VITAMIN E PROTECTION OF THE LIVER FROM PARACETAMOL IN THE RAT

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(Received 21 May 1974)

SUMMARY
1. Control, vitamin E-deficient, vitamin E-supplemented (deficient with added ‘normal’ intake) and vitamin E-treated rats were given paracetamol at a dose of 25.5 mmol (4 g)/kg body weight. Control rats were also given paracetamol with or without simultaneous vitamin E.
2. Plasma aspartate aminotransferase and alanine aminotransferase activities increased to very high values (mean 2842 and 1241 i.u./l respectively) in the control group, and even higher (mean 8220 and 2320 i.u./l respectively) in the vitamin E-deficient group.
3. In the vitamin E-supplemented group the rises in activity were similar but rather less than in the control group (mean 2417 and 815 i.u./l) and in the vitamin E-treated group only very small rises (mean 177 and 98 i.u./l) were seen.
4. Histological evidence of hepatic necrosis correlated closely with plasma enzyme activities.
5. It appears that paracetamol-induced hepatic necrosis is potentiated in vitamin E deficiency and reduced by prior treatment with α-tocopherol.
6. Vitamin E administered simultaneously with paracetamol at 12.8 or 19.2 mmol/kg also greatly reduced the expected rise in serum enzyme activities.
7. These observations may shed some light on the mechanism of paracetamol-induced hepatic necrosis, and may form a basis for preventing or reducing this lesion in man.

Key words: paracetamol, hepatotoxicity, antioxidant protection.

Large single doses of paracetamol in man may cause massive hepatic necrosis. Provided that death does not occur during the acute phase of the lesion complete recovery seems to follow (Clark, Thompson, Borirakechanyavat, Widdop, Davidson, Goulding & Williams, 1973; Prescott, Wright, Roscoe & Brown, 1971). Antioxidants provide some protection against the

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hepatotoxic effects of certain substances which cause a similar hepatic necrosis, e.g. carbon tetrachloride (Gallagher, 1962; Di Luzio & Costales, 1965). We have therefore investigated the possibility that the antioxidant α-tocopherol may provide some protection against the hepatotoxic effect of paracetamol, and that the findings might shed some light on the mechanism of the hepatotoxicity produced by paracetamol.

MATERIALS AND METHODS

Female Tuck-Wistar rats, weighing about 200 g, were used for all experiments.

In the first experiment twelve rats were housed under identical conditions. Six were fed a synthetic diet deficient in vitamin E (Kelleher, Davies, Smith, Walker & Losowsky, 1972) for 16 weeks. The remaining six rats were given the same diet but supplemented with 0.21 mmol (100 mg) of α-tocopherol acetate/kg of diet, which was intended to restore the intake to normal, for 16 weeks. Both diets were readily accepted by the animals, the consumption of each approximating to 20 g per rat/day. Each animal then received paracetamol, 25.5 mmol (4 g)/kg body weight, in a suspension [1.9 mol/l (300 mg/ml)] with 0.2% tragacanth by stomach tube without anaesthesia. The animals were starved for 16 h from 18.00 hours on the day before paracetamol administration at 09.00 hours.

In the second experiment thirteen rats were housed under identical conditions and fed a standard pelleted diet (diet 41B, Oxoid Ltd) containing 0.079 mmol (37.4 mg) of vitamin E/kg. Six rats were given 0.105 mmol (50 mg) of α-tocopherol acetate by stomach tube at 09.00 hours each day for 8 days before the experiment. The six vitamin E-treated animals, along with the remaining seven control rats, were then each given paracetamol at a dose of 25.5 mmol (4 g)/kg body weight, by stomach tube without anaesthesia, at 09.00 hours after overnight starvation from 18.00 hours the previous day. The last dose of α-tocopherol acetate was given 24 h previously.

