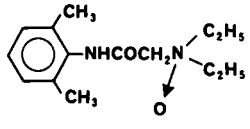
J. Pharm. Pharmacol. 1986, 38: 326
Communicated January 31, 1986

Letters to the Editor

In-vitro metabolism of lignocaine to its *N*-oxide

L. H. PATTERSON*, G. HALL, B. S. NIJJAR, P. K. KHATRA, D. A. COWAN†, *Department of Pharmaceutical Chemistry, School of Pharmacy, Leicester Polytechnic, Leicester, LE1 9BH and †Department of Pharmacy, KQC, University of London, Manresa Road, London SW3 6LX, UK*

Lignocaine, the most widely used local anaesthetic and antiarrhythmic drug in the clinic, possesses a tertiary amine functional group which by analogy with other compounds possessing dialkylamino-side chains, should be susceptible to metabolic *N*-oxidation. Despite extensive studies in animals and man (Benowitz & Meister 1977; Nelson et al 1977) the formation of lignocaine *N*-oxide (I) has not previously been described. We have incubated lignocaine HCl (500 μM) with NADPH-fortified rat liver microsomes. The incubations were



stopped and extracted with dichloromethane (4 × 5 ml), the extracts pooled and concentrated to approx. 50 μl under N_2. The metabolites were separated by TLC and their chromatographic properties compared to those of synthetic lignocaine *N*-oxide prepared as described by Nelson et al (1977). The TLC system used was 0·25 mm silica gel on glass plates with methanol–chloroform (20:80) as developing solvent. Spots corresponding to authentic lignocaine *N*-oxide (R_F 0·55) were evident from incubates of 15 min and 45 min duration. The longer reaction time led to no further appreciable metabolism of lignocaine *N*-oxide, in particular no reduction to lignocaine was observed. Chemical ionization mass spectrometry (CIMS) of TLC extracts confirmed the presence of lignocaine *N*-oxide (Fig. 1).

The protonated molecular ion $[M + H]^+$ at *m/z* 251, loss of oxygen atom ($[M - 16] + H)^+$, loss of water ($[M - 18] + H)^+$, the protonated ω-amino-2,6-dimethylacetanilide ($[M - 73] + H)^+$ and an intense fragment at *m/z* 74 ($CH_2 = NHOC_2H_5$) from a

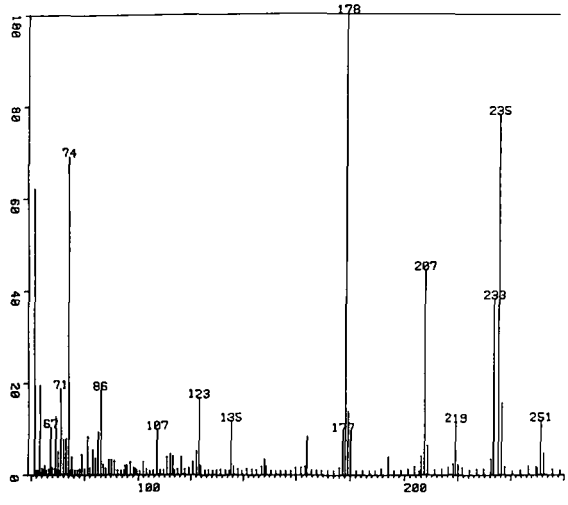


FIG. 1. Chemical ionization mass spectrum of lignocaine *N*-oxide generated by incubating lignocaine in the presence of NADPH-fortified rat (Sprague-Dawley) liver microsomes. X-axis, *m/z*; Y-axis, relative intensity (%).

Meisenheimer rearrangement of the *N*-oxide are all characteristic of CIMS of authentic lignocaine *N*-oxide.

This study shows that rat liver microsomes tissue can oxidise lignocaine to lignocaine *N*-oxide, an extremely water soluble Phase 1 metabolite. This may account for its lack of detection in a previous study by Nyberg et al (1977).

* Correspondence.

REFERENCES

Benowitz, N. L. & Meister, W. (1977) Clin. Pharmacokinet. 3: 177–201

Nelson, S. D., Garland, W. A., Breck, G. D., Trager, W. F. (1977) J. Pharm. Sci. 66: 1180–1190

Nyberg, G., Karlén, B., Hedlund, I., Grundin, R., Von Bahr, C. (1977) Acta Pharmacol. Toxicol. 40: 337–346