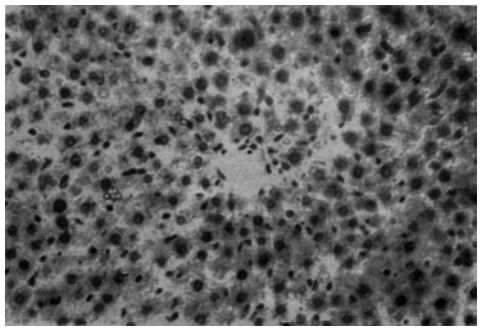
| **Table 4:** Changes in livers in control and paracetamol and Liv.52 + paracetamol treated rate | | | | | | |
|---|---|---|---|---|---|---|
| Group | Days 7 | | | Days 14 | | |
| | Weight | Centrilobular necrosis | Bile stasis | Weight | Centrilobular necrosis | Bile stasis |
| Control | 3.34 ± 0.16 | Absent | Absent | 3.95 ± 0.25 | Absent | Absent |
| Paracetamol (1 g/kg) | 5.70 ± 0.25* | ++ | + | 4.96 ± 0.25 | +++ | + |
| Paracetamol (1 g/kg) + Liv.52 (1 ml/100 g) | 4.32 ± 0.15$^{\#}$ | + | – | 3.60 ± 0.26 | + | – |



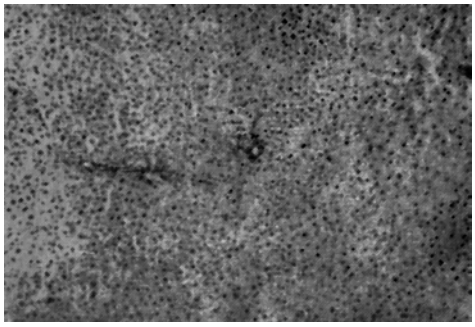
Liver from rats treated with paracetamol showing necrosis and round cell infiltration in the surrounding area

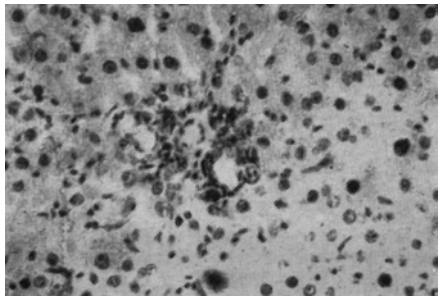


Liver from rats treated with paracetamol. Many cells without nuclei indicating necrotic process at work. Severe round cell infiltration.



Liver from control rat





Liver from paracetamol + Liv.52 treated rats shows normal liver with slightly increased round cells near the canaliculi

**DISCUSSION**

Paracetamol has been reported to cause liver damage in humans, which could be eventually fatal. In our experiments paracetamol in large doses caused liver damage in rats as judged by histological examination of liver and mortality recorded in the group treated with paracetamol alone. The paracetamol-treated groups also showed an increase in adrenal gland weight at 7 days, which returned to near normal at 15 days. Concomitant administration of Liv.52 with paracetamol seemed to protect the animals against the toxic effect of paracetamol as judged by lack of mortality, no loss of body weight, no increase in adrenal weight at 7 days and the condition of livers on histological examination.

The increase in adrenal gland weight at 7 days in paracetamol treated group may be the result of stress caused by liver damage. Prolonged stress causes failure of compensation, which might explain the return to near normal of adrenal gland weights and further increase in mortality between 7 and 14 days. In these experiments Liv.52 was given 30 minutes before administration of paracetamol. A possibility here is that Liv.52 interfered with the absorption of paracetamol. But in experiments in rabbits under similar conditions the antipyretic effect of paracetamol was not affected. This indicates that Liv.52 does not grossly interfere with the absorption of paracetamol.

The present study suggests that Liv.52 protects rats against hepatic damage caused by high doses of paracetamol.

**SUMMARY**

Large doses of paracetamol have been reported to produce toxic effects on the liver in human patients. In the present study in rats, paracetamol in doses of 1 g/kg produced hepatotoxic effects

and also stress reaction as shown by the increase in adrenal gland weights. The simultaneous administration of Liv.52 minimised these toxic effects of paracetamol. From the study on rabbits, it is evident that Liv.52 did into interfere with the antipyretic action of paracetamol thereby indicating that Liv.52 does not grossly interfere with the intestinal absorption of paracetamol.

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