3-carboxyanthraquinone. J. Label. Compound. & Radiopharm. 25: 23–33
Dodsworth, D. J., Calgagno, M.-P., Ehrmann, E. U., Devadas, B., Sammes, P. G. (1981) A new route to anthraquinones. J. Chem. Soc. Perkin Trans. 1: 2120–2124
Donowitz, M., Wicks, J., Battisti, L., Pike, G., DeLellis, R. (1984) Effect of Senokot on rat intestinal electrolyte transport: evidence of calcium dependence. Gastroenterology 87: 503–512
Fujita, M., Furuya, T., Matsuo, M. (1961) Studies on the metabolism of naturally occurring anthraquinones. I The metabolism of 1-hydroxyanthraquinone and 2-hydroxyanthraquinone. Chem. Pharm. Bull. Tokyo 9:962–966
Garcia-Villar, R., Leng-Peschlow, E., Ruckebusch, Y. (1980) Effect of anthraquinone derivatives of canine and rat intestinal motility. J. Pharm. Pharmacol. 32: 323–329
Gebhardt, H. (1936) Das Schicksal der Sennastoffe im Organismus, Naunyn-Smiedeberg's Arch. Exp. Path. Pharmak. 182: 521–526
Hardcastle, J. D., Wilkins, J. L. (1970) The action of sennosides and related compounds on human colon and rectum. Gut 11: 1038–42
Lemli, J., Lemmens, L. (1980) Metabolism of sennosides and rhein in the rat. Pharmacology 20 (Suppl. 1): 50–57
Lemmens, L. (1978) Metabolisme en werkingsmechanisme van laxerende antraceen derivaten. Ph.D. thesis, Catholic University Leuven, Belgium
Lemmens, L. (1979) The laxative action of antracene derivatives. II Absorption, metabolism and excretion of sennoside A and B in the rat. Pharm. Weekblad 114: 178–185
Lemmens, L., Dreessen, M. (1979) The laxative action of antracene derivatives. III Absorption, metabolism and excretion of rhein in the rat. Pharm. Weekblad 114: 950–956
Leng-Peschlow, E. (1986) Acceleration of large intestine transit time in rats by sennosides and related compounds. J. Pharm. Pharmacol. 38: 369–373.
Moreau, J. P., Moreau, S., Skinner, S. (1985) Comparative physiological disposition of some anthraquinone glycosides and aglycones. Biopharmaceutics & Drug disposition, 6: 325–334
Moss, M. J. R. (1969) Studies in absorption and biotransformation of anthraquinones. Ph.D. thesis, University of London, England.
Stoll, A., Becker, B., Helfenstein, A. (1950) Die Konstitution de. Sennoside Helv. Chim. Act. 33: 313–336
Thomson, R. H. (1971) in Naturally Occurring Quinones. 2nd edition, Academic Press (London & N.Y.), pp 40–41
Wienbeck, M., Kortenhaus, E., Wallenfels, M., Karaus, M., Erckenbrecht, J. (1985) Sennosides and loperamide induce opposite motor patterns in the rat colon. Gastroenterology 88: 1631

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Antihistaminic and anticholinergic activities of mequitazine in comparison with clemizole

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Abstract—The antihistamine and anticholinergic properties of mequitazine have been investigated and compared with those of clemizole. Both mequitazine and clemizole antagonized the effect of histamine in guinea-pig ileum competitively, the pA_2 values calculated by Schild plot were 9.95 ± 0.44 for mequitazine and 10.54 ± 0.44 for clemizole. Mequitazine at 10^{-7} M produced a parallel shift of the dose-response curve to acetylcholine in the rat duodenum, clemizole and the lower doses of mequitazine failed to modify the effect of acetylcholine. The potency of mequitazine and clemizole as H_1-histamine blockers is similar, but only mequitazine at highest concentration used showed anticholinergic activity.

