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Relaxant effect of the H_2-receptor antagonist oxmetidine on guinea-pig and human airways

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1 The effects of three different H_2-receptor antagonists (cimetidine, ranitidine and oxmetidine) were tested on isolated preparations of guinea-pig trachea and human bronchus against contractions induced by acetylcholine, histamine and potassium chloride (KCl). In addition, their influence on calcium concentration-response curves in guinea-pig tracheal spirals was examined in a potassium-rich solution (30 mM). Finally, their effects were studied *in vivo* against acetylcholine and histamine-induced bronchoconstriction in anaesthetized guinea-pigs.

2 In guinea-pig isolated trachea, oxmetidine – in contrast to cimetidine and ranitidine, which were completely inactive – induced a concentration-dependent relaxation regardless of the excitatory stimulus: its $-\log EC_{50}$ values (i.e. the negative log concentration that caused a 50% relaxation) were 3.46 ± 0.11, 4.61 ± 0.09 and 4.20 ± 0.12 against acetylcholine, histamine and KCl, respectively. In Ca^{2+}-free, K^+-enriched solution, the compound was able to inhibit Ca^{2+}-induced contractions at concentrations close to those needed to counteract the spasmogenic effect of histamine in normal Krebs solution. Results obtained in the human bronchus preparation were similar to those observed in guinea-pig tracheal spirals.

3 When tested against acetylcholine or histamine-induced bronchoconstriction *in vivo*, oxmetidine (10 and 30 mg Kg^{-1} intravenously) significantly reduced the increase in pulmonary airway resistance (R_{aw}) induced by both agents. Once again, cimetidine and ranitidine were completely ineffective.

4 In summary, oxmetidine displayed non-specific antispasmogenic activity on guinea-pig and human airways. This effect, which is independent of H_2-receptor blockade, represents a side-effect of the drug which may be connected to its interference with Ca^{2+} influx and the action or release of intracellular Ca^{2+}.

Introduction

H_2-receptor antagonists represent a well-known class of antiulcer drugs, their established mechanism of action being the inhibition of gastric acid secretion through H_2-receptor blockade on parietal cells (Bertaccini & Dobrilla, 1980). This antisecretory effect is the consequence of their primary pharmacological action (i.e. competitive antagonism at H_2-receptors) and it is shared by all the members of this group of drugs. However, both experimental and clinical studies have shown that many of these compounds possess some pharmacological actions completely independent of H_2-receptor blockade. These 'side-effects' are peculiar to an individual member rather than the entire class of the drugs (Bertaccini & Coruzzi, 1984a). Ranitidine, a compound bearing an alkyl furan ring, can be used to illustrate this point. Ranitidine possesses, as a side-effect, a cholinergic-like action, first demonstrated on gastrointestinal motility (Bertaccini & Coruzzi, 1982; Bertaccini & Scarpignato, 1982) and later also demonstrated on salivary secretion in the rat and on the guinea-pig urinary bladder (for review see Bertaccini & Coruzzi, 1984b). This cholinomimetic effect is involved in the increase in lower oesophageal sphincter (LES) pressure (Bertaccini *et al.*, 1981) and in the decrease in gastric emptying (Scarpignato *et al.*, 1982) observed in man and may be, therefore, of clinical relevance.

A more recent member of this class of drugs, oxmetidine (an imidazole compound which differs from cimetidine in carrying an isocytosine ring instead of the cyanoguanidine group in the side chain, Figure 1) is endowed, in contrast, with inhibitory

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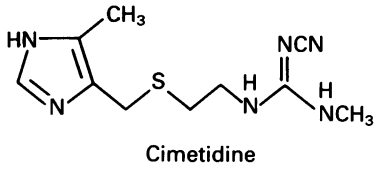
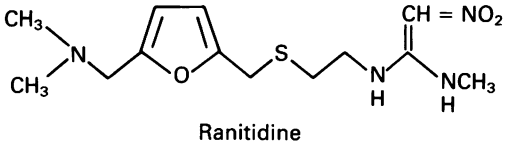
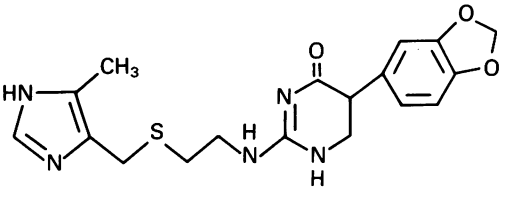


