5-Hydroxytryptamine antagonists related to cinanserin in human isolated smooth muscle

Cinanserin is a potent 5 hydroxytryptamine (5-HT) antagonist on human isolated smooth muscle preparations (Metcalfe & Turner, 1969) and has strong immunosuppressive activity (Krapcho, Millonig & others, 1969). One of its derivatives SQ10631 (2-chloro-2′-{[3-(dimethylamino)propyl]thio} cinnamanilide hydrochloride) is also a potent 5-HT antagonist but has weak immunosuppressive properties. Another derivative SQ11276 (6′-[3-(dimethylamino)propoxy]-*m*-cinnamotoluididehydrochloride) has weak anti-5-HT and potent immunosuppressive activity in animals (Krapcho & others, 1969). The anti-5-HT and anti-acetylcholine properties of SQ10631 and SQ11276 on isolated human smooth muscle preparations are now reported.

Circular or longtitudinal strips of human stomach, ileum, colon and appendix were used with acetylcholine and circular saphenous vein spirals with 5-HT. The strip was set up in an isolated organ bath in Krebs-bicarbonate solution gassed with 5% carbon dioxide in oxygen. pA_2 determinations (Schild, 1949) were made for acetylcholine and 5-HT contractions and the shift of dose response curves to acetylcholine was also measured. A pA_{10} for SQ10631 against 5-HT was also obtained.

No differences in anti-acetylcholine effects were found between SQ10631 and SQ11276 (Table 1), but the anti-5-HT activity of SQ10631 was significantly lower than SQ11276. The acetylcholine dose response curves were shifted to the right in the presence of each compound but the maximum was reduced, indicating a non-competitive antagonism. The anti-acetylcholine activity of these compounds is similar to that of cinanserin (Metcalfe & Turner, 1969). This group of 5-HT antagonists does not share the ability to potentiate the action of acetylcholine in human smooth muscle which is shown by methysergide (Metcalfe & Turner, 1969; Glegg & Turner, 1971).

The pA_{10} determination with SQ10631 against 5-HT gave a value of 3·87. The pA_2–pA_{10} value, 5·64–3·87, was 1·77 which shows that the antagonism against 5-HT was also non-competitive as a value of 0·95 would be expected for a competitive reaction (Schild, 1957). A pA_{10} determination could not be made for SQ11276 because of the difficulty in obtaining tissue which gave a sufficiently shallow dose response curve for ten times a single dose to be used. Furthermore, when high doses of 5-HT, above 10 μg/ml bath fluid, were used tachyphylaxis frequently developed despite the use of prolonged cycle times of up to 1 h. Should SQ11276 be used in man

Table 1. *Summary of pA_2 values of SQ10631 and SQ11276 against acetylcholine and 5-hydroxytryptamine on human smooth preparations.*

Agonist/ antagonist	Tissue	Number of determinations	Range	Mean pA_2
ACh/SQ10631	L. Appendix	1	3·02	3·02
	C. Ileum	3	2·84–3·81	3·29
	L. Colon	1	4·75	4·75
	Stomach	1	4·65	4·65
ACh/SQ11276	L. Appendix	2	3·88–4·09	3·99
	C. Colon	1	4·16	4·16
	stomach	2	3·57–3·98	3·78
5-HT/SQ10631	C. Saphenous vein	3	5·60–5·70	5·64
5-HT/SQ11276	C. Saphenous vein	3	4·85–5·27	5·04

L. = Longititudinal muscle; C. = Circular muscle; ACh = Acetylcholine.

for its immunosuppressive properties it may also be expected to have some anti-5-HT activity.

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REFERENCES

GLEGG, A. M. & TURNER, P. (1971). *Archs int. Pharmacodyn. Thér.*, **191**, 301–309.
KRAPCHO, J., MILLONIG, R. C., TURK, C. F., AMREIM, B. J. (1969), *J. mednl Chem.*, **12**, 164–166.
METCLAFE, H. L. & TURNER, P. (1969). *Br. J. Pharmac.*, **37**, 519–521P.
SCHILD,H. O. (1949). *Br. J. Pharmac. Chemother.*, **2**, 189–206.
SCHILD, H. O. (1957). *Pharmac. Rev.*, **9**, 242–246.

Ulceration of the colon in rabbits fed sulphated amylopectin

A synthetic sulphated amylopectin (SN-263) derived from potato starch has recently been investigated clinically in the treatment of gastric and duodenal ulcers (Cayer & Ruffin, 1967; Zimmon, Miller & others, 1969; Sun & Ryan, 1970). This preparation, like some other polysaccharides (heparin, chondroitin sulphate, dextran sulphate, degraded carrageenan), is known to inhibit peptic activity and to protect against experimental gastric ulceration (Levey & Sheinfeld, 1954; Anderson & Watt, 1959; Bianchi & Cook, 1964; Barnes, Redo & others, 1967; Ellis, Lunseth & Nicoloff, 1970). Because of its high molecular weight and polyanionic behaviour in solution, it seemed reasonable to suspect that sulphated amylopectin may have a deleterious effect on the colon similar to that of degraded carrageenan in laboratory animals (Marcus & Watt, 1969).

In this communication we report the results of experiments in which rabbits were fed various concentrations of the sulphated amylopectin.

Twenty male New Zealand White rabbits of 3925 g average weight were housed in separate cages and fed a standard cube diet (S.G.1). Three experimental groups, 5 rabbits in each group, received as drinking fluid 1, 0·5 and 0·1 % respectively aqueous solutions of sulphated amylopectin.* The drinking fluids were freshly prepared daily, supplied freely in drinking bottles, and the volume consumed per animal per day was measured throughout the 2 to 4 week period of the experiment. Control animals received water freely but without the addition of sulphated amylopectin. At weekly intervals, the animals were weighed and their faeces examined for occult blood using the Haematest method. At the end of the experiment, the rabbits were killed with intravenous phenobarbitone, the colons removed, emptied of faeces, and examined for the presence of ulceration.

Animals fed sulphated amylopectin at the 1 % concentration in their drinking water received on average a daily dose of 0·37 g/kg weight over the first week; thereafter, their fluid intake fell and the average daily dose over the remaining 3 weeks was