In the third experiment groups of rats (twelve in most instances) fed on the standard pelleted diet were starved overnight from 18.00 hours and dosed by stomach tube without anaesthesia at 09.00 hours. Paracetamol was given at three doses, 25.5 mmol (4 g), 19.2 mmol (3 g) and 12.8 mmol (2 g)/kg body weight, with and without added α-tocopherol acetate, to six separate groups of rats. The paracetamol was prepared as a suspension (1.9 mol/l) in 8% Cremophor E.L. with or without α-tocopherol acetate at a concentration of 0.21 mol/l.

In each experiment, at 1 h after the paracetamol, 1 ml of blood was withdrawn from the tail vein for paracetamol, aspartate aminotransferase (EC 2.6.1.1; ASAT), alanine aminotransferase (EC 2.6.1.2; ALAT), vitamin E and erythrocyte haemolysis estimations. The enzyme activities at 1 h were not influenced by paracetamol and were used as control values for each rat. For all rats used in these experiments the mean 1 h enzyme activities were 129 (± 64 SD) i.u./l for ASAT and 29.4 (± 10.5 SD) i.u./l for ALAT.

Samples of blood for paracetamol and enzyme estimations were also taken immediately before killing the animals by cardiac puncture under light ether anaesthesia at 24 h. The experiments were terminated at 24 h because our preliminary studies showed this to be the usual time of maximum elevation of enzyme activity in the rat.

Free paracetamol was determined in 0.1 ml of whole blood by gas-liquid chromatography as described by Prescott (1971). Serum ASAT and ALAT were determined by the Henry modification (Henry, Chiamori, Golub & Berkman, 1960) of the methods of Karmen (1955)
and Wroblewski & La Due (1956) respectively. The volumes and concentrations of reagents used were as follows. For ASAT, 3 ml of phosphate buffer, pH 7.4, containing 2-oxoglutarate 30 μmol, L-aspartic acid 140 μmol, NADH 0.5 μmol, malic dehydrogenase 0.5 i.u. and 30 μl of serum. For ALAT, L-alanine 30 μmol, and lactic dehydrogenase 0.5 i.u. were substituted for L-aspartic acid and malic dehydrogenase respectively. Assays were carried out at 37°C, and the results expressed as international units (i.u.)/l (i.u. are defined as μmol of substrate converted/min). The complete Eskalab system of reagents, equipment and spectrophotometer (Smith Kline Instrument Co. Ltd, Welwyn Garden City, Herts, U.K.) was used throughout. Plasma α-tocopherol was determined by the spectrofluorimetric micro-method of Hansen & Warwick (1966). The susceptibility of erythrocytes to haemolysis by hydrogen peroxide in vitro was determined by the Horwitt (1962) modification of the method of Rose & György (1952).

After killing each animal the liver was removed immediately and a series of cuts were made into the organ to allow adequate penetration of the 10% buffered formol–saline in which it was immersed. After fixation the lobes were separated and the liver was cut into thin (2–3 mm) slices. Alternate slices were taken for histology, providing eight to sixteen ‘blocks’ of liver for each animal (mean = 10.7). Paraffin sections (5 μm) were cut and stained with haematoxylin and eosin.

The sections were examined ‘blind’ and the amount of necrosis in each block was graded according to the following arbitrary scale:

Grade 0 = no evidence of coagulative necrosis, but including minimal single-cell necrosis, which occurred rarely.
Grade 1 = scattered small foci of centrilobular necrosis.
Grade 2 = most centrilobular areas show foci of necrosis.
Grade 3 = more severe necrosis affecting most centrilobular areas.
Grade 4 = confluent centrilobular and mid-zonal necrosis.
Grade 5 = massive necrosis with only a narrow periportal zone of surviving hepatocytes.

A mean grade was calculated for each animal.