Cimetidine



Ranitidine



Oxmetidine

Figure 1 Chemical structures of the H_2-receptor antagonists studied.

activity on the motility of the digestive tract (Bertaccini *et al.*, 1983). In addition, this compound has been shown to possess a negative inotropic effect on isolated heart preparations from rabbits (Coruzzi *et al.*, 1982) and guinea-pigs (Black *et al.*, 1985) and on human atria (Coruzzi *et al.*, 1983). Also, it was able to antagonize the contractile effects of KCl, angiotensin and noradrenaline on rabbit isolated aorta (Bertaccini *et al.*, 1984). Concentrations required for this effect were 10 to 100 times higher than those needed to inhibit histamine H_2-receptors.

The mechanism of the cholinomimetic action of ranitidine involves both direct and indirect (through inhibition of acetylcholinesterase and butyryl cholinesterase) effects on muscarinic receptors (Bertaccini & Coruzzi, 1984b). In contrast, the mechanism of the antispasmogenic action of oxmetidine is not completely understood. Calcium antagonist activity (Coruzzi *et al.*, 1982) and effects on the availability of intracellular calcium (Bertaccini *et al.*, 1984) were suggested to explain this peculiar pharmacological action.

In contrast to cimetidine and ranitidine, oxmetidine was able to modify bronchomotor tone after oral administration in healthy humans (Dal Negro *et al.*, 1984). In this connection we tested oxmetidine, as well as ranitidine and cimetidine, for effects on guinea-pig airways both *in vitro* and *in vivo*. Additional experiments were performed on the human isolated bronchus preparation.

Preliminary results of the present investigation have been presented to the French Society of Pharmacology and have appeared in abstract form (Gnassounou *et al.*, 1986).

Methods

Guinea-pig trachea in vitro

Tracheal spirals were obtained from male guinea-pigs (250–300 g) anaesthetized with urethane (1.25 g kg^{-1}) and were equilibrated under an initial tension of 1.5 g in Krebs solution at 37°C, gassed with 95% O_2 and 5% CO_2. The initial tension ensured that, after 1 h 15 min equilibration, the resting tension ranged between 0.4 and 0.6 g. Responses to agonists were reproducible under these conditions. Tension was measured isometrically with a Ugo BASILE isometric transducer and recorded on a Ugo BASILE writing microdynamometer. The Krebs solution had the following composition (mM), NaCl 113, KCl 4.7, $CaCl_2$ 1.9, $MgSO_4$ 1.2, $NaHCO_3$ 25, KH_2PO_4 1.2, glucose 11.5.

Preparations were first tested for maximal tension with acetylcholine (ACh, 3×10^{-4} M) and for maximal relaxation with isoprenaline (3×10^{-6} M). Afterwards, the effects of oxmetidine, ranitidine and cimetidine were studied on contractions induced by ACh (2×10^{-5} M), histamine (2×10^{-5} M) and KCl (1×10^{-2} M). These H_2-receptor antagonists were added to the bath 15 min before the addition of the contractile agent. Test tissues were exposed to only one spasmogen followed by increasing concentrations of the H_2-receptor antagonists.

The effects of the H_2-receptor antagonists were expressed as % reduction of the initial contraction obtained with the stimulatory compound alone. $-\log EC_{50}$ values (i.e. the negative log of the drug concentration that caused a 50% reduction) were calculated from the log concentration-effect curves for each H_2-receptor antagonist.

Experiments in Ca^{2+}-free, K^+-enriched medium

Ca^{2+} concentration-response curves were established according to Godfraind *et al.* (1968). Tracheal spirals were incubated for 1 h in a Krebs solution similar to the one described above, but without $CaCl_2$ then for 15 min in $CaCl_2$-free solution in the presence of ethylenediaminetetraacetic acid (EDTA) 10^{-3} M. The preparations were washed at intervals of 15 min. Subsequently, the spirals were incubated in a calcium-free solution with additional K^+. The composition of the potassium-enriched solution was (mM): NaCl 109,

KCl 30, $MgCl_2$ 0.49, $NaHCO_3$ 11.9, Na_2HPO_4 0.4 and glucose 5.5. This medium was gassed with 95% O_2 plus 5% CO_2 and, after equilibration, its final pH was 7.46. After incubation, the concentration-response curves to Ca^{2+} 0.01 to 3 mM were constructed by cumulative addition. The contact time between the tissue and each Ca^{2+} concentration was 10 to 15 min. The H_2-receptor antagonists were added to the bath 20 min before the addition of Ca^{2+}. Three Ca^{2+} concentration-response curves (without and with two different concentrations of an H_2-antagonist) were constructed on each tissue, so it acted as its own control.

