Human, Methanol
Wow Formate
Ethanol
Kidney

10 ml ethanol/hour
required to completely ~~suppress~~ metabolise
of methanol

Excretion of Formate after Methanol Ingestion in Man

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Experiments which demonstrated the ability of ethanol to depress the metabolism of methanol in man were described briefly by Zatman (1946) and have recently been reported in detail (Leaf & Zatman, 1952). In these experiments urinary methanol concentration was used as an index of methanol concentration in the body water. It was shown that the decline in methanol concentration, subsequent to the attainment of a peak concentration after dosage, could be very greatly retarded by administration of ethanol. Agner & Belfrage (1947) determined the level of methanol in the blood of rabbits which had been dosed with the alcohol, and showed that the decline in methanol concentration was slower when ethanol was also given. Bartlett (1950), by studies of the radioactivity of expired carbon dioxide after administration of ^{14}C-labelled methanol, proved that the oxidation of methanol to carbon dioxide in the rat was depressed by the administration of ethanol. Bastrup (1947*a*), using dogs and rabbits, has confirmed an earlier observation of Asser (1914) that the excretion of formate which follows methanol administration is considerably reduced when ethanol has also been given to the animal. In these experiments on the dog, rabbit and rat, the dose of methanol (1–2 g./kg. body weight) was above the range which is of practical interest in relation to man. So far as we are aware no studies of formate excretion after the experimental administration of methanol to man have been reported; in this paper the result of a short series of such studies are presented.

SUBJECTS

The subjects were two adult males. Both (A.H.G. and L.P.K.) had been used 4 years before in studies of methanol elimination, and the data then obtained are to be found in the paper of Leaf & Zatman (1952). At least a week was allowed to elapse between successive experiments on the same subject.

METHODS

The dose of methanol was 4 ml., i.e. about 0·05 g./kg. body weight, in all the experiments. It was diluted to about 100 ml. with water, and taken orally immediately after the

40 gm/l, i.v. 40 000 p.p.m. solution
4000 mg.

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bladder had been emptied. Urine was collected during a period of generally about 12 hr. after the dose had been taken, and the volume of each specimen was measured. In each urine sample the methanol concentration was determined as described by Leaf & Zatman (1952), and the formate concentration according to Bastrup (1947*b*). Urine voided before the dose of methanol was taken was never found to contain measurable amounts of formate.

RESULTS

Methanol entering the body of the dog has been found to become distributed rapidly and uniformly throughout the body water (Yant & Schrenk, 1937). Leaf & Zatman (1952) found urinary methanol concentration to be a reliable index of blood methanol concentration in the cat, the kidney having no selective action on the alcohol. We feel justified in making the assumption that in man too the concentration of the alcohol in the urine is an index of its concentration in the body water during the period in which the urine is secreted.

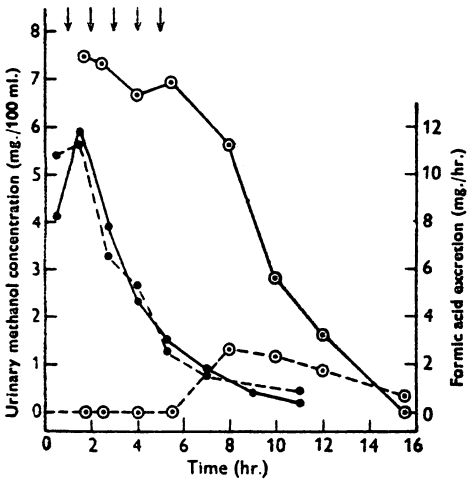

Fig. 1. Urinary methanol concentration (——) and formic acid excretion (– – –) after an oral dose of 4 ml. (3·2 g.) methanol. ●, Without ethanol; ⊙, with 15 ml. ethanol simultaneously and 10 ml. ethanol each hour, ↓, afterwards. Subject L. P. K. The total amounts of methanol and formic acid excreted in corresponding periods in the two cases were as follows:

	Methanol (mg.)		Formic acid (mg.)	
	0–6 hr.	6–12 hr.	0–6 hr.	6–12 hr.
Without ethanol	36	3	41	7
With ethanol	69	19	0	12

Typical results are illustrated in Fig. 1, which represents data obtained in two experiments on the same subject, in one of which the dose of methanol was unaccompanied by ethanol, whilst in the other 15 ml. of ethanol was taken with the methanol and a further 10 ml. of ethanol was taken each hour for 5 hr. afterwards. The curves of urinary methanol concentration follow closely the curves obtained with the same subject 4 years previously. The earlier finding, that the administration of ethanol in this amount reduced the elimination of methanol to a level such as might result from elimination in the urine and expired air only, was confirmed.