RESULTS

First experiment

In the first experiment the vitamin E-deficient animals had a mean plasma vitamin E of 3.96 μmol ± 2.55 SD/1 (188 μg/100 ml), n = 6, which was significantly lower (P < 0.001) than that for the vitamin E-supplemented animals (15.58 μmol ± 2.48 SD/1 (740 μg/100 ml), n = 6). The animals in the vitamin E-deficient group all showed 100% erythrocyte haemolysis with hydrogen peroxide, whereas the erythrocytes from the supplemented group did not haemolysed.

The mean 1 h and 24 h blood paracetamol concentrations for the six supplemented animals (1.25 mmol ± 0.64 SD/1 and 1.40 mmol ± 1.01 SD/1 respectively) did not differ significantly (P > 0.2 and P > 0.8) from those of the deficient group (1.76 mmol ± 0.62 SD/1 and 1.50 mmol ± 0.67 SD/1 respectively).

The values of ASAT and ALAT at 1 h and 24 h in the vitamin E-deficient and vitamin E-supplemented animals are shown in Fig. 1, and the individual enzyme values at 24 h in Table 1. All rats in these groups had higher values for ASAT and ALAT at 24 h than at 1 h. In the vitamin E-deficient group, five of the six animals had values for ASAT at 24 h which were very much higher than the highest value for the supplemented group. At 24 h five of the six vitamin
**TABLE 1. Serum aspartate aminotransferase (ASAT) and alanine aminotransferase (ALAT) activities and grade of liver necrosis in rats 24 h after an oral dose of paracetamol (25.5 mmol/kg)**

Grades of necrosis are identified in the Materials and Methods section. * Significantly greater (P<0.05) than the corresponding means for supplemented group and for vitamin E-treated group. ** Significantly greater (P<0.05) than corresponding means for vitamin E-treated group.

<table>
<thead>
<tr>
<th>Rat no.</th>
<th>Vitamin E-deficient rats</th>
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<th>Vitamin E-treated rats</th>
<th>Control rats</th>
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<td>ALAT (i.u./l)</td>
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![Graph](image)

Fig. 1. Plasma concentration of ASAT and ALAT 1 and 24 h after dosage with paracetamol [25.5 mmol (4 g)/kg] in (a) six vitamin E-supplemented and (b) six vitamin E-deficient animals.

E-deficient rats had values of ALAT exceeding 1000 i.u./l whereas only two of the vitamin E-supplemented group exceeded this value.

**Second experiment**

In the second experiment the mean plasma vitamin E for the control animals (8.34 μmol ± 1.0 SD/1 (396 μg/100 ml), n = 7) was significantly lower (P < 0.001) than that for the vitamin E-treated group (26.10 μmol ± 11.9 SD/1, n = 6). The mean 1 h and 24 h concentrations of paracetamol in the control animals (1.32 mmol ± 0.62 SD/l, n = 7, and 0.45 mmol ± 0.24 SD/l, n = 7 respectively) did not differ significantly (P > 0.3, and P > 0.8) from those in the treated animals (1.01 mmol ± 0.38 SD/l, n = 6, and 0.48 mmol ± 0.26 SD/l, n = 6 respectively). Although the 1 h concentrations of paracetamol for rats in this second experiment did not differ significantly from the 1 h values in the first experiment, the 24 h values (mean 0.46 mmol ± 0.27 SD/l, n = 13) were significantly lower in the rats of this second experiment compared with the 24 h values (mean 1.45 mmol ± 0.82 SD/1, n = 12) in the first experiment (P < 0.005).

The plasma ASAT and ALAT activities in these rats are shown in Fig. 2, and the individual enzyme activities at 24 h in Table 1. In the control group (those fed on a standard diet) all rats showed a rise in both ASAT and ALAT activities at 24 h compared with the 1 h value. For ASAT five out of seven rats had 24 h values of greater than 1000 i.u./l. Two rats showed much smaller increases in ASAT activity (134–464 i.u./l and 153–300 i.u./l). For the group of rats which received daily doses of vitamin E before paracetamol the rises in enzyme activities were much smaller than for the control group. Only one rat showed substantial rises (87–475 i.u./l for ASAT and 58–365 i.u./l for ALAT) and even these were very small when compared with the rises found in the majority of rats in the control group.
Histology