Experiments on human isolated bronchus

The human isolated bronchus was prepared according to Advenier *et al.* (1986). Human bronchial tissue (usually with an inner diameter of 4–12 mm) obtained from patients undergoing surgery for lung cancer, but taken at distance from malignancy, was dissected free of parenchyma and transported to the laboratory in ice-cold Krebs solution previously gassed with a mixture of 95% O_2 and 5% CO_2. The tissue was stored overnight at 4°C and the experiments were carried out on the next day. Previous investigations have shown that overnight storage of tissue does not alter its reactivity (Brink *et al.*, 1980; Ghelani *et al.*, 1980; Guillot *et al.*, 1984; Vincenc *et al.*, 1984). Spirally-cut strips from a segmental bronchus were suspended in Krebs solution under an initial tension of 2.5 g in the conditions described for guinea-pig isolated trachea. They were first contracted to maximal tension with carbachol (1×10^{-4} M). The effect of oxmetidine was subsequently tested against contractions induced by histamine, acetylcholine or KCl (at the concentrations stated above). When a stable contraction was obtained, cumulative concentration-response curves to oxmetidine (10^{-6} to 3×10^{-4} M) were obtained by adding increasing concentrations of the drugs at 10–20 min intervals. After the last concentration of oxmetidine, theophylline (3×10^{-3} M) was added to the bath.

Relaxation produced by oxmetidine was expressed as percentage of the effect induced by theophylline and $-\log EC_{50}$ values were calculated.

Pulmonary airway resistance in vivo

Pulmonary airway resistance (R_{AW}) was determined according to the method of Advenier *et al.* (1983). Male guinea-pigs weighing 400–500 g were anaesthetized with urethane (1.25 g kg^{-1}) and small polyvinylchloride catheters were inserted into the left jugular vein and carotid artery. Intrathoracic pressure was measured by pleural puncture with a needle inserted into the pleural space through the sixth or seventh intercostal space and connected through a catheter to a differential pressure transducer (Sanborn 2688). The animals were then placed in a body plethysmograph.

A Sanborn A 440 pneumotachometer was inserted through one of the plethysmograph walls thus allowing the measurement of air flow. Tidal volume was determined by electronic integration of the flow signal. Calculation of R_{AW} was made according to Amdur & Mead (1958). With this method, mean airway resistance is expressed as the ratio of transpulmonary pressure change to flow change occurring at two points of equal volume during inspiration and expiration. Since compliance is the same at these two points, this factor is eliminated from mean airway resistance calculations.

The experiments were performed on groups of at least 6 animals. An interval of 30 min elapsed before any drug administration. The actions of oxmetidine, cimetidine and ranitidine on the bronchoconstriction induced by histamine or acetylcholine (ACh) was tested on six groups of guinea-pigs, one group for each bronchoconstrictor and each H_2-receptor antagonist. Each animal received 3 or 4 intravenous doses of ACh (25 $\mu g\ kg^{-1}$) or histamine (20 $\mu g\ kg^{-1}$) at intervals of 5–10 min and the mean response was calculated. Oxmetidine, ranitidine and cimetidine were then administered intravenously and ACh or histamine was injected once more 10 min after each dose of antagonist. The results are expressed as percentage change of the initial increase in R_{AW} induced by the bronchoconstrictor agents. Under our experimental conditions, pulmonary airway resistance increased by 227 ± 38% and 102 ± 15% after ACh and histamine, respectively. These values were not modified by prior administration of saline.

Statistical evaluation of data

Results obtained are presented as a mean ± s.e.mean. Significant differences between the means were assessed by using one way analysis of variance. All the calculations were made according to Barlow (1983) by using a program running on an Apple IIe microcomputer.

Drugs

Oxmetidine (SKF 92994) and cimetidine were the generous gifts of Dr M.E. Parsons (Smith, Kline & French, Welwyn, U.K.); ranitidine hydrochloride was supplied by Laboratoires Glaxo (Paris, France); acetylcholine dihydrochloride and histamine hydrochloride were purchased from Laboratoires Lematte et Boinot (Paris, France) and Prolabo (Paris, France), respectively.

