its peripheral action in inhibiting vasomotor reflexes, would be expected to produce a rise not a fall of osmotic reactivity of thirst mechanism.

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# The effect of chloral hydrate on the metabolism of ethanol in mice

The enhancement of the hypnotic effect of ethanol by chloral hydrate is well documented (Maynert, 1965). Bardodej (1965) described an disulfiram-like reaction in man after this drug combination and suggested increased acetaldehyde as the cause. However, Kaplan, Forney & others (1967) were unable to show any alteration in ethanol metabolism in man after chloral hydrate and attributed the additive effect to the formation of trichloroethanol. Gessner & Cabana (1967) showed significant differences in the rate of disappearance of chloral hydrate and of the formation of trichloroethanol and trichloroacetic acid in mice when chloral hydrate was given with ethanol. We have now measured ethanol and acetaldehyde in the blood after intravenous injection of ethanol into mice pretreated with chloral hydrate.

Adult male DBA/2 mice, 25 g, received chloral hydrate 200, 400, or 600 mg/kg intraperitoneally. Thirty min later they were injected with ethanol 1·33 g/kg as an 8·33% solution in isotonic saline into the tail vein. The duration of the injection was 1 min and blood samples were withdrawn at 5, 20, 35 and 50 min after the injection was complete. Samples were taken from the retro-orbital sinus directly into a 50 $\mu$l disposable micropipette and the acetaldehyde and ethanol concentrations determined by the method previously described (Roach & Creaven, 1968).

With 200 mg/kg of chloral hydrate, increases in blood acetaldehyde of 131% ($P < 0{\cdot}005$), 60% ($P = 0{\cdot}01$), 42% ($P = 0{\cdot}05$), and 27% (N.S.) are seen at 5, 20, 35, and 50 min after ethanol injection. With 400 mg/kg the increases are 318, 341 and 121% ($P < 0{\cdot}001$ for each) and 55% ($P = 0{\cdot}01$) at the same four time intervals; with 600 mg/kg, they are 270, 342, 171 and 93% ($P < 0{\cdot}001$ for each). With 200 mg/kg of chloral hydrate, but twice the dose of ethanol (2·67 mg/kg), acetaldehyde is significantly greater than control values only at 5 min (207%, $P < 0{\cdot}005$). At all four times the values are lower than those found with the same dose of chloral hydrate and the smaller dose of ethanol, and at 35 and 50 min they are significantly lower ($P = 0{\cdot}02$). (For treated groups $n = 6$; for the control group $n = 13$.)

The effect on blood ethanol levels are less dramatic. In control animals the decline in the level of blood ethanol is nearly linear with time, in agreement with previous findings in this laboratory for the dose of ethanol (1·33 g/kg) used. Chloral hydrate, 200 mg/kg, causes a 10% increase in the blood ethanol level at 5 min but the rate of decrease is the same as for the controls (Fig. 1). At doses of 400 and 600 mg/kg of chloral hydrate, the 5 min blood ethanol levels are somewhat higher than the control values (16 and 22% respectively; $n = 6$ for each experiment) but the rate of decrease is no longer constant, being greatest in the first 15 min and

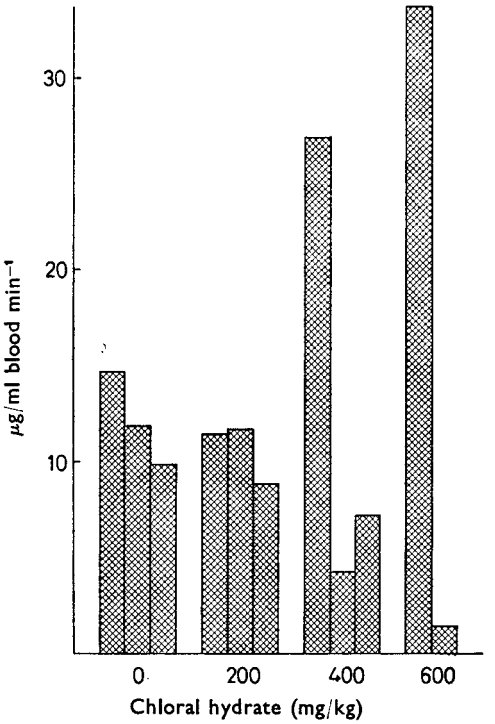


FIG. 1. Rate of decline in blood ethanol levels in each of the three 15 min periods after ethanol (1·33 g/kg), preceded by chloral hydrate in the doses shown. For treated groups n = 6; for the control group n = 13. The first column at each dose represents the 15 min period 5–20 min, the second column 20–35 min, the third 35–50 min (this is on the base line at the 600 mg/kg dose). At 200 mg/kg there are no significant differences. At 400 mg/kg, columns 1 and 2 differ significantly from the control, $P = 0{\cdot}01$. At 600 mg/kg, columns 1 and 3 show a highly significant, difference, $P = 0{\cdot}001$ and column 2 a significant difference, $P = 0{\cdot}01$, from the control.

declining thereafter. This is the pattern of ethanol metabolism previously shown to occur after a dose of ethanol (2·67 g/kg) twice as large as that used here (Roach & Creaven, 1969).

It is clear from these findings that chloral hydrate alters both ethanol and acetaldehyde metabolism and that this can explain at least in part the synergistic effect of the two drugs.

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