in the number of collisions and negligence of the rules, but a new phenomenon was serious steering errors. Codeine potentiated alcohol in the same way as diazepam, and both codeine and diazepam reduced the tachycardia induced by an emergency situation. Isoniazid alone exerted minimal effects and only slightly enhanced alcohol effects. Generally, the most sensitive variables to the drug effects were changes in the steering direction, flashing lights, brakes, and clutching.

The results confirm our previous results concerning the harmful effects of combining diazepam and alcohol on driving skill. They also suggest that relatively simple laboratory procedures could be used to predict drug interactions which reduce driving skill.

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Lignocaine metabolism in man

K. K. ADJEPON-YAMOAH and L. F. PRESCOTT

University Department of Therapeutics, The Royal Infirmary, Edinburgh EH3 9YW

Metabolites of lignocaine with potential antiarrhythmic activity include ethylglycylxylidide (EGX) and glycylxylidide (GX). Because of methodological difficulties, it has not been possible previously to measure their concentrations in the plasma of patients treated with lignocaine and there is little data on their urinary excretion pattern. A specific and sensitive gas-liquid chromatographic method has been developed for the simultaneous estimation of the three compounds in human plasma and urine.

Lignocaine metabolism was studied in four fasting healthy volunteers given lignocaine hydrochloride 400 mg orally and 200 mg intramuscularly on separate occasions. Venous blood and urine samples were collected at regular intervals. Urine pH was not controlled. Preliminary studies have also been carried out in hospital patients.

Following oral administration, mean peak plasma concentrations (μg/ml, mean $\pm$ S.E.) were $0{\cdot}81 \pm 0{\cdot}02$ for lignocaine, $0{\cdot}6 \pm 0{\cdot}11$ for EGX and $0{\cdot}26 \pm 0{\cdot}05$ for GX. Maximum concentrations were reached at 0·5 h, 1 h and 2 h respectively. The apparent mean plasma half life was 1·4 h for lignocaine, 2·8 h for EGX and about 15 h for GX.

Following intramuscular injection, mean peak plasma concentrations were $1{\cdot}25 \pm 0{\cdot}09$ for lignocaine at 0·5 h, $0{\cdot}18 \pm 0{\cdot}02$ for EGX at 2 h and $0{\cdot}12 \pm 0{\cdot}02$ for GX at 6 hours. The apparent mean plasma half-life was 1·7 h for lignocaine and 4·6 h for EGX. The plasma half-life of GX could not be determined since the mean peak concentration occurred at 6 h and blood samples were taken for only 8 hours.

Lignocaine and EGX could not be detected in the urine after 24 h and 36 h respectively (limit of detection 0·02 μg/ml). In contrast, GX was still easily measurable after 48 h and the maximum urinary excretion occurred in the period 10–24 h after intramuscular injection. Cumulative urinary excretion of these compounds is shown in Fig. 1. The observation of Boyes & Keenaghan (1972), that 4-hydroxyxylidine is a major urinary metabolite of lignocaine has been confirmed.

These studies indicate that GX is an important metabolite of lignocaine and has a very long biological half-life. Cumulation of GX may be relevant to the therapeutic and toxic effects of lignocaine. As much as 19% of a dose of lignocaine has been recovered as GX in the urine of a patient in 24 hours.

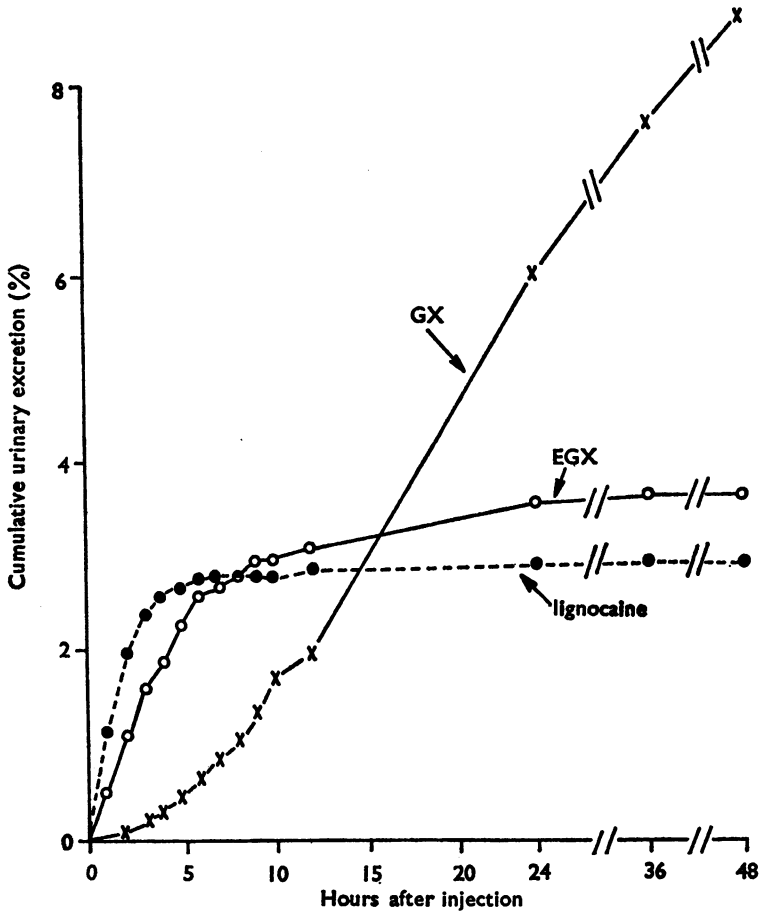

FIG. 1. Mean cumulative urinary excretion of lignocaine, ethylglycylxylidide and glycylxylidide in four healthy male volunteers after intramuscular injection of 200 mg lignocaine hydrochloride.

We are grateful to W.H.O. and Scottish Hospitals Endowment Research Trust for financial support. EGX and GX were supplied by Dr. N. Boyes of Astra Pharmaceuticals, Neponset Road, Worcester, Mass. 01606, U.S.A.

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The effect of AH 5158, pindolol, propranolol, D-propranolol on acute exercise tolerance in angina pectoris

A. J. BOAKES and B. N. C. PRICHARD

Clinical Pharmacology Department, Medical Unit, University College Hospital Medical School, London WC1

Numerous reports have established that propranolol and other β-adrenoceptor blocking drugs improve exercise tolerance in angina pectoris. Benefit is progressive as dosage is increased (Prichard & Gillam, 1971).

In the present study we have assessed the effect on acute exercise tolerance in angina pectoris of the β-adrenoceptor blocking drug pindolol, LB 46 (Saameli, 1967; Hill &