For the preparation of stock solutions, cimetidine was first dissolved in 0.1 N HCl and subsequently

adjusted to pH 6 with 0.1 N $NaHCO_3$. Ranitidine and oxmetidine were dissolved in distilled water. Dilutions were made with nutritive solutions or saline for *in vitro* and *in vivo* experiments, respectively.

Results

In vitro *experiments*

The effects of oxmetidine, ranitidine and cimetidine on guinea-pig isolated trachea are summarized in Figure 2. Oxmetidine was able to inhibit in a concentration-dependent fashion the contractions induced by ACh (2×10^{-5} M), histamine (2×10^{-5} M) and KCl (1×10^{-2} M), its $-\log EC_{50}$s being 3.46 ± 0.11, 4.61 ± 0.09 and 4.20 ± 0.12, respectively. Figure 3 depicts the results of a typical experiment in which histamine or KCl was employed as a contractile agent. In contrast to oxmetidine, the other H_2-antagonists tested, namely ranitidine and cimetidine, were completely ineffective (Figure 2). Each of the three compounds, when added alone to the bath, was unable to modify the basal tone of the preparation.

When tested in Ca^{2+}-free, K^+-enriched medium, the inhibitory effect of oxmetidine on Ca^{2+}-induced contractions was observed at concentrations close to those needed to counteract the spasmogenic effect of histamine in normal Krebs solution (Figure 4). In these experimental conditions, both cimetidine and ranitidine were again inactive.

The effect of oxmetidine on human bronchi precon-

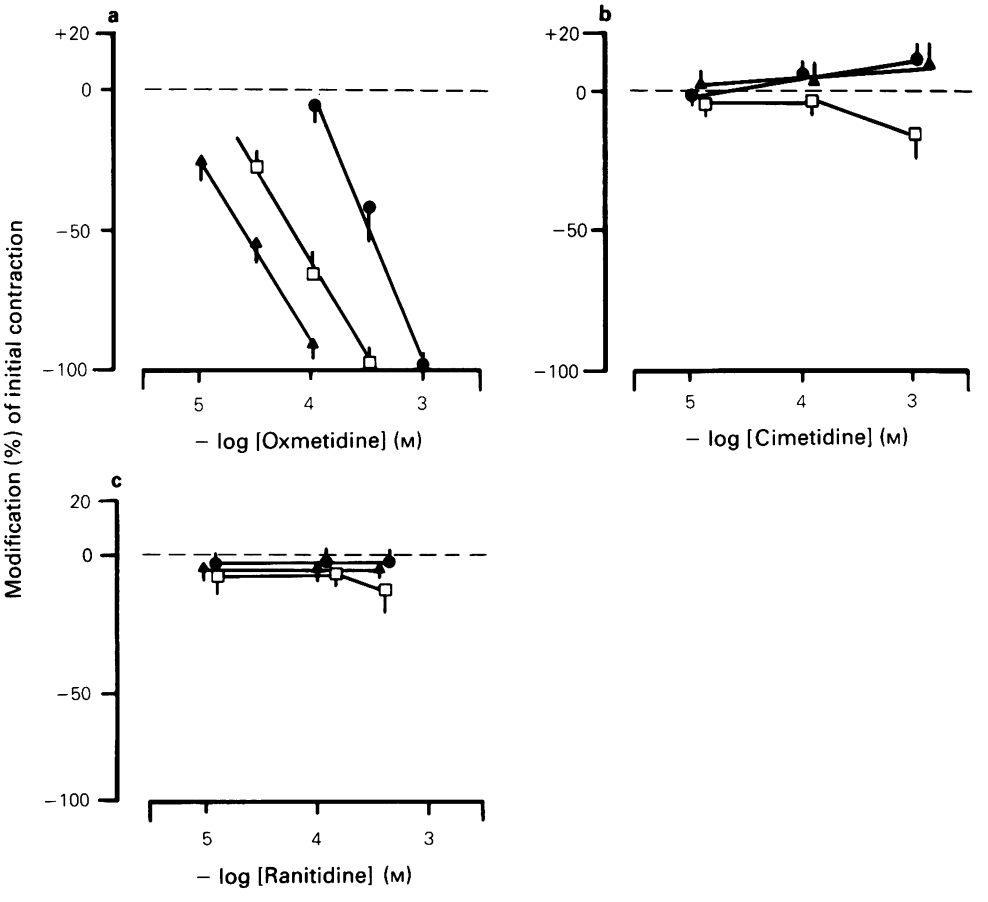


Figure 2 Effect of (a) oxmetidine, (b) cimetidine and (c) ranitidine on acetylcholine (2×10^{-5} M, ●), histamine (2×10^{-5} M, ▲) and KCl (1×10^{-2} M □)-induced contractions in guinea-pig isolated trachea. Each point represents the mean of the values obtained from 6–8 experiments. Vertical lines show s.e.mean.