There has been a resurgence of interest in H_1-antihistamines and their clinical effects. The new antihistamine drugs such as astemizole, terfenadine or mequitazine have in common the property of crossing the blood-brain barrier with difficulty, and thus they do not cause sedation in usual dosages (Brandon 1985). Blockade of H_1-receptors is of particular therapeutic value in the treatment of several allergic symptoms. Studies to establish the clinical efficacy of these drugs have frequently been carried out, but in contrast, little attention is paid to in-vitro studies on the action of the new antihistamine drugs on the smooth muscle, and usually the information concerning their pharmacological characteristics is not available.

In this communication we describe the effect of mequitazine, a phenothiazine derivative (Fujimura et al 1981; Kanba & Richelson 1984), on the contraction induced by histamine and acetylcholine in the intestinal smooth muscle of the guinea-pig and rat in-vitro. The results are compared with those obtained with clemizole, a well-known anti-H_1 agent, in the same preparations.

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Materials and methods

Adult guinea-pigs, 350–450 g, and Wistar rats, 200–250 g, were used. Segments of ileum of the guinea-pig and of duodenum of the rat were mounted in a 20 mL organ bath containing a Tyrode solution at 37 °C of the following composition (M): NaCl 136, KCl 2·7, $CaCl_2$ 1·4, $MgSO_4$ 0·04, KH_2PO_4 0·4, $NaHCO_3$ 11·9 and glucose 5·6, aerated with 5% CO_2 in O_2. Changes in length were recorded by means of an isotonic transducer (Ugo Basile 7004) and a Ugo Basile (model Gemini 7070) recorder.

The preparations were allowed to equilibrate under a load of 1 g for at least 30 min before any drug was added. Concentration response curves to histamine (ileum) or acetylcholine (duodenum) in the absence or presence of antihistamine drugs were obtained by adding the agonist drugs cumulatively. Antagonists were incubated for 15 min.

Contractile responses to agonists were expressed as a percentage of the maximum response obtained. Effective concentration 50% (EC50) was calculated graphically from a plot of log concentrations vs percentages of the maximum response (Emax) produced by each agonist in individual experiments.

The calculation of the pA_2 values was according to Arunlakshana & Schild (1959) as described previously (Aguilar et al 1986). All data are shown as mean ± standard error of the mean. Statistical analysis of the data was carried out using Student's *t*-test at a 5% significance level.

The drugs used were acetylcholine hydrochloride and histamine dihydrochloride (Sigma Co.); clemizole hydrochloride (Schering España, S.A.) and mequitazine hydrochloride (Rhône Poulenc Farma S.A.E.).

Results

Histamine (6.5×10^{-8} to 1.08×10^{-3} M) induced concentration

related contractions of the guinea-pig ileum. The EC50 value was $7.39 \pm 1.9 \times 10^{-7}$ M. Mequitazine and clemizole shifted the concentration-response curve for histamine induced contraction to the right in a dose dependent manner (Fig. 1). Analysis of this

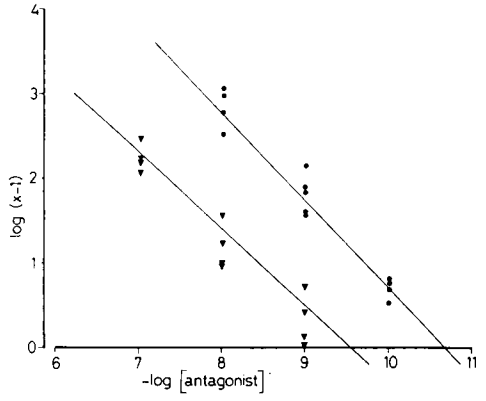

FIG. 1. Histamine dose-ratio as a function of mequitazine (▼) and clemizole (●) concentration. The intercepts on the abcissa scale of the regression lines for log (dose-ratio^{-1}) vs the negative log mequitazine and clemizole concentration give pA_2 values of 9·95 and 10·54, respectively.

displacement by use of the Arunlakshana and Schild plot yielded a pA_2 value of 9.95 ± 0.44 with a slope of 0.903 ± 0.07 for mequitazine. For clemizole the pA_2 value is 10.54 ± 0.44 with a slope of 1.03 ± 0.03. The values of both slopes are not significantly different from unity.