Table 1 shows the severity of necrosis and the serum enzyme activities at 24 h in each animal and also the mean values ± SD for each group in both experiments. The vitamin E-deficient group, which showed the greatest mean increase in activity of each of the serum enzymes, also showed the most severe degree of necrosis. All animals within this group had severe necrosis affecting most centrilobular areas. The vitamin E-supplemented animals, which had a lesser increase in serum enzyme activities, also generally showed less severe necrosis, whereas the vitamin E-treated animals, which showed only very slight increases in serum enzyme activities, had no evidence of necrosis in three animals and only scattered small foci of centrilobular necrosis in the remaining three. In the control group two of the seven animals showed only a slight increase in serum enzyme activities and little if any histological evidence of necrosis, and the other five had large increases in serum enzyme activities and severe necrosis affecting most centrilobular areas.

There was a close correlation between the logarithm of serum enzyme activities at 24 h and the severity of necrosis at 24 h (r=0.922, P<0.001 and r=0.859, P<0.001 for ASAT and ALAT respectively).

Third experiment

The mean plasma concentration of paracetamol at 1 h in the group given 12.8 mmol/kg
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(0.91 mmol ± 0.33 SD/l, n = 24) is significantly less (P < 0.001) than either of the other two groups (mean 1.49 mmol ± 0.44 SD/l, n = 25 in the 19.2 mmol/kg group, and mean 1.70 mmol ± 0.76 SD/l, n = 24 in the 25.5 mmol/kg group). There was no significant difference (P > 0.15) between the mean paracetamol concentrations at 1 h in the latter two groups. The mean paracetamol concentration at 24 h in the 12.8 mmol/kg group (0.16 mmol ± 0.08 SD/l, n = 23) is significantly less (P < 0.01) than either of the other two groups (mean 0.42 mmol ± 0.29 SD/l, n = 22 in the 19.2 mmol/kg group, and mean 0.85 mmol ± 0.154 SD/l, n = 20 in the 25.5 mmol/kg group). The mean 24 h paracetamol concentration in the 19.2 mmol/kg group was significantly greater (P < 0.01) than in the 25.5 mmol/kg group.

Table 2. Serum aspartate aminotransferase (ASAT) and alanine aminotransferase (ALAT) activities in rats 24 h after oral doses of paracetamol with or without added α-tocopherol acetate

P values show significance of results for correspondingly dosed groups with (+) and without (−) added α-tocopherol acetate. Enzyme activities are in i.u./l.

<table>
<thead>
<tr>
<th>Rat no.</th>
<th>12.8 mmol of paracetamol/kg</th>
<th>19.2 mmol of paracetamol/kg</th>
<th>25.5 mmol of paracetamol/kg</th>
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<tr>
<td></td>
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<td>ALAT</td>
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</tr>
<tr>
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The plasma enzyme activities at 24 h for this experiment are shown in Table 2. As in the first two experiments, the enzyme responses at all doses of paracetamol were variable. At 12.8 mmol/kg in the absence of α-tocopherol ten out of twelve animals had ASAT activity greater than 1000 i.u./l whereas in the group given α-tocopherol only two out of ten rats had enzyme activities above this value. For ALAT three out of six rats without α-tocopherol had activities above 1000 i.u./l and none of ten rats given α-tocopherol had enzyme activities above this value. The mean ASAT and ALAT activities for the group not given α-tocopherol were significantly greater (P < 0.01) than in the group given α-tocopherol simultaneously.

At 19.2 mmol/kg six out of twelve rats not given α-tocopherol had ASAT activities above 2000 i.u./l, whereas only one out of thirteen rats given α-tocopherol had enzyme activities above
this value. For ALAT six out of twelve rats had enzyme activities above 1000 i.u./l, whereas only one out of thirteen in the group given α-tocopherol had values above this. The mean ASAT and ALAT activities for the group not given α-tocopherol were significantly greater ($P < 0.025$ and $P < 0.05$ respectively) than the means for the group given α-tocopherol simultaneously.