tracted with ACh (2×10^{-5} M), histamine (2×10^{-5} M) or KCl (1×10^{-2} M) is depicted in Figure 5. In this preparation, too, the compound induced a concentration-dependent relaxation regardless of the excitatory stimulus. The calculated $-\log EC_{50}$ values were 4.56 ± 0.12, 4.55 ± 0.09 and 4.62 ± 0.05 against ACh, histamine and KCl, respectively.

In vivo *experiments*

In line with the *in vitro* experiments, oxmetidine was able to reduce significantly the increase in R_{AW} induced by both ACh and histamine in the anaesthetized guinea-pig (Table 1). Once again, ranitidine and cimetidine did not have any significant effects.

Discussion

Results of the present investigation show that, unlike ranitidine and cimetidine, oxmetidine was able to inhibit the contractions induced by the different test agents (ACh, histamine and KCl) on guinea-pig airways both *in vitro* and *in vivo*, as well as on human bronchi *in vitro*. The concentrations required to exert such a pharmacological action in the *in vitro* experiments were much higher than those shown to block H_2-receptors in guinea-pig atria and papillary muscle (Blakemore *et al.*, 1980; Coruzzi *et al.*, 1983a,b). These concentrations are, however, in the same range as those found by Bertaccini *et al.* (1983) and Black *et al.* (1985) to affect cardiac and vascular smooth muscle. In accordance with *in vitro* data, doses employed in *in vivo* experiments were greater than those required to inhibit histamine or pentagastrin-induced acid secretion (Blakemore *et al.*, 1980).

Besides the high doses required, two further observations suggest that this peculiar effect of oxmetidine is completely independent of H_2-receptor blockade: (1) the inactivity – under the same experimental conditions – of ranitidine and cimetidine, and (2) the knowledge that H_2-receptor

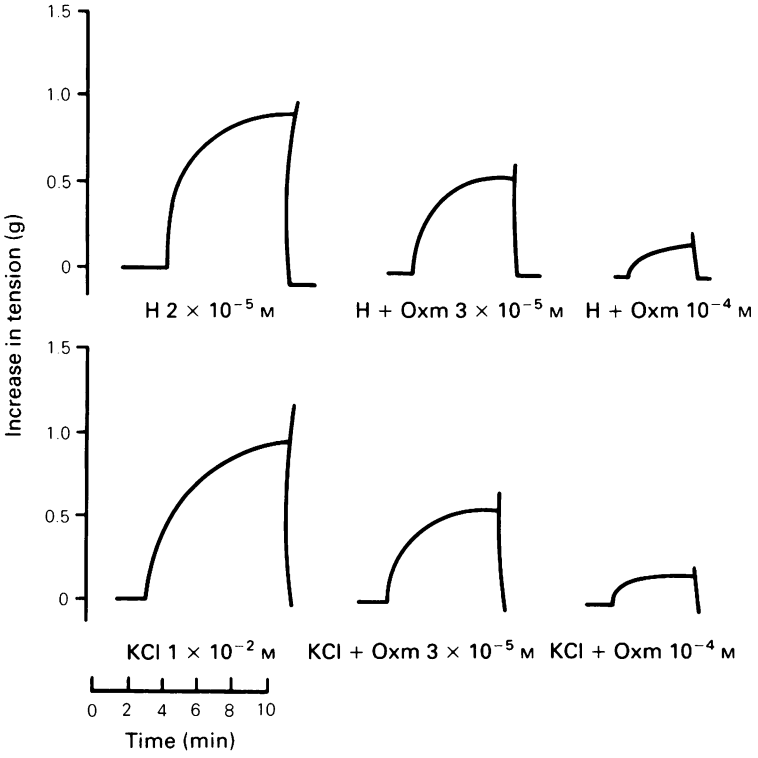


Figure 3 Guinea-pig isolated trachea: results of a typical experiment showing the inhibitory effect of oxmetidine (Oxm) on histamine (H, 2×10^{-5} M) and KCl (1×10^{-2} M)-induced contractions.

