Table 1. *Comparison of the apparent inotropic affinities of isoprenaline, salbutamol and dobutamine obtained with spontaneously beating atria* vs *electrically stimulated left atrial strips of the guinea-pig.*

Compound	Strip* pD_2 values	Atria† pD_2 values	RA‡ strip	RA‡ atria	*P*
Isoprenaline	6·8 ± 0·2	7·5 ± 0·2	100	500	<0·01
Salbutamol	5·1 ± 0·3	6·3 ± 0·8	2	30	<0·005
Dobutamine	5·5 ± 0·3	6·1 ± 0·3	5	15	<0·1

* Electrically stimulated.
† Spontaneously beating.
‡ Relative pD_2-value of isoprenaline on left atrial strip taken as 100.
RA—relative affinities.

(see Table 1). The higher apparent affinities obtained in the case of the spontaneously beating preparations may be ascribed to the fact that the drugs also increased the frequency of contraction which potentiated the force of contraction.

From our results we could conclude that changes in frequency of contraction do influence apparent affinity values for the inotropic receptors for β-adrenergic agonists to varying degrees. Since affinities for chronotropic and inotropic β_1-adrenoceptors may differ, the influence of changes in frequency on the apparent affinity for the inotropic receptors may vary from one drug to the next. Since β-adrenergic agonists may be chronotropic or inotropic selective, their chronotropic effects may influence the determination of relative inotropic affinities to varying degrees when spontaneously beating *in vitro* preparations are used for the assessment of the inotropic effects.

This study was supported by the South African Medical Research Council.

May 24, 1976

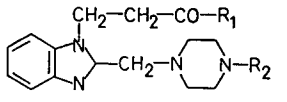
REFERENCES

BOWDITCH, H. P. (1871). *Ber. sächs. Ges. (Akad.) Wiss.*, 652–689.
BRITTAIN, R. T., FARMER, J. B., JACK, D., MARTIN, L. E. & SIMPSON, W. T. (1968). *Nature (Lond.)*, **219**, 862.
DREYER, A. C. & OFFERMEIER, J. (1975). *Pharmac. Res. Comm., 7, No. 2*, 151–161.
KOCH-WESER, J. & BLINKS, J. R. (1963). *Pharmac. Rev.*, **15**, 601–643.
TUTTLE, R. R. & MILLS, J. (1975). *Circulation Res.*, **36**, 185–196.
VAN ROSSUM, J. M. (1963). *Archs int. Pharmacodyn. Thér.*, **143**, 299–330.

A benzimidazole derivative (7110 MD) with gastric antisecretory and antiulcer activity

N. DORME, G. RAYNAUD*, *Department of Pharmacology, Centre de Recherche Delalande, 10, rue des Carrières, 92500 Reuil-Halmaison, France*

The compound 7110 MD 1-(2-benzoyl ethyl) 2-(cinnamyl piperazinyl 1-methyl) benzimidazole dimaleate belongs to a series of benzimidazole derivatives of general structure (I) (Fauran, Eberlé & others, 1972) which possess gastric antisecretory and antiulcer properties.



I

7110 MD

$R_1 = C_6H_5$ $R_2 = CH_2-CH=CH-C_6H_5$

The compound shows notable gastric antisecretory activity (Table 1). Administered orally, intravenously (i.v.) or intraduodenally (i. d.) to the 4 h pylorus-ligated rats, it decreases the volume and acid concentration of gastric secretion at doses well below the LD50. The large difference between the LD50 doses for the oral and intravenous routes is not the result of poor absorption from the gut because the ED50 values for gastric secretion are low for both routes.

* Correspondence.

In the urethane anaesthetized rat (1·75 g kg^{-1}, i. m.), gastric secretion stimulated by carbachol 5 μg kg^{-1} h^{-1} (i. v.) is reduced to 53% by the compound at 1·50 mg kg^{-1} (i.v.) and gastric secretion stimulated by pentagastrin 2 μg kg^{-1} h^{-1} (i.v.) is reduced by 50% at 3 mg kg^{-1} (i.v.), but hypersecretion induced by histamine 0·69 mg kg^{-1} h^{-1} (i.v.) is not modified at 10 mg kg^{-1} (i.v.). The antagonism of 7110 MD towards pentagastrin 2 μg kg^{-1} h^{-1} (i.v.) was confirmed in one conscious dog with a Heidenhain pouch: at 2 mg kg^{-1} (i.v.), the drug decreased gastric juice output by 53% and free acid output by 69%. This gastric antisecretory activity is accompanied by antiulcer properties since the drug given orally or intraduodenally prevents the formation of experimental ulcers of various origins (ED50 by the oral route ranging from 4·2 to 38 mg kg^{-1} and intraduodenally from 1·6 to 28·5 mg kg^{-1}, Table 2). Yet, even at high doses the drug has little effect on duodenal ulcer and none on the gastric ulcer due to histamine.

