Effect of SKF 525A on the fate of thiopentone

The initial rapid decline in thiopentone blood concentrations in all species after intravenous injection is attributed mainly to redistribution either into lean tissue (Price, Kevnat & others, 1959), or lean tissue and fat (Mark & Brand, 1963). The further slow decline of thiopentone blood levels may be due to further redistribution or to a combination of the two.

Mark, Brand & others (1965) in man, and Saidman & Eger (1966) in the dog, have demonstrated an arterial hepatic venous difference in thiopentone concentrations and have claimed that metabolism by the liver is of importance in lowering the blood concentrations of thiopentone.

Many of the estimations of thiopentone metabolism by the liver both *in vivo* and *in vitro* (Winters, Spector & others, 1955; Spector & Shideman, 1959) are of doubtful validity because they use methods which result in the degradation of thiopentone to pentobarbitone (Bush, Mazel & others 1961); thus, the rate of thiopentone metabolism has been variously put at 2, to 40%/h.

A method of demonstrating the contribution of metabolism in the termination of the anaesthetic action of thiopentone would be by measuring the effect of a liver enzyme inhibitor.

Shideman, Kelly & Adams (1947) have shown that carbon tetrachloride markedly prolongs thiopentone sleeping times in rats and this was assumed to arise from the hepatotoxicity of carbon tetrachloride. Megirian (1964) however, has since shown that carbon tetrachloride alters the distribution of thiopentone and that its action in prolonging sleeping times may be due to this effect.

SKF 525A (β-diethylaminodiphenylpropyl acetate), an inhibitor of liver microsomal enzymes, has been shown to prolong the sleeping times in rats produced by hexobarbitone and other barbiturates (Fouts & Brodie, 1956). It was of interest, therefore, to measure the effect of SKF 525A on thiopentone blood concentrations and on thiopentone sleeping times.

Five dogs (3 greyhounds, 2 terriers) were given SKF 525A (10 mg/μg) intravenously and after 30 min thiopentone (30 mg/kg) intravenously. Blood samples were taken at intervals.

Thiopentone blood concentrations were measured by the method of Brodie & others (1950) except that ethylene dichloride was used as the extraction solvent, whereby less than 1% degradation of thiopentone occurs in the extraction procedure.

It should be noted that the greyhounds maintained higher blood concentrations of thiopentone, presumably through lack of body fat, and were correspondingly anaesthetized and ataxic for longer than the other two dogs.

SKF 525A did not produce any alteration in the rate of decline of thiopentone blood levels in the five dogs.

Hooded inbred rats were injected intraperitoneally with SKF 525A (10 mg/kg) 30 min before thiopentone. A control group of rats were given saline. The rats were then injected with thiopentone (25 mg/kg) in a tail vein and the sleeping times measured.

SKF 525A did not produce any significant difference in thiopentone sleeping times in rats ($52{\cdot}2 \pm 10{\cdot}8$, $n = 13$) compared with animals given thiopentone alone ($47{\cdot}8 \pm 5{\cdot}5$, $n = 12$) ($P > 0{\cdot}4$).

These results would indicate that hepatic metabolism is not important in the termination of the anaesthetic action of thiopentone.

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REFERENCES

BRODIE, B. B., MARK, L. C., PAPPER, E. M., LIEF, P. A., BERNSTEIN, E. & ROVENSTINE, E. A (1950). *J. Pharmac. exp. Ther.*, **98**, 85–96.

BUSH, M. T., MAZEL, P. & CHAMBERS, J. (1961). *Ibid.*, **134**, 110–116.

FOUTS, J. R. & BRODIE, B. B. (1956). *J. Pharmac. exp. Ther.*, **116**, 480–485.

MARK, L. C. & BRAND, L. (1963). *Bull. N.Y. Acad. Med.*, **40**, 476–482.

MARK, L. C., BRAND, L., KAMVYASI, S., BRITTON, R. C., PEREL, J. M., LANDRAU, M. A. & DAYTON P. C. (1965). *Nature, Lond.*, **206**, 1117–1119.

MEGIRIAN, R. (1964). *J. Pharmac. exp. Ther*, **144**, 331–336.

PRICE, H. L. KEVNAT, P. J., SAFER, J. N., CONNER. E. H. & PRICE, M. L. (1959). *Clin. Pharmac. Ther.*, **1**, 16–22.

SAIDMAN, L. J. & EGER, E. I. (1966). *Anesthesiology*, **27**, 118–126.

SHIDEMAN, F. E., KELLY, A. R. & ADAMS, B. J. (1947). *J. Pharmac. exp. Ther.*, **91**, 331–339.

SPECTOR, E. & SHIDEMAN, F. E. (1959). *Biochem. Pharmac.*, **2**, 182–196.

WINTERS, W. D., SPECTOR, E., WALLACH, D. P. & SHIDEMAN, F. E. (1955). *J. Pharmac. exp. Ther.*, **114**, 343–357.

2-Mercaptobenzothiazole, an inhibitor of dopamine β-hydroxylase

The presence of copper in purified preparations of dopamine β-hydroxylase and the functional role of cupric ions in the oxidative conversion of dopamine to noradrenaline have been reported (Friedman & Kaufman, 1965). The critical role of cupric ions in the activity of dopamine β-hydroxylase renders this enzyme vulnerable to inhibition by copper chelating agents. Chelation of the cupric ion is the probable mechanism for the inhibition of this enzyme by inhibitors which include disulfiram (Goldstein, Anagnoste & others, 1964), phenylethyldithiocarbamate (Jonsson, Grobecker & Gunne, 1967), tropolone (Goldstein, Lauber & McKereghan, 1964) and various aromatic and alkyl thioureas, including U-14,624 [1-phenyl-3-(2-thiazolyl)-2-thiourea] (Johnson, Boukma & Kim, 1969, 1970). The irreversible inhibition of a banana polyphenoloxidase, also a copper enzyme, by 2-mercaptobenzothiazole (MBT) (Palmer & Roberts, 1967) prompted our investigation of this drug as a potential inhibitor of dopamine β-hydroxylase.

In vitro inhibition of dopamine β-hydroxylase isolated from bovine adrenal medulla (Friedman & Kaufman, 1965) was measured (Goldstein, Prochoroff & Sirlin, 1965). The animals were CF-1 male mice, 18–22 g, and Upjohn Sprague-Dawley male rats, 180–190 g. The drugs were dissolved or suspended in 0·25% aqueous methylcellulose before intraperitoneal administration. Noradrenaline and dopamine in paired mouse brains were measured (Veldkamp, Johnson & Keasling, 1968). The repletion of rat myocardial noradrenaline from exogenous dopamine after the depletion of noradrenaline with metaraminol was examined as described by Nikodijevic, Creveling, & Udenfriend (1963). Myocardial noradrenaline was adsorbed onto alumina (Anton & Sayre, 1962), eluted with 0·5M acetic acid and assayed (von Euler & Floding, 1958).

Spontaneous motor activity was recorded in actophotometer cages (Woodward Research Corp.). Mice received MBT (300 mg/kg, i.p.) or vehicle and two mice from the same treatment group were placed in each cage. After an initial 10 min acclimation period, activity was recorded in each 30 min interval for 4 h.