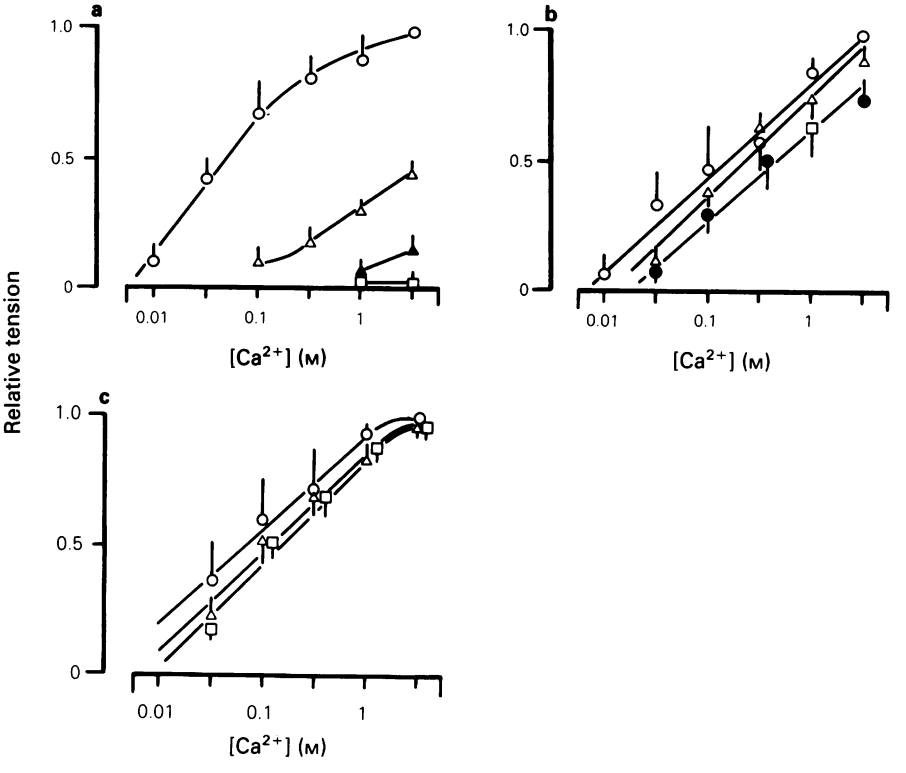


Figure 4 Guinea-pig tracheal spirals: effect of (a) oxmetidine, (b) cimetidine and (c) ranitidine on concentration-response curves to calcium. Responses were obtained in a potassium-rich (30 mM) solution in the absence (○) and presence of different concentrations (●, 3×10^{-6} M; △, 3×10^{-5} M; ▲, 1×10^{-4} M; □, 3×10^{-4} M) of the antagonists. The contraction caused by $CaCl_2$ 3 mM in control experiments was arbitrarily taken as 1. Each point represents the mean of the values obtained from 4–6 preparations. Vertical lines show s.e.mean.

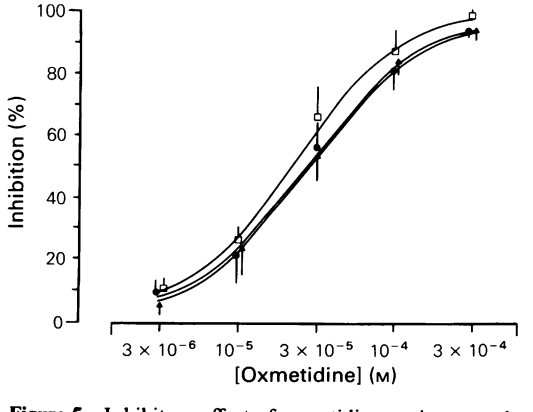


Figure 5 Inhibitory effect of oxmetidine against acetylcholine (2×10^{-5} M, ●), histamine (2×10^{-5} M, ▲) and KCl (1×10^{-2} M, □)-induced contractions on human isolated bronchus preparation. Each point represents the mean of values obtained from 4–6 experiments. Vertical lines show s.e.mean.

