Effect of aminophylline, butalamine and imolamine on human isolated smooth muscle

Butalamine, (3-phenyl-5-dibutylaminoethyl-amino-1,2,4-oxadiazole) and imolamine, (3-phenyl-5-imino-4-diethylaminoethyl-1,2,4-oxadiazole), have been shown to produce in animals coronary vasodilation, local anaesthesia, analgesia and a papaverine like action in duodenal preparations (Sterne & Hirsch, 1964, 1965). We have now investigated the spasmolytic activity of these drugs on isolated, spontaneously-active, human smooth muscle tissue and compared them with aminophylline. The tissue was fresh from operation specimens. Strips were prepared and suspended in an organ bath containing Krebs bicarbonate solution at 37° gassed with 5% carbon dioxide in oxygen. The effects of the drug on the rate of spontaneous activity, the amplitude of contractions and tone were recorded on a smoked kymograph drum. The results are in Table 1. The anti-acetylcholine properties of the compounds were also investigated by measuring the reduction in height of acetylcholine-induced contractions.

From Table 1, it can be seen that butalamine, like aminophylline, caused a slowing in rate of spontaneous activity, a decrease in amplitude and a reduction in tone of the tissues studied. Butalamine appeared more potent on ileum and one piece of uterus but it was otherwise approximately equipotent with aminophylline. Imolamine increased the tone of uterus and ileum and this was accompanied by a reduction in amplitude of contraction. The response of the stomach tissue to imolamine was similar to that of butalamine and aminophylline, i.e. a relaxant action on smooth muscle. Butalamine has a more potent anti-acetylcholine activity than imolamine. Butalamine (10 μg/ml final bath concn) reduced contractions of the uterus preparation by 90% while imolamine (1 and 10 μg/ml) gave no response. Both drugs at 4 μg/ml caused a 20% reduction in the contractions of the longitudinal muscle of the appendix. Butalamine (10 μg/ml) caused a 50% reduction and imolamine (10 μg/ml) a 20%

Table 1. *The effect of aminophylline, butalamine and imolamine on the spontaneous activity of isolated human smooth muscle*

Tissue	No of expts	Drug	Dose μg/ml (final bath concn)	Effect on: Rate of spontaneous activity	Effect on: amplitude of contraction	Effect on: tone
Uterus Hysterectomy	3	Aminophylline	2·5–10	Slowed	No change	Decreased
		Butalamine	1	No change	No change	No change
			10	Slowed	No change	Relaxation
		Imolamine	10	No change	Increased	No change
			50	No change	Reduced	Increased
			100	Slowed	Reduced	No change
Uterus Hysterectomy	1	Aminophylline	500–2 mg	No change	No change	Decreased
		Butalamine	25–200	No change	No change	Decreased
		Imolamine	25–200	No change	No change	Increased
Ileum Circular muscle	2	Aminophylline	25–100	Slowed	No change	Decreased
			200	Slowed	Reduced	Decreased
			400–500	Abolished	Abolished	Decreased
		Butalamine	100	Abolished	Abolished	Decreased
		Imolamine	100	No change	Reduced	Increased
Stomach Longitudinal muscle	1	Aminophylline	25	Slowed	No change	Decreased
			100	Abolished	Abolished	Decreased
		Butalamine	50–100	Abolished	Abolished	Decreased
		Imolamine	100	Abolished	Abolished	Decreased

reduction of the contractions induced in the stomach preparation. This supports the results of one further separate experiment on longitudinal stomach strips where imolamine (10 μg/ml) did not alter the acetylcholine dose-response curve but butalamine (10 μg/ml) caused a shift to the right and a flattening of the curve.

From these preliminary experiments, it would appear that butalamine is a more effective smooth muscle relaxant compound than imolamine. It has a similar potency to aminophylline on isolated human smooth muscle. Imolamine has a variable action on tone, producing an increase in ileum and uterus and a decrease in stomach.

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Clinical Pharmacology Division,
Medical Professorial Unit,
St. Bartholomew's Hospital,
*London, E.C.*1.

I. M. COUPAR
ANNMARIE HEDGES
HELEN L. METCALFE
P. TURNER

April 14, 1969

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Protection against *m*-fluorotyrosine convulsions and lethality in mice exposed to hypobaric hypoxia

Acute exposure to hypoxia shifts brain metabolism to anaerobic pathways (Gurdjian, Webster & Stone, 1949) and elevates γ-aminobutyric acid (Wood, Watson & Ducker, 1968). Drugs which cause convulsions and impair aerobic metabolism or deplete brain γ-aminobutyric acid should therefore induce fewer convulsions during hypoxia.

Semicarbazide is thought to act in this way (Killam & Bain, 1957) and the convulsions it induced were antagonized by hypobaric hypoxia (Baumel, Shatz & others, 1969). *m*-Fluorotyrosine impairs oxidative metabolism in brain (Weissman & Koe, 1967), and we now show acute hypoxia to antagonize the convulsions and mortality it produces.

Swiss albino, random-bred male mice (Charles River Farms), 22–26 g were housed at 21–23° with room lights alternating on a 12-h light-dark cycle. The hypobaric chambers (Baumel, Robinson & Blatt, 1967) were plexiglass desiccators (internal diameter 10 in, height 14 in) connected, in parallel, to a vacuum pump through a manifold which exhausted room air.

Drug solutions were freshly prepared immediately before intraperitoneal injection. The animals were injected and immediately placed, in pairs, in the four altitude-chambers which were then decompressed over a 10-min period to 364 mm Hg (10% O_2). Controls were placed in identical chambers open to room air (760 mm Hg, 21% O_2).

Hypobaric hypoxia protected against *m*-fluorotyrosine convulsions at 3 and 4 h after administration of the drug. Lethality was decreased throughout the exposure period (Fig. 1).