1200–2000 h ($n=4$). 6-FT (120 mg/kg, i.p.) or vehicle was administered at the start of a recording period. The EEG was scored visually in 20 s epochs for awake (W), slow-wave sleep (S) and paradoxical sleep (PS).

Data from pre- and post-drug days were averaged and compared with drug day data using the Wilcoxon signed-ranks test. Rats used for biochemical determinations were housed for at least one week under identical conditions to the sleep-recorded rats. After decapitation, brains were dissected, using a modification of the procedure of Glowinski & Iversen (1966), into 4 regions; medulla oblongata, hypothalamus, midbrain and 'cortex' (cerebral cortex, corpus striatum and hippocampus). Brain tissue was immediately frozen on a stainless steel plate cooled by solid $CO_2$, stored at −20°C, and assayed for 5-HT (Curzon & Green, 1970) and noradrenaline (Miller, Cox, Snodgrass & Maickel, 1970). Determinations were made on groups of 15 rats at various times after drug administration.

Over the first 4 h period 6-FT significantly decreased S ($P<0.02$) and PS ($P=0.0078$); W being significantly increased ($P=0.0078$). These effects were apparent only during the second and third hour of recording. 6-FT also significantly reduced sleep latency ($P=0.05$) and increased the number of awakenings ($P<0.02$). No changes in any sleep parameter were apparent during the 1600–2000 period of recording. Brain 5-HT was maximally depleted 3 h after drug injection. The greatest depletion was obtained in the medulla (35% of control) and least in the hypothalamus (58% of control). However, noradrenaline levels were also significantly lowered in all brain regions at this time.

The sleep changes produced by 6-FT appeared to follow a similar time-course to the depletion of brain monoamines. However, the biochemical effects of 6-FT were non-specific. This is surprising in view of a previous report indicating a high degree of specificity (Peters, 1971). The fact that our rats were isolated and of a different strain may account for this discrepancy.

**References**


CURZON, G. & GREEN, A.R. (1970). Rapid method for the determination of 5-hydroxytryptamine and 5-hydroxyindoleacetic acid in small regions of rat brain. *Br. J. Pharmac.*, **39**, 653–655.

GLOWINSKI, J. & IVERSEN, L.L. (1966). Regional studies of catecholamines in the rat brain. *I. J. Neurochem.*, **13**, 655–669.

JOUVET, M. (1972). The rôle of monoamines and acetylcholine-containing neurones in the regulation of the sleep-waking cycle. *Ergebnisse der Physiologie*, **64**, 166–307.

McGEER, E.G., PETERS, D.A.V. & McGEER, P.L. (1968). Inhibition of rat brain tryptophan hydroxylase by 6-halotryptophans. *Life Sci.*, **7**, 605–615.

MILLER, F.P., COX, R.H., SNODGRASS, W.R. & MAICKEL, R.P. (1970). Comparative effects of p-chlorophenylalanine, p-chloroamphetamine and p-chloro-N-methylamphetamine on rat brain norepinephrine, serotonin, and 5-hydroxyindole-3-acetic acid. *Biochem. Pharmac.*, **19**, 435–442.

PETERS, D.A.V. (1971). Inhibition of serotonin biosynthesis by 6-halotryptophans in vivo. *Biochem. Pharmac.*, **20**, 1413–1420.

RECHTSCHAFFEN, A., LOVELL, R.A., FREEDMAN, D.X., WHITEHEAD, W.E. & ALDRICH, M. (1973). The effect of parachlorophenylalanine on sleep in the rat: some implications for the serotonin-sleep hypothesis. In *Serotonin and Behaviour*, ed. Barchas, J. and Usdin, E. pp. 401–418. New York: Academic Press.

ROSS, C.A., TRULSON, M.E. & JACOBS, B.L. (1976). Depletion of brain serotonin following intraventricular 5,7-dihydroxytryptamine fails to disrupt sleep in the rat. *Brain Res.*, **114**, 5171–523.

TIMO-IARIA, C., NEGRÃO, N., SCHMIDEK, W.R., HOSHINO, K., DE MENEZES, C.F.L. & DaROCHA, T.L. (1970). Phases and states of sleep in the rat. *Physiol. Behav.*, **5**, 1057–1062.