At 25.5 mmol/kg seven out of twelve rats not given α-tocopherol had ASAT activities above 2000 i.u./l whereas only two out of twelve in the group given α-tocopherol had enzyme activities above this. For ALAT seven out of twelve rats not given α-tocopherol had enzyme activities above 1000 i.u./l, whereas only one out of twelve rats in the group given α-tocopherol had values above this. At this dose, however, the mean ASAT and ALAT activities for the group not given α-tocopherol were not significantly greater ($P > 0.05$ and $P > 0.15$ respectively) than the mean for the group given α-tocopherol.

**DISCUSSION**

In man, self-poisoning from an overdose of paracetamol is becoming increasingly common and such patients may die from acute liver failure (Clark *et al.*, 1973). Histological examination of the liver in these patients shows extensive centrilobular necrosis such as occurs with single large doses of carbon tetrachloride both in man and the rat (Hashimoto, Glende & Recknagel, 1968; Cameron & Karunaratne, 1936).

We have shown that after paracetamol overdose in the rat histological findings correlate well with plasma enzyme evidence of liver necrosis both from group to group and from animal to animal within each group. There was variability in the response of individual animals to paracetamol, a finding in agreement with the experience of other workers both in experimental animals (Jollow, Mitchell, Potter, Davis, Gillette & Brodie, 1973) and in man (Prescott *et al.*, 1971).

Even among our control animals two out of seven showed little if any increase in serum enzyme activities after paracetamol and these two animals also had minimal necrosis. In all animals the serum enzyme activities at 24 h reflected well the severity of necrosis at that time.

Although the mean 1 h blood concentrations of paracetamol were similar in all groups, the mean 24 h values differed in the first two experiments. In the first experiment, in which the animals were maintained on a synthetic diet, the mean 24 h values were significantly greater than in the second experiment, in which the animals were fed on a standard pelleted diet. This suggests, perhaps, that some constituent of the diets may have induced alterations of the microsomal drug-metabolizing enzyme system but this suggestion can only be speculative. The half-life of blood paracetamol has been employed as a useful prognostic index in human subjects (Prescott *et al.*, 1971), but in these groups of rats the ultimate extent of necrosis bore no relationship to the plasma concentrations of paracetamol at 1 or 24 h.

The precise mechanism of paracetamol hepatotoxicity is not known. Microsomal enzyme induction with either 3-methylcholanthrene (Mitchell, Jollow, Potter, Davis, Gillette & Brodie, 1973a) or phenobarbitone (Mitchell *et al.*, 1973a; Walker, Kelleher, Dixon & Losowsky, 1973) potentiates the hepatotoxicity whereas inhibitors of the microsomal drug-metabolizing enzymes can prevent the liver injury (Mitchell *et al.*, 1973a). Further recent studies indicate that paracetamol hepatotoxicity may be mediated by a chemically reactive metabolite binding covalently with hepatic macromolecules (Jollow *et al.*, 1973a; Potter, Davis, Mitchell, Jollow, Gillette & Brodie, 1973). It is possible that the toxic metabolite responsible for such binding is the
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N-hydroxy derivative (Hinson, Mitchell & Jollow, 1974). Whatever its identity, however, the free metabolite produced by this minor pathway is under normal circumstances conjugated with glutathione: the mercapturate thus formed (Jollow, Thorgeirsson, Potter, Mitchell, Gillette & Brodie, 1973) is excreted in the urine along with the major paracetamol conjugates, the glucuronide and sulphate (Jagenburg, Nagy & Rödjer, 1968). After very high doses, the rate of formation of the toxic metabolite may exceed the availability of glutathione; the free metabolite would then become covalently bound to protein and cell injury ensue.