While the drug is active on the stomach *in vivo*, its anti-acetylcholine activity *in vitro* against acetylcholine-induced contractions in the rat duodenum is weak (50% inhibition at 22·5 mg ml^{-1}, 1/5000 of atropine). *In vivo*, 7110 MD has no intestinal spasmolytic properties in the

Table 1. *Acute toxicity and gastric antisecretory action of 7110 MD in the rat.*

Route (LD50 mg kg^{-1})	Dose including a decrease of 50% comparatively with control groups mg kg^{-1} (95% confidence limits) Gastric juice output	Free acid output	Free acid conc.	n
Oral 3400 (n = 50)	2·5 (1·0–6·3)	1·8 (0·8–3·9)	8·7 (4·9–15·2)	42
i.d.	2·2 (1·6–2·8)	2·0 (1·7–2·2)	7·1 (5·9–8·3)	48
i.v. 39 (n = 50)	0·9 (0·4–1·3)	0·8 (0·5–1·1)	2·6 (0·6–4·6)	42

rabbit (at 7·5 mg kg^{-1}, i.v., and at 150 mg kg^{-1}, i.d.), or in the dog (i.v. perfusion of 4 mg kg^{-1} h^{-1} for 3 h). In the guinea-pig, the compound shows no activity on Oddi's morphinic spasm (at 15 mg kg^{-1}, i.v.) but in the mouse, intestinal transit of charcoal is decreased (ED50 = 30 mg kg^{-1} by the oral route). Gastric motor activity is not changed by 7110 MD, either in the rat (15 mg kg^{-1} orally), or in the dog (4 mg kg^{-1} h^{-1}, i.v., for 3 h).

The drug given orally to the conscious dog does not modify cardiac heart rate at 7·5 mg kg^{-1}, but at 10 mg kg^{-1} the heart rate is accelerated from 100 to 190 beats min^{-1}; with only 1 mg kg^{-1} of atropine, the rhythm increases from 50 to 120 beats min^{-1}.

In the rat 7110 MD produces total mydriasis in 50% of the animals at an oral dose of 66 mg kg^{-1}; atropine has the same effect at 2 mg kg^{-1}. In the dog the drug produces 50% mydriasis after repeated oral treatment for three days with doses of 11 mg kg^{-1} day^{-1}, but it has no effect on pupillary diameter after single oral doses of 10 mg kg^{-1} or intravenous perfusion of 9 mg kg^{-1} h^{-1} over 2 h.

7110 MD antagonizes oxotremorine- and carbachol-induced salivation in the mouse rat and dog, mecholyl-induced chromodaccryorhea in the rat, acetylcholine-induced bronchospasm in the guinea-pig and acetylcholine-induced pressure fall in the cat at oral or intravenous doses generally higher than the gastric antisecretory ones. The drug antagonizes bradykinin (0·025 μg ml^{-1}) *in vitro* on the guinea-pig ileum and on the rat uterus (ED50 = 1·5 and 1·9 μg ml^{-1}) and *in vivo* on the bronchoconstrictive action induced by the polypeptide in the guinea-pig (ED50 = 30 mg kg^{-1}, i.d.).

7110 MD shows local anaesthetic activity on rabbit cornea (1·7 cocaine at concentration of 0·25 %). At gastric antisecretory and antiulcer doses, the drug has no effect on the central nervous system in the mouse, rat and rabbit, or on the respiration in the rabbit.

The preliminary pharmacological results on 7110 MD give some idea on the mechanism of its gastric and antiulcer activity.

Table 2. *Action of 7110 MD on experimental ulcers showing doses which reduce by 50% the number of rats showing ulcers ED50 mg kg^{-1} 95% confidence limits.*

Technique	Species	Route	EDSO	n
7 h restraint	Rat	Oral	4·2 (2·6–6·7)	48
24 h restraint	Rat	Oral	38·0 (26·0–50·0	40
18 h Shay ligature	Rat	i.d.	28·5 (13·5–60·0)	30
Vasopressin 0·8 U kg^{-1}, i.v. for 3 days + 1·6 U kg^{-1}, i.v. the 4th day	Rat	Oral	5·1 (3·1–7·2)	18
Shay ligature + adrenaline 0·4 mg kg^{-1}, i.p.	Rat	i.d.	haemorrhage: 1·7 (1·2–2·1) oedema: 0·6 (0·4–0·9)	36
5-HT 15 mg kg^{-1}, s.c.	Rat	Oral	10·2 (5·1–21·4)	30
Polymyxin 40 mg kg^{-1}, s.c.	Rat	Oral	21·0 (6·0–74·0)	18
Histamine (gastric ulcer) 5 mg kg^{-1}, i.p.	G.-P.	Oral	Inactive at 113	8
Histamine (duodenal ulcer) 0·5 mg kg^{-1}, i.m. every 30 min for 2·5 h	G.-P.	Oral	Protection of 38% at 80	8
Phenylbutazone 200 mg kg^{-1}, i.m. for 2 days	Rat	Oral	14·3 (10·0–20·2)	18

The effects seem to be partly due to a peripheral anti-acetylcholine action, especially pronounced on gastric secretion. But the product does not act like atropine, since, in the rat the mydriatic effect needs much higher doses (66 mg kg^{-1}) than those active on gastric secretion, while atropine modifies pupillary diameter and gastric secretion at the same dose (2 mg kg^{-1}); in the dog, 7110 MD induces tachcardia at 10 mg kg^{-1} while atropine increases the cardiac rhythm at 1 mg kg^{-1}; *in vivo*, 7110 MD intravenously has little intestinal spasmolytic activity and *in vitro* hardly any antagonizing effect on acetylcholine. Interaction with gastrin is probable since 7110 MD inhibits the secretory effect of pentagastrin. The local anaesthetic effect might be also involved in the gastric antisecretory activity. There seems to be no H_2 antihistaminic effect.

The antiulcer activity might be explained by an action on gastric mucosa vasomotricity (protection with low doses against ulcers induced by vasoconstrictors like adrenaline after Shay ligature, or vasopressin) or interaction with kinins (antagonism *in vitro* and *in vivo* with bradykinin).

The authors wish to thank Mrs M. Hebert and Mr M. Laville, J. P. Defaux and G. Guillou for their excellent technical assistance.

June 28, 1976

REFERENCE

FAURAN, C., EBERLÉ, J., LE CLOAREC, A. Y., DORME, N. & RAYNAUD, G. (1972). Delalande S. A., Brevet [France 7224544.