

## DEMONSTRATIONS

## Evaluation of the peripheral and central antagonistic activities against 5-hydroxytryptamine of some new agents

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Three new antagonists for 5-hydroxytryptamine (5-HT) were compared with methysergide by oral administration for peripheral and central effects (Table 1). Peripheral antagonism was measured as percentage reduction of oedema formation 30 min after intraplantar injection of 10  $\mu$ g 5-HT when the drugs had been given at various times earlier. Foot volumes were measured on a plethysmographic apparatus as described by Garland, Smith & Sim (1968). Doses giving 50% inhibition (ID<sub>50</sub>) were derived quantitatively. Central antagonism was measured as ability to reduce the numbers of head twitches caused by intraventricular injection of 40  $\mu$ g 5-HT in mice. The method of injection was based on that of Brittain (1966), being made by insertion of a 30 G 1/8 inch needle through the soft bone 2 mm anterior to the parietal-interparietal intersection, the head having been depilated. Doses that at least halved the number of head twitches in the following 30 min, by comparison with controls, in 50% of mice (ED<sub>50</sub>) were determined by probit analysis.

The relative peripheral activities of the four compounds varied with the interval between their administration and injection of 5-HT. Methergoline, a lysergic acid derivative (Beretta, Ferrini & Glässer, 1965) and  $\alpha$ -anilino-*N*-2-*m*-chlorphenoxy-propylacetamide hydrochloride monohydrate, referred to as B.W. 501C67 (Hodson, 1969), had much more persistent effects than methysergide and the phenylacetamide, xylamide (Copp, Green, Hodson, Randall & Sim, 1967).

TABLE 1. *Peripheral ID<sub>50</sub> values determined from foot oedema and central ED<sub>50</sub> values from antagonism of head twitch for four 5-HT antagonists.*

Drug	Peripheral ID <sub>50</sub> mg/kg orally (95% limits) Hours before 5-HT			ED <sub>50</sub> mg/kg orally (95% limits)
	1	5	24	
Xylamide	0.49 (0.06-4.10)	0.25 (0.04-1.62)	24.26 (0.95-616.5)	114 (85-133)
B.W. 501C67	0.38 (0.06-2.60)	0.045 (0.007-0.27)	0.91 (0.24-3.46)	157 (127-186)
Methergoline (Farmitalia FI6337)	0.25 (0.03-2.32)	0.16 (0.05-0.52)	1.01 (0.21-4.92)	0.46 (0.18-0.85)
Methysergide	0.25 (0.04-1.80)	0.87 (0.25-2.99)	41.6 (6.1-284.1)	3.91 (2.81-5.07)

Of the three new compounds, only methergoline exhibited central antagonism of 5-HT at doses close to that causing peripheral antagonism, whereas the two acetamide derivatives were effective only at very high dosage.

## REFERENCES

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