EFFECT OF ANTIHISTAMINE DRUGS ON GASTRIC SECRETION IN RATS

M. É. Kaminka, S. M. Tupikina,
and Academician M. D. Mashkovskii*

UDC 615.218.2.015.4:612.323

KEY WORDS: phencarol; diamine oxidase activation; inhibition of gastric secretion.

The original Soviet antiallergic drug phencarol (quinuclidyl-3-diphenylcarbinol) is a member of a new chemical class of antihistamine drugs, the quinuclidylcarbinol derivatives [2]. It is a competitive antagonist of histamine in its effect on H_1-receptors and in addition, unlike antihistamine drugs already known (diphenhydramine, promethazine, pyrilamine, ciproheptadine) phencarol acitvates the enzyme diamine oxidase, accelerates the oxidative deamination of histamine, and lowers the histamine level in the body tissues [1].

It can be tentatively suggested that, by lowering the tissue histamine concentration, phencarol must also reduce the effect of histamine on H_2 receptors. Since H_2 receptors play an important role in the regulation of gastric secretion, experiments were carried out on rats to study the effect of phencarol on gastric secretion and to compare it with the action of H_1 receptor antagonists of various chemical classes (diphenhydramine, omeril, pyrilamine, ciproheptadine) and the specific H_2 receptor antagonist cimetidine.

EXPERIMENTAL METHOD

Experiments were carried out on 300 noninbred male rats weighing 180-200 g; gastric secretion was studied by a modified Shay's method [4]. The rats were deprived of food for 24 h but given water ad lib. Under ether anesthesia laparotomy was performed and a ligature applied to the pyloric part of the stomach. The drugs were injected in the form of a suspension in 1% carboxymethylcellulose solution by gastric tube 60 min before ligation of the pylorus. Control animals received the same volume of carboxymethylcellulose. After 4 h the rats were decapitated, the stomach removed, and the volume of gastric contents measured and expressed per 100 g body weight; free hydrochloric acid in the gastric juice was determined (in ml 0.1 N NaOH/100 ml gastric contents). To analyze the mechanism of action of phencarol experiments were carried out on animals in which secretion was stimulated by subcutaneous injection of carbachol (0.25 mg/kg) or histamine (2.5 mg/kg); diamine oxidase was blocked by subcutaneous injection of aminoguanidine (5 mg/kg).

The results were subjected to statistical analysis and the confidence interval of the arithmetic mean was determined at the $P = 0.05$ level.

EXPERIMENTAL RESULTS

It will be clear from Table 1 that with a dose of 100 mg/kg (internally) only cimetidine and phencarol reduced the volume of gastric secretion and the content of free hydrochloric acid. Pyrilamine, ciproheptadine, and diphenhydramine, in doses with a powerful and prolonged antihistamine action, caused no statistically significant change in the secretion parameters, whereas omeril actually increased the free hydrochloric acid in the gastric contents of the rats.

With respect to their effect on the volume of gastric secretion ED_{50} for phencarol was 70 (28-168) mg/kg and for cimetidine 125 (47-325) mg/kg; for their effect on the free hydrochloric acid content it was 100 (64-156) and 70 (38-124) mg/kg, respectively.

Phencarol and cimetidine in a dose of 100 mg/kg (internally) reduced the volume of histamine-stimulated gastric secretion and the free hydrochloric acid content. In relation to

*Academy of Medical Sciences of the USSR.

Laboratory of Pharmacology, S. Ordzhonikidze All-Union Pharmaceutical Chemical Research Institute, Moscow. Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 95, No. 5, pp. 44-46, May, 1983. Original article submitted July 19, 1982.

 0007-4888/83/9505-0616$07.50

TABLE 1. Effect of Antihistamine Drugs on Basal and Stimulated Gastric Secretion in Rats