## Interactions between intravenous anaesthetic agents and suxamethonium in mice


J.B. GLEN (introduced by M.J. TURNBULL)

*Biology Department, ICI Ltd., Pharmaceuticals Division, Alderley Park, Macclesfield, Cheshire SK10 4TF*


In man, the duration of apnoea and respiratory depression produced by suxamethonium is increased when this drug is administered following induction of anaesthesia with propanidid. No similar potentiation is found with methohexitone or thiopentone (Clarke, Dundee & Daw, 1964).

Interactions between currently used agents have been investigated in mice, to establish the validity of a model for the prediction of similar interactions between suxamethonium and potential new anaesthetic agents.

Two groups of 10 male Alderley Park mice (18–20 g) were used for each combination investi-

**Table 1** The effect of the combination of suxamethonium and intravenous anaesthetic agents on sleeping time, duration of apnoea, and respiratory rate measured 2 min after injection, in mice

| *Intravenous anaesthetic agent* | *Thiopentone* | | *Alphaxalone/Alphadolone* | | *Methohexitone* | | *Propanidid* | |
|---|---|---|---|---|---|---|---|---|
| *Dose (mg/kg)* | 40 | | 5.25/1.75 | | 16 | | 40 | |
| ‡ | A | S | A | S | A | S | A | S |
| *Sleeping time (min)* | 3.3 ± 0.8 | 5.6* ± 1.6 | 2.6 ± 0.3 | 3.6* ± 0.6 | 1.6 ± 0.3 | 3.3* ± 1.0 | 1.0 ± 0.2 | 3.2* ± 0.9 |
| *Duration of apnoea (s)* | 0 | 40 ± 19.3 | 0 | 34 ± 9.4 | 0 | 32 ± 14.6 | 0 | 38 ± 11.6 |
| *Respiratory rate/min 2 min after injection* | 203 ± 20 | 149* ± 29 | 158 ± 11 | 172 ± 37 | 190 ± 23 | 174 ± 357 | 220 ± 25 | 91*† ± 31 |

‡ A = anaesthetic alone S = anaesthetic + 1 mg/kg suxamethonium. Figures are means ± s.d. $n = 10$.
Statistical analysis with students *t* test * $P < 0.001$. Comparison of propanidid (S) with other (S) groups. † $P < 0.001$

gated. One group received the anaesthetic alone at twice the median hypnotic dose ($2 \times$ HD50) as estimated by a previously described technique (Glen, 1977). The other group received the same anaesthetic dose combined with suxamethonium (1 mg/kg). The dose volume was 0.1 ml in mice receiving anaesthetic alone and 0.2 ml when one of the mixtures was given. Injections were given into a tail vein over 20 seconds. Sleeping time (loss of righting reflex) and the duration of apnoea, ending with the return of regular respiration, were noted. Respiratory rate was measured 2 min after injection by the method described by Bradshaw, Biswas & Pleuvry (1973). Mice were kept in a warm box at an ambient temperature of $35 \pm 1°C$ and 100% $O_2$ was delivered at 1 l/min with a face mask during the period of sleep.

The results in Table 1 show that the combination of propanidid and suxamethonium produced a marked reduction in respiratory rate in mice. The combination with thiopentone produced a much smaller reduction and no significant effect was found with mixtures containing alphaxalone/alphadolone or methohexitone. In this respect, the model duplicates the clinical findings in man. On the other hand, the period of apnoea produced by drug combinations in mice appears of no predictive value as similar durations were found with all the agents investigated.

Sleeping times were increased with all the combinations examined, this effect again being most marked with propanidid.

## References

BRADSHAW, E.G., BISWAS, T.K. & PLEUVRY, B.J. (1973). Some interactions between morphine and diazepam in the mouse and rabbit. *Brit. J. Anaesth.*, **45**, 1185–1189.

CLARKE, R.S.J., DUNDEE, J.W. & DAW, R.H. (1964). The influence of some intravenous anaesthetics on the respiratory effects and sequelae of suxamethonium. *Brit. J. Anaesth.*, **36**, 307–313.

GLEN, J.B. (1977). A technique for the laboratory evaluation of the speed of onset of intravenous anaesthesia. *Brit. J. Anaesth.*, **49**, 545–549.