Antagonists of the embryocidal effect of 5-hydroxytryptamine in the rat

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5-hydroxytryptamine (5-HT) administered late in pregnancy was embryotoxic, producing changes in the placenta said to be reminiscent of those in toxaemia of pregnancy (Poulson, Botros & Robson, 1960).

In the following experiments rats were dosed subcutaneously with 5-HT (10 mg/kg) on day 15 of pregnancy and killed on day 20 for examination (the day of finding sperm in the vaginal smear was counted as day 0). The 5-HT caused the death of about 94% of foetuses as judged by implantation sites. Foetal loss in controls was about 4%. Oral or subcutaneous dosing with the following 5-HT antagonists, 3 h previously, could fully prevent the embryocidal effect of 5-HT:

α-Anilino-*N*-2-*m*-chlorophenoxypropylacetamidine hydrochloride monohydrate (B.W. 501C67) (Hodson, 1969).

α-*m*-Methylanilino-*N*-2-*m*-methoxyphenoxypropyl-acetamidine hydriodide (B.W. 204C67) (Hodson, 1969).

Xylamidine (Copp, Green, Hodson, Randall & Sim, 1967).

Table 1 shows the results of probit analysis of the data from tests using groups of 5–24 rats (total, 396 rats).

TABLE 1. *Doses of 5-HT antagonists which reduced the embryocidal effect of 5-HT to* 50%

Compound	Route	ED50 mg/kg	*P* 95% limits	Ratio
B.W. 501C67	s.c.	0·011	0·007–0·016	9:1
	p.o.	0·101	0·037–0·292	
B.W. 204C67	s.c.	0·003	n/c	110:1
	p.o.	0·33	0·15–0·58	
Xylamidine	s.c.	0·031	n/c	29:1
	p.o.	0·90	0·47–1·34	

n/c, Limits not calculable.

B.W. 501C67 was the most active orally and had the lowest ratio of oral to subcutaneous doses.

No foetal toxicity occurred with daily administration of 5–10 mg/kg subcutaneously on days 8–16 of pregnancy in rats (ten does) or in rabbits (twenty-seven does). With subcutaneous treatment on days 16–19 no ill effect followed 5–10 mg/kg in rats (fourteen does), but in rabbits (nine does) 5 mg/kg on days 19–27 reduced the weight gain of the does and 10 mg/kg (eleven does) also significantly increased foetal loss and reduced the mean weight of the foetuses.

A single oral dose of B.W. 501C67 of 500 mg/kg given to groups of two to six rats on any one day between day 8 and 16 (total thirty-four rats), although lethal to 40% of does, had no effects on the litters of survivors.

If high 5-HT levels are involved in toxaemia of pregnancy (Senior, Fahim, Sullivan & Robson, 1963) then B.W. 501C67 may be of use for treatment without risk to the foetus.

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