stimulation is usually associated with bronchial smooth muscle relaxation. As a consequence, antagonists acting at H_2-receptors usually enhance the response of guinea-pig tracheo-bronchial smooth muscle to histamine (for review see Eyre & Chand, 1982). Based on the results obtained on the rabbit isolated heart, Coruzzi *et al.* (1982) suggested that oxmetidine has a mechanism of action resembling that of the 'classical calcium channel antagonists', such as verapamil. Results of the present investigation, however, do not support this hypothesis. Indeed, on the guinea-pig isolated trachea as well as in the human bronchi, oxmetidine concentrations required to inhibit K^+- or Ca^{2+}-induced contractions are close to those necessary to counteract both ACh and histamine-induced contractions. It has been shown previously that, in these preparations, the 'classical' calcium channel antagonists (e.g. verapamil, diltiazem, nicardipine) are able to inhibit K^+-induced as well as Ca^{2+}-induced contractions at much lower concentrations than those required to inhibit the contractile effect of

Table 1 Effects of oxmetidine, cimetidine and ranitidine on the increase in pulmonary airway resistance R_{AW} induced in anaesthetized guinea-pigs by acetylcholine or histamine

Compound	*Dose* (mg kg^{-1}) *3*	*10*	*30*
Acetylcholine			
Oxmetidine	+ 32 ± 27	− 30 ± 16	− 48 ± 15*
Cimetidine	− 8 ± 28	+ 62 ± 41	+ 31 ± 15
Ranitidine	− 8 ± 13	+ 17 ± 21	+ 19 ± 16
Histamine			
Oxmetidine	+ 38 ± 27	− 26 ± 6*	− 53 ± 14*
Cimetidine	+ 24 ± 27	+ 18 ± 22	+ 28 ± 31
Ranitidine	− 31 ± 26	+ 29 21	+ 22 ± 17

Results, expressed as % change (increase (+), decrease (−)), are means ± s.e.mean of the values obtained from 6–8 experiments.
*$P < 0.05$

ACh and histamine (Advenier *et al.*, 1984). On guinea-pig isolated trachea, as on the rabbit isolated aorta (Bertaccini *et al.*, 1984), oxmetidine behaved as an antispasmogenic agent, its effect being independent of the type of stimulant employed to contract the preparation.

The ability of oxmetidine to antagonize, to approximately the same extent, the stimulatory effect of compounds acting via different mechanisms (KCl exerts a direct action on tracheal smooth muscle and involves both depolarization and influx of Ca^{2+} (Foster *et al.*, 1983), whereas ACh and histamine involve depolarization with little effect on Ca^{2+} influx (Ahmed *et al.*, 1984) suggests that it may have a complex action, interfering with the transport at the membrane level and with the release or utilization of calcium ions at intracellular sites. Indeed, in the rabbit aorta oxmetidine behaved similarly to nitroglycerin, a compound which is assumed to act predominantly on intracellular calcium (Ito *et al.*, 1980).

In our experimental conditions, neither ranitidine nor cimetidine modified the bronchoconstrictor effects of ACh and histamine either *in vitro* or *in vivo*. Our results are in accord with those of Duncan *et al.* (1980), who showed that, even at high doses, cimetidine and ranitidine were unable to produce a significant displacement of the concentration-response curves of airway smooth muscle preparations from guinea-pigs to contractile agents. However, Opkapo *et al.* (1978) found that histamine- but not ACh-induced contractions were greater in the presence of metiamide, a former imidazole H_2-receptor antagonist. This potentiation has been attributed to the block of H_2-receptors mediating relaxation and was further confirmed by subsequent investigations involving the use of selective H_2-agonists, e.g. dimaprit or 4-methylhistamine (Eyre & Chand, 1982).

The lack of activity of ranitidine on ACh-induced contractions in guinea-pig trachea shows that in this tissue, unlike others, this H_2-antagonist is devoid of cholinomimetic action. Therefore, in agreement with the conclusions of Bertaccini (Bertaccini & Coruzzi, 1984b), the cholinergic-like effect of ranitidine is not ubiquitous and varies conspicuously between the different tissues and animal species.

Our results *in vivo* with the other two H_2-antagonists concord with the finding that metiamide and cimetidine are inactive against the antigen-induced allergic bronchospasm in guinea-pigs (Pare & Miller, 1980).

We concluded that, in contrast to ranitidine and cimetidine, oxmetidine displays non-specific antispasmogenic activity on airway smooth muscle both *in vitro* and *in vivo*. This action, which is independent of H_2-receptor blockade, represents a side-effect of the drug which may be connected with effects on the cellular influx of Ca^{2+} and the intracellular release or action of this ion.

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