The curves in the figure which relate to formate excretion show that after methanol alone the peak rate of formate excretion corresponds well with the peak methanol concentration, and formate excretion and urinary methanol concentration subsequently decline in a similar way. This early formate excretion is seen to have been completely suppressed during the administration of ethanol; formate appeared in the urine only some 2 hr. after the last dose of ethanol had been given, and its appearance coincided with the rapid decline in body methanol concentration which then occurred.

An attempt was made to determine whether the metabolism of methanol at the 4 ml. dose level could be effectively prevented by dosage with ethanol at lower levels than were maintained in the above experiment. When the methanol was accompanied by 10 ml. ethanol followed by 2·5 ml. ethanol every half-hour, formate did not appear in the urine while the dosage with ethanol was continued, but the urinary methanol concentration fell during this period at a significantly greater rate than at the higher ethanol dosage. Such experiments suggested that a rate of 10 ml. ethanol/hr. represents very nearly the minimal requirement for a substantially complete suppression of the metabolism of the methanol.

DISCUSSION

The effect of ethanol on the formate excretion which follows the ingestion of methanol in man has proved to be of the same kind as was found by Bastrup for the dog and the rabbit. In each species, in the absence of ethanol, the capacity for oxidizing methanol to formic acid clearly exceeds the capacity for oxidizing formic acid, which consequently accumulates sufficiently to be excreted in the urine. The maximum urinary formic acid concentration observed in our experiments was 6·6 mg./100 ml. This would represent a total of nearly 3 g. of formic acid if this were distributed throughout the body water at the same concentration. A rough calculation, from the urinary methanol concentration, of the probable total body methanol at the time when this urine was secreted indicates that not more than about 0·7 g. of methanol can have undergone the first stage of oxidation by that time. Thus the concentration of formate in the blood and body water must have been much lower than the concentration

in the urine, and the kidney must have a considerable power of concentrating formate.

The inhibition of the appearance of formate during the administration of ethanol is in accordance with Zatman's (1946) interpretation of the earlier experiments, namely, that a primary oxidation of methanol to formaldehyde through the agency of alcohol dehydrogenase is competitively inhibited by ethanol. More recently, Jacobsen (1952) has expressed a doubt as to whether alcohol dehydrogenase is involved in methanol oxidation *in vivo*, a doubt based chiefly on the claim of Theorell & Bonnichsen (1951) that pure crystalline alcohol dehydrogenase of horse liver does not react with methanol to any measurable extent. But it has been our experience that cruder preparations of the horse-liver enzyme can easily be shown to reduce diphosphopyridine nucleotide in the presence of methanol; also, for the study of the back-reaction with reduced coenzyme, formaldehyde is in some ways a more convenient substrate to use than is acetaldehyde even with the pure enzyme (Theorell & Chance, 1951). The properties of the pure crystalline enzyme are not necessarily more closely relevant to events *in vivo* than are the properties of the cruder preparation. Jacobsen's alternative suggestion, that the principal mode of oxidation of methanol *in vivo* may be the catalase-hydrogen peroxide mechanism discovered by Keilin & Hartree (1945), does not at the moment seem to provide a sufficient explanation of the striking inhibitory effect of ethanol. More evidence is required to make it possible to decide whether either of the views so far put forward is correct.

SUMMARY

The appearance of formate in the urine of man, which otherwise follows the administration of a small dose of methanol, was completely inhibited during the repetitive administration of ethanol to the subject. Formate appeared in the urine an hour or two after the cessation of ethanol administration, and its appearance was coincident with the rapid decline in body methanol concentration which then ensues.

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