Acetylcholine (0.85×10^{-8} M to 70.4×10^{-5} M) induced concentration related contractions of the rat duodenum. The EC50 value was $1.69 \pm 0.5 \times 10^{-6}$ M. Clemizole (10^{-9}, 10^{-8} and 10^{-7} M) failed to modify the contractile effect of acetylcholine. Mequitazine 10^{-7} M, but not 10^{-9} and 10^{-8} M, produced a parallel shift of the concentration response curve for acetylcholine to the right (Table 1).

Table 1. EC50 and Emax values for acetylcholine in the absence and presence of mequitazine or clemizole in the rat isolated duodenum.

	n	E_{max}	EC_{50}
Acetylcholine	25	100	$1.69 \pm 0.5 \times 10^{-6}$ M
+mequitazine 10^{-9} M	4	107.4 ± 4.0	$6.67 \pm 3.2 \times 10^{-7}$ M
+mequitazine 10^{-8} M	4	92.0 ± 5.6	$1.45 \pm 0.7 \times 10^{-6}$ M
+mequitazine 10^{-7} M	4	104.2 ± 2.3	$7.60 \pm 3.2 \times 10^{-6}$ M*
+clemizole 10^{-9} M	5	107.1 ± 10.2	$4.50 \pm 0.9 \times 10^{-7}$ M
+clemizole 10^{-8} M	4	96.5 ± 4.1	$6.30 \pm 1.5 \times 10^{-7}$ M
+clemizole 10^{-7} M	4	102.8 ± 4.9	$2.42 \pm 1.9 \times 10^{-6}$ M

* Statistically different from control values, $P < 0.05$.

Discussion

The contractile response to histamine in guinea-pig ileum was antagonized in a dose-dependent manner by both mequitazine and clemizole. The pA_2 value and the slope of the Schild plot, in each case, strongly suggest the existence of a competitive antagonism between histamine and both antagonists. The pA_2 value calculated for clemizole in the present experiments is similar to those obtained for the same drug using the guinea-pig colon (Aguilar et al 1986). The pA_2 value for mequitazine is closely related with the K_D value obtained by Kanba & Richelson (1984) in human brain studies using a binding technique. The comparison of the values of pA_2 obtained for each drug demonstrated that the potency of mequitazine as H_1-antihistamine is similar to that of clemizole.

Clemizole did not have antimuscarinic properties, but mequitazine at the highest concentration tested showed anticholinergic activity. Although sedative effects of antihistaminic drugs have been associated with anticholinergic action, as well as the blockade of the other kinds of central receptors (Nicholson 1983), the result described in the present study of anticholinergic properties of mequitazine is not in contrast with the lack of the sedative effects shown by Nicholson & Stone (1984) in clinical studies, since this compound has been considered to cross the blood brain barrier in low amounts.

The anticholinergic property of mequitazine should be taken in account when this compound is used as an antihistamine in in-vitro studies.

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References

Aguilar, M. J., Morales-Olivas, F. J., Rubio, E. (1986) Pharmacological investigation into the effects of histamine and histamine analogues on guinea-pig and rat colon in vitro. Br. J. Pharmac. 88: 501–506

Arunlakshana, O., Schild, H. O. (1959) Some quantitative uses of drug antagonists. Br. J. Pharm. Chemother. 14: 48–58

Brandon, M. L. (1985) Newer non-sedating anthistamines, will they replace older agents? Drugs 30: 377–381

Fujimura, H., Tsurumi, K., Yanagihara, M., Hiramatsu, Y., Tamura, Y., Shimizu, Y., Hojo, M., Yoshida, Y. (1981) Pharmacological study of mequitazine (LM-209) (I) antagonistic actions of chemical mediators. Folia Pharmacol. Jap. 78: 279–289

Kanba, S., Richelson, E. (1984) Histamine H_1 receptors in human brain labelled with (^{3}H) doxepin. Brain Research 304: 1–7

Nicholson, A. N. (1983) Antihistamines and sedation. Lancet i: 211–212

Nicholson, A. N., Stone, B. M. (1984) H_1- and H_2-receptor antagonists: studies on sleep. Brit. J. Clin. Pharmacol. 17: 618P–619P