*Short communications*

# Immediate decrease by hydrocortisone of the plasma half-life of antipyrine

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Infusion of hydrocortisone in man caused an immediate shortening of the plasma half-life of antipyrine. There was no change in the 'apparent' volume of distribution of antipyrine and the plasma concentrations of hydrocortisone during the infusion remained within physiological limits. Similar changes in plasma half-lives of antipyrine were observed in the dog, but *in vitro* studies of drug oxidation with dog liver failed to show any difference between biopsy samples taken before and during steroid infusion.

Many drugs and chemicals are known to stimulate rates of drug oxidation in both man and animals. Administration of these inducing agents results in an increase in the activity of enzymes catalyzing drug oxidation, most of which are located within the endoplasmic reticulum of liver cells. In man there is usually a delay of 4–8 days before an appreciable change in rates of drug metabolism is seen when such an agent is administered (Breckenridge, Orme, Thorgeirsson, Davies & Brooks, 1971); in rats, the administration of enzyme-inducing agents causes increased rates of drug metabolism only 24–48 h after their administration.

We wish to report in this paper an immediate and hitherto undescribed effect of hydrocortisone on rates of antipyrine elimination in man.

**Methods.**—(a) Antipyrine (900 mg) was taken orally by 4 fasting normal adults. Over the next 6 h blood samples were taken at hourly intervals. Hydrocortisone hemisuccinate (Efcortelan) was then given as a single injection of 3 mg in 2 ml 0·9% w/v sodium chloride solution (saline), and thereafter infused i.v. at the rate of 3 mg per hour for 6 hours. During this time plasma samples were taken every 30 minutes. The experiment was repeated 2 weeks later in 3 of the 4 subjects. On this occasion the hydrocortisone loading dose was given and the infusion started 2 min before antipyrine administration.

In two subjects who received antipyrine on 2 separate occasions, urine was collected for 6 h following the dose of the drug and the excretion of free antipyrine was estimated. The 'apparent' volume of distribution of antipyrine was calculated by dividing the dose of antipyrine by the extrapolated plasma concentration at time zero. No correction was made for drug excreted unchanged in urine as the amount was negligible.

(b) Two studies were done on a conscious, trained greyhound. The plasma half-life of antipyrine was measured following the intravenous injection of 20 mg/kg. In the first study the half-life was measured during a control period of 3 h, and then during a further 3 h period in which hydrocortisone (1 mg loading dose followed by an infusion of 1 mg/h) was given. Fourteen days later a second study was carried out in the same animal in which the hydrocortisone infusion was started before the antipyrine administration. Blood samples were taken every 30 min during the 3 h of the infusion and for a further 3 h period. No urine was collected in these studies.

Antipyrine concentration was measured by the method of Brodie, Axelrod, Soberman & Levy (1949), and plasma hydrocortisone (cortisol) concentration by the method of Beardwell, Burke & Cope (1968).

**Results.**—Figure 1a shows that in subject 1 the infusion of hydrocortisone caused an immediate reduction in the plasma half-life of antipyrine from 15·7 to 8·0 h, this change coinciding with the start of the infusion. It also shows (Fig. 1b) that when the hydrocortisone infusion was started before the administration of antipyrine, the half-life of antipyrine was 8·1 h during the infusion and there was an immediate lengthening to 15·1 h on stopping the hydrocortisone. The figure shows the plasma concentrations of hydrocortisone measured before and during the infusion. At no time did the plasma concentration exceed the highest values found in 7 normal subjects at 9 a.m. (Burke, 1969).

In three other adults, similar results were obtained with the infusion of hydrocortisone. The plasma half-life of antipyrine