Drug	Dose (internally), mg/kg	Volume of gastric contents, ml/100 g body weight	%	Content of free HCl, in ml 0.1N NaOH/100 ml gastric contents	%
		Basal secretion			
Control	—	2,18(2,52—1,84)	100	53(59—47)	100
Omeril	100	1,94(2,34—1,54)	88	69(80—58)	130
Diphenhydramine	100	2,6(3,1—2,1)	119	53(63—43)	100
Pyrilamine	100	3,4(3,63—3,14)	155	61(81—41)	1 5
Ciproheptadine	10	1,8(2,3—1,3)	82	50(54,5—45,5)	94
Phencarol	100	1,0(1,16—0,84)	45	2(2,3—1,7)	3
Cimetidine	100	1,5(1,8—1,2)	68	0	0
		Stimulated secretion			
Control	—	2,18(2,52—1,84)	100	53(59,2—48,6)	100
Histamine		2,6(3,13—2,0)	119	110(128—108)	207
Phencarol + histamine	100	0,76(1,01—0,51)	34	12(15—3)	22
Cimetidine + histamine	100	1,38(1,67—1,05)	63	8(12—4)	15
Diphenhydramine + histamine	100	3,6(4,72—2,50)	165	66(79—53)	124
Control	—	2,2(2,69—1,71)	100	31(40—22)	100
Carbachol		4,2(4,53—3,87)	190	42(48,1—35,9)	135
Phencarol + carbachol	100	2,4(2,99—1,81)	109	43(58—28)	138
Cimetidine + carbachol	100	4,5(5,2—3,8)	204	13(18—8)	41
Diphenhydrazine + carbachol	100	5(6,0—4,0)	227	54(68—40)	174
Control	—	2,7(3,3—2,1)	100	57(69—45)	100
Aminoguanidine		3,0(3,9—2,1)	111	72(81—63)	126
Phencarol + aminoguanidine	100	1,0(1,4—0,6)	37	3,0(3,89—2,11)	5
Cimetidine + aminoguanidine	100	2,1(2,5—1,7)	77	23(24,1—21,9)	40
Aminoguanidine + phencarol	100	2,4(2,94—1,86)	88	40(46,5—33,5)	70
Aminoguanidine + cimetidine	100	1,3(1,62—0,98)	48	22(25—19)	38

the effect on the volume of secretion phencarol had a stronger action than cimetidine. Diphenhydramine had no significant effect on the secretion parameters.

During carbachol-induced gastric secretion cimetidine, while not affecting its volume, reduced the content of free hydrochloric acid, whereas phencarol, which did not affect the free hydrochloric acid, prevented an increase in the volume of gastric secretion. After preliminary administration of diphenhydramine carbachol increased the volume of gastric secretion and the free hydrochloric acid content.

Aminoguanidine, an inhibitor of diamine oxidase, administered after phencarol or cimetidine, did not affect their antacid activity. After preliminary (30 min beforehand) injection, aminoguanidine almost completely prevented the action of phencarol but did not affect the action of cimetidine.

This investigation showed that phencarol (an H_1 receptor blocker), like cimetidine (an H_2 receptor blocker), has a marked effect on gastric function — it reduces the volume of secretion and the content of free hydrochloric acid. H_1 receptor antagonists — diphenhydramine, pyrilamine, ciproheptadine — did not affect gastric secretion. Omeril, which in certain cases may have an irritant action on the gastric mucosa [3], increased the volume of secretion and the free hydrochloric acid content.

The antacid action of phencarol and cimetidine is evidently effected through histaminergic systems of gastric secretion control. In fact, both drugs prevented stimulation of secretion by histamine; phencarol under these circumstances did not affect stimulation of secretion by carbachol, i.e., it had no anticholinergic action.

Blockade of diamine oxidase by preliminary administration of aminoguanidine prevented the antacid action of phencarol but did not affect the action of cimetidine. As regards the mechanism of their action on histaminergic systems and their effect on the volume of gastric secretion and the content of free hydrochloric acid, phencarol thus differs from cimetidine. Moreover, according to data in the literature [1], unlike other antihistamine drugs phencarol activates diamine oxidase and lowers the tissue histamine level.

It can accordingly be concluded from these observations that the antacid action of phencarol is the result of its activating effect on diamine oxidase, which leads to a fall in the level of active histamine in the tissues and a reduction in its effect on H_2 receptors.

On the basis of this investigation phencarol can thus be regarded as a compound with a new type of action, with an inhibitory effect on gastric secretion.

LITERATURE CITED

1. É. A. Baumanis, V. Z. Gorkin, I. É. Kalninya, et al., Farmakol. Toksikol., No. 1, 36 (1980).
2. M. É. Kaminka, Farmakol. Toksikol., No. 2, 158 (1977).
3. D. A. Kharkevich, Farmakol. Toksikol., No. 6, 46 (1957).
4. R. T. Meyer, B. L. Cummings, P. Bass, et al., J. Med. Chem., 8, 515 (1965).