We have been impressed by the similarity between the hepatotoxic effects of paracetamol and carbon tetrachloride, not only on the basis of their analogous response to modification of microsomal enzyme function (Garner & McLean, 1969; Stenger, Miller & Williamson, 1970) but also on the basis of the parallel morphological changes seen at both light-microscopic (Dixon, Nimmo & Prescott, 1971) and ultrastructural (M.F. Dixon, B. Dixon, S. R. Aparicio & D. P. Loney, unpublished work) levels. Although the degree of fatty change induced by paracetamol is not as great as that produced by carbon tetrachloride, in the latter case the mechanism responsible for fatty change is thought to be different from that causing necrosis (Rees, 1964). Although the mechanism of the hepatotoxic effect of carbon tetrachloride is not clear, much work indicates that it may involve lipid peroxidation (Recknagel & Ghoshal, 1966). Part of the evidence for this is that antioxidants, including vitamin E, seem to provide some protection against the toxic effect. This mechanism of carbon tetrachloride hepatotoxicity has, however, been disputed by Green, Bunyan, Cawthorne & Diplock (1969), who concluded from a detailed study of vitamin E and hepatotoxic agents that no tangible evidence exists to support the lipid-peroxidation hypothesis, and suggest that the mode of action may be indirect and operate by several mechanisms including an effect on drug-processing enzymes (Cawthorne, Bunyan, Sennitt, Green & Grasso, 1970).

Judged by plasma ASAT and ALAT activities and by histological evidence, vitamin E-deficient rats are, on average, more susceptible to the hepatotoxic effect of paracetamol than rats given a standard diet or an adequate nutritional supplement. Rats given large doses of α-tocopherol for several days before the paracetamol, although showing similar plasma concentrations of paracetamol to the other groups showed very much smaller rises in plasma enzyme activities and little hepatic necrosis, providing a further similarity between paracetamol and carbon tetrachloride. α-Tocopherol, when administered simultaneously with the paracetamol, also protects against its hepatotoxic effect as judged by plasma ASAT and ALAT activities. This protection was not as effective at a very high paracetamol intake but this may be explained by insufficient α-tocopherol being administered or absorbed.

The protective action of α-tocopherol might suggest that the mechanism of paracetamol toxicity may perhaps be mediated by lipid peroxidation. However, it is also possible that a more specific biochemical function involving microsomal drug-metabolizing systems may be involved (Carpenter, 1972). It is noteworthy that glutathione, another potential antioxidant present in tissues, has been shown to reduce paracetamol hepatotoxicity in mice, perhaps by protecting nucleophilic protein groups from a toxic metabolite (Mitchell, Jollow, Potter, Gillette & Brodie, 1973b).

In man it seems likely that the hepatotoxic effect of paracetamol will in many cases have taken place by the time the patient reaches medical attention; nevertheless, animal experiments suggest that mortality might be reduced (Rosner, Romero-Ferret & Mottot, 1973; Dixon, Dixon & Aparicio, 1973), and a clinical trial of cysteamine has given promising results (Prescott,
Newton, Swainson, Wright, Forrest & Matthew, 1974). In our experiments protection was obtained either by prior treatment with α-tocopherol, or by simultaneous administration of α-tocopherol with the paracetamol. This evidence may form a basis for preventing or reducing the hepatotoxic effect of paracetamol in man. If α-tocopherol were incorporated into paracetamol tablets then its effect would be simultaneous with that of the paracetamol, the dose taken would be related to the amount of paracetamol taken, and it might be possible to incorporate sufficient to reduce or even prevent toxic effects to the liver.

ACKNOWLEDGMENTS

We are grateful to Miss E. Balodis for the preparation of the paracetamol suspension, to Mr D. Loney and Mrs S. Mitchell for the histological preparations, to Mrs D. Shillitoe and Mrs D. Chippindale for expert technical assistance and for financial support from the Medical Research Council, Sterling-Winthrop Group Ltd and the West Riding Medical Research Trust.

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