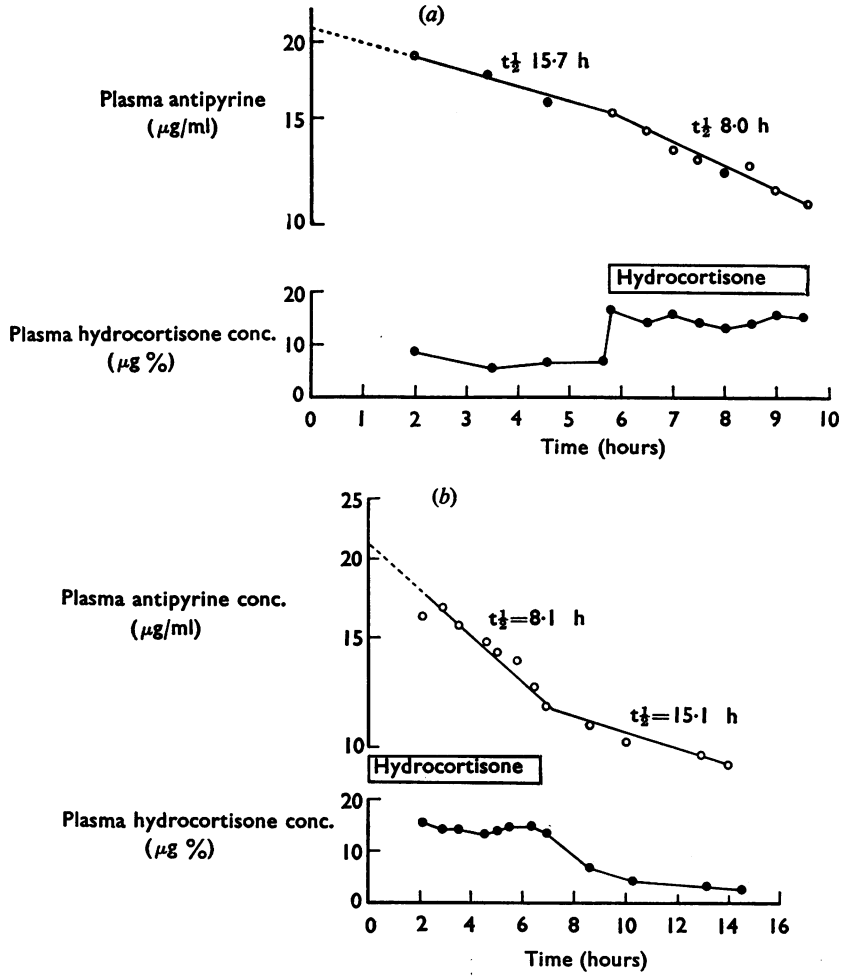


FIG. 1. The effect of an infusion of hydrocortisone 3 mg/hr on the rate of decline of plasma antipyrine concentration and on the plasma hydrocortisone (cortisol) concentration following an oral dose of antipyrine. (a) Hydrocortisone infusion started after the administration of antipyrine which was given at time zero. (b) Hydrocortisone infusion started before administration of antipyrine which was given at time, 2 min.

changed from 14·5 to 9·8 h (subject 2), from 13·3 to 7·3 h (subject 3) and from 21·3 to 13·2 h (subject 4).

The 'apparent' volume of distribution of antipyrine was calculated in 3 subjects, once in the experiment in which antipyrine was given before the hydrocortisone and also in the experiment in which it was given after the hydrocortisone. The values expressed as a percentage of body weight for the control and steroid infusion period were 66·06% and 60% in subject 1, 60·7% and 53·1% for subject 2 and 60% and 53% for subject 3. Thus hydrocortisone did not change the 'apparent' volume of distribution of antipyrine significantly.

The excretion of unchanged antipyrine in urine did not increase significantly during the infusion of steroid in the two subjects studied. Subject 1 excreted 1·65% of the dose in the 6 h following administration in a control study and 0·8% in a steroid infusion study. The corresponding values for subject 4 were 1·1% during a control period and 1·05% during the steroid infusion. In similar studies in 2 of the subjects saline was infused instead of the steroid. No changes were observed in antipyrine half-lives.

The same effect as in man was observed in a conscious dog, where infusion of hydrocortisone shortened the plasma half-

life of antipyrine from 120 to 75 min, and in a second experiment, from 157 to 88 minutes. This change was immediate. The 'apparent' volume of distribution of antipyrine was 71% in the control study and 78% of the body weight during the study in which hydrocortisone was infused before the antipyrine. Liver biopsy samples taken before and during the hydrocortisone infusion failed to show any change in the *in vitro* rates of oxidation of ethylmorphine, amylobarbitone or antipyrine in the microsomal fraction or in the 9,000 × *g* supernatant.

**Discussion.**—Antipyrine is a lipid soluble drug which, after oral administration, is rapidly and completely absorbed, distributes rapidly to total body water but is slowly eliminated. Significant amounts are not excreted in urine (Soberman, Brodie, Levy, Axelrod, Hollander & Steele, 1949). Its plasma half-life is dependent on its rate of oxidation in the liver. This has been used to assess individual differences in drug oxidation in man (Davies and Thorgeirsson, 1971).

The mechanism whereby hydrocortisone decreases the plasma half-life of antipyrine is not known. A change in antipyrine absorption would not explain our results because the effect of the steroid on antipyrine half-life was seen when hydrocortisone was given before or after the drug. Further, the hydrocortisone administration decreased the half-life of intravenous antipyrine in the dog.

It was conceivable that hydrocortisone might act by preventing the reabsorption of antipyrine from the renal tubules and therefore increasing renal excretion of unchanged drug. Our results show that this was not so.

The plasma half-life of antipyrine is directly proportional to its 'apparent' volume of distribution (VD) and inversely proportional to the metabolic clearance in the liver

$$t\tfrac{1}{2} = \frac{0{\cdot}693 \text{ VD}}{\text{Clearance}}$$

(Rowland, 1972).

Since in these studies VD was not decreased significantly by hydrocortisone infusion, it must be concluded that the rate of metabolic clearance was increased. Our inability to demonstrate an increased rate of oxidation of three substrates with liver microsomes and 9,000 × *g* supernatant, prepared from biopsy samples obtained from a dog during the period of hydrocortisone infusion, does not refute this suggestion. Intact cells or the intact organism may be necessary for demonstration of this effect of hydrocortisone.

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