(1 mg/kg i.p.). At different time intervals after the operation, rats were weighed and killed by exsanguination. Having weighed the liver, microsomes were prepared (Ernster, Sickevitz & Palade, 1962) and assayed (Orrenius, Ericsson & Ernster, 1965) for cocaine N-demethylating activity. In addition, liver sections were stained using a modified Heidenhain's iron haematoxylin stain (Gurr, 1965) and examined microscopically.

Phenobarbitone increased liver weight and microsomal N-demethylating activity in normal and sham operated rats. Partial hepatectomy increased the mitotic index and was followed by rapid liver regeneration. When the responses to partial hepatectomy and phenobarbitone were examined in the same rat, the normal responses to both treatments were modified. In this case, the magnitude of the enzyme induction produced by phenobarbitone was reduced but its duration was prolonged. In addition, the normal rate of liver weight gain after partial hepatectomy was considerably increased by phenobarbitone. This effect was due to cell growth rather than increased cell division, the rate of which was reduced in these rats. The former result confirms that of Chiesara, Conti & Meldolesi (1970). The results suggest that there is some mutual interference between liver regeneration and microsomal enzyme induction.

REFERENCES

CHIESARA, E., CONTI, F. & MELDOLESI, J. (1970). Influence of partial hepatectomy on the induction of liver microsomal drug-metabolising enzymes produced by phenobarbital. A biochemical and ultrastructural study. *Lab. Invest.*, **22**, 329–338.

ERNSTER, L., SICKEVITZ, P. & PALADE, G. E. (1962). Enzyme-structure relationships in the endoplasmic reticulum of rat liver. A morphological and biochemical study. *J. cell Biol.*, **15**, 541–562.

GURR, E. (1965). In: *The Rational Use of Dyes in Biology and General Staining Methods*, p. 361, London: Leonard Hill.

ORRENIUS, S., ERICSSON, J. L. E. & ERNSTER, L. (1965). Phenobarbitol-induced synthesis of the microsomal drug-inducing enzyme systems and its relationship to the proliferation of endoplasmic membranes. *J. cell Biol.*, **25**, 627–669.

Absorption, distribution and excretion of methsuximide in male rats

P. J. NICHOLLS and T. C. ORTON*
Welsh School of Pharmacy, UWIST, Cardiff CF1 3NU

Methsuximide (N, 2-dimethyl-2-phenyl succinimide) is used clinically in the management of petit mal epilepsy (Chen, Weston & Bratton, 1963). However, there is no information available regarding the fate of this drug in animals and man.

Methsuximide was labelled with ^{14}C in the N-methyl position and the distribution of this compound (0·1 μCi/mg in a dose of 100 mg/kg) was determined in male rats (90–100 g, CFHB strain, Carworth Europe, Huntingdon). Soon after oral administration significant levels of radioactivity appeared in the brain, liver, kidney, heart, adrenal, spleen, testis, lung, salivary gland, eye, fat and skeletal muscle. This rapid distribution into the tissues is probably related to the nonpolar, lipophilic character of the drug. The levels of radioactivity in body fat tended to be higher than in most other tissues. Using a gas–liquid chromatographic assay procedure, the maximum concentration of ^{14}C-methsuximide in the plasma (27 μg/ml) was reached 1 h after administration. The level of radioactivity in most tissues declined with time.

Radioactivity was excreted into the urine (25·6% in 24 h), bile (13·7% in 6 h), faeces (8·6% in 24 h) and expired air (28·6% as $^{14}CO_2$ in 24 h). The total excretion of radioactivity after 72 h was 69·5% of the administered dose. The expiration of $^{14}CO_2$ suggests that ^{14}C-methsuximide is demethylated to 2-methyl-2-phenyl succinimide.

Both the unchanged drug and its demethylated metabolite were detected in the 24 h urine of rats by thin layer, paper and gas–liquid chromatography after the oral administration of either labelled or unlabelled methsuximide (100 mg/kg). These excretory products have also been detected in the urine of human volunteers receiving methsuximide (300 mg, orally).

Rats receiving unlabelled methsuximide (100 mg/kg, orally) exhibited measurable anticonvulsant (anti-leptazol) activity for up to 6 hours. At this time little methsuximide is present in the brain as judged from the pattern of radioactive distribution so that anticonvulsant activity cannot be due to the unchanged drug. As 2-methyl-2-phenyl succinimide possesses anticonvulsant activity it is possible that this demethylated metabolite contributes to the overall effectiveness of methsuximide. A similar phenomenon occurs with certain other N-alkylated anti-epileptic drugs (Butler & Waddell, 1958).

T.C.O. is in receipt of a Wellcome Studentship.

REFERENCES

BUTLER, T. & WADDELL, W. (1958). N-methylated derivatives of barbituric acid, hydantoin and oxazolidinedione used in the treatment of epilepsy. *Neurology*, **8**, 106–112.

CHEN, G., WESTON, J. & BRATTON JR. A. (1963). Anticonvulsant activity and toxicity of phensuximide, methsuximide and ethosuximide. *Epilepsia*, **4**, 66–76.

Anti-thrombotic activity of a benzo[c][1,6]naphthyridine

H. OTT and G. M. SMITH*

Pharmaceutical Chemistry Laboratories and Biological and Medical Research Division, SANDOZ LTD., CH 4002 Basle/Switzerland

A new group of synthetic compounds inhibits platelet aggregation *in vitro*. The activity of one of these substances, cis-1,2,3,4,4a,10b-hexahydro-8,9-dimethoxy-2-methyl-6-phenylbenzo[c][1,6]naphthyridine, is described. Citrated human and rabbit platelet rich plasma (PRP) was prepared by the method of Born & Cross (1963). The PRP was diluted with saline to give a platelet count of 3×10^8/ml. Aggregation of platelets was measured by the tubidimetric method of Born & Cross (1963). The compound was added to 1 ml of PRP, 1 min before the addition of a concentration of adenosine diphosphate (ADP) producing a submaximal aggregation of platelets. Concentrations of 10–50 μM produced a dose dependent inhibition of aggregation. Similar concentrations also inhibited aggregation of human platelets induced by adrenaline and collagen. Adrenaline abolishes the effects of several substances which inhibit ADP-induced aggregation (Ardlie, Glew & Schwartz, 1966). The inhibition of ADP-induced aggregation of rabbit platelets by the compound was not reversed by adrenaline, but was significantly potentiated ($P<0{\cdot}005$).

Antithrombotic activity has also been found in *in vivo* models. Administration of 10 mg/kg intravenously of the compound to rabbits anaesthetized with pentobarbitone reduced the adhesion of platelets to glass beads (Philp & Lemieux, 1968). In this test, samples of blood (2·5 ml) are citrated and pumped through a column of glass beads. The difference in the platelet count before and after the column enables adhesiveness to be measured. Using the rat carotid artery thrombosis test (Chan, 1967), in which a small piece of polythene tubing is inserted into the carotid artery, the compound reduced thrombus formation proximal and distal to the polythene tubing. Thrombi