Prevention of Steroid Induced Ulcers with an Anticholinergic Drug. (24710)

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Since development of peptic ulcer is one of the clinical side effects of corticoid therapy, an assay was recently developed to better study the pathogenesis of this type of ulcer. In this assay, ulcers are produced in the glandular portion of rat stomach in 4 days of intensive corticoid treatment(1). The results are expressed in terms of "ulcer index." In the present experiment, an anticholinergic drug, methscopolamine bromide,* was administered together with an ulcerogenic dose of Δ^1-cortisol (Δ^1-COL) in order to assess the rôle of vagal influences in the formation of this lesion.

Materials and methods. Eighty female Sprague-Dawley rats of average body weight of 155 g were divided into 8 groups (Table I). The animals were placed in individual cages and, beginning at 9 a.m., food was withheld for 4 days. During fasting period, they were treated with compounds listed in Table I, in a volume of 0.2 cc subcutaneously at following doses: Methscopolamine: either 1, 3 or 5 mg/kg of body weight twice daily (this corresponded to 80, 240 and 400 μg/injection respectively); Δ^1-COL: 5 mg once a day. Group 1 received 0.2 cc of CMC (carboxymethylcellulose, polysorbate 80, propylparaben and water), which was the vehicle for both methscopolamine and Δ^1-COL, subcutaneously, once a day. In addition, all animals were given a mixture of 5000 u of Penicillin G crystalline and 4 mg of dihydrostreptomycin sulfate subcutaneously twice a day. The antibiotics were mixed with methscopolamine in groups receiving anticholinergic. In other groups (Groups 1 and 5) they were given in separate injections of 0.2 cc. Animals were killed with chloroform after 4 days, and body weights recorded. Stomachs were dissected out, opened along lesser curvature and examined under a binocular magnifier for presence of ulceration.

* Pamine, Registered trademark, Upjohn Co., Kalamazoo, Mich.

Results. Table I summarizes the data obtained for each group.

Forestomach ulcers. A 4-day period of fasting induced formation of edema and ulcerations in this nonglandular portion in 40% of control animals, with an average of 4.1 ulcers/rat. Both methscopolamine and Δ^1-COL, either alone or in combination, completely prevented appearance of these ulcers.

Glandular ulcers. Control animals (Group 1) showed an incidence of glandular ulcers of 20%, and these were very mild. In the authors' experience, such low incidence and severity can be considered negligible; most often, controls do not show any glandular ulcers. Δ^1-COL produced, as usual, a high incidence of numerous and severe ulcers. When methscopolamine was given together with Δ^1-COL, it prevented formation of glandular ulcers proportionately to dose. In fact, with the highest dose of 5 mg/kg, the "ulcer index" was identical to that of the controls.

Mucus. Although the amount of mucus was not measured, it was obvious that with methscopolamine alone the gastric surface was covered with a thicker layer than in control animals. On the other hand, no mucus was visible on mucosa of animals receiving Δ^1-COL even when methscopolamine was also administered.

Discussion. The present experiment confirms the observation that glucocorticoids prevent appearance of fasting ulcers in the forestomach(1). It was previously shown that forestomach ulcers that develop in the Shay rat (pylorus ligation in fasted animal) are also inhibited by glucocorticoid treatment(2). Methscopolamine has been reported to prevent Shay ulcers as well as fasting ulcers in the forestomach(3).

Our results support the clinical findings that anticholinergic drugs are of value in treatment of peptic ulcer. Furthermore, they can specifically prevent development of ulcers

TABLE I. Effect of Methscopolamine Bromide (Methsc) on Steroid Induced Ulcers (Glandular portion) and on Fasting Ulcers (Forestomach).

Group	1	2	3	4	5	6	7	8
						Δ^1-COL		
		Methsc				Methsc,	Methsc,	Methsc,
Treatment	CMC	1 mg/kg	3 mg/kg	5 mg/kg	Δ^1-COL	1 mg/kg	3 mg/kg	5 mg/kg
Initial body wt	155	155	156	155	155	156	155	156
Final " "	111	110	110	109	102	101	100	101
Difference	−44	−45	−46	−46	−53	−55	−55	−55
Forestomach								
Edema, %	40	0	0	0	0	0	0	0
Ulcers, %	40	0	0	0	0	0	0	0
No./rat	4.1							
Glandular ulcers								
%	20	0	0	0	100	100	90	20
Severity (+)	.2				1.8	1.1	.6	.2
No./rat	.4				6.8	4.1	1.6	.4
Ulcer index*	2.6	0	0	0	18.6	15.2	11.2	2.6

* "Ulcer index" for glandular portion of stomach is determined by calculating the sum of: incidence in % divided by 10, severity (in pluses) and No. of ulcers/rat. A maximum "ulcer index" is around 20.

due to corticoid therapy. In this same connection, Carbone *et al.*(4) made the interesting observation that while prednisone increased both gastric pepsin and urinary uropepsin in normal subjects, addition of an anticholinergic drug nullified these effects of the steroids. According to our results, there is also a possibility that part of the protection afforded by methscopolamine was due to stimulation of mucus secretion.

Summary. Ulcers were produced in glandular portion of stomach of fasting rats with Δ^1-cortisol (Δ^1-COL). When methscopolamine bromide, an anticholinergic, was administered, these steroid induced ulcers were prevented proportionately to dose. Methscopolamine, given alone, increased the amount of visible mucus on mucosal surface. Methscopolamine would protect by counteracting some effects of corticoids on gastric secretion and perhaps also by stimulating mucus formation.

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Coenzyme Q. IV. Coenzyme Activity of 6-Isoprenoid and Other Derivatives of 2,3-Dimethoxy-5-Methylbenzoquinone. (24711)

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Discovery(1) and chemical structures(2) of the coenzyme Q group and additional characterization of ubiquinone(3) have been described recently. Synthesis of 6-(3′-methyl-2′-butenyl)-, (IV), 6-geranyl-, (V) and 6-farnesyl-, (VI), derivatives of 2,3-dimethoxy-5-methylbenzoquinone has been reported(4). These 3 compounds are lower isoprenoid analogs of the coenzyme Q group and may be considered as coenzyme Q_1, Q_2, and Q_3, respec-