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The Inhibitory Effect of Acetazoleamide on Indomethacin-induced Gastric Ulcer in Guinea Pig ❁

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INTRODUCTION

Indomethacin (1-(P-chlorobenzoyl) 5-2-methyl - indole-3-acetic) is a new synthetic non-corticosteroid drug with anti-inflammatory, anti-pyretic and pain-relieving properties. The most serious, but not the major and frequent, side effect of indomethacin is gastrointestinal bleeding and peptic ulceration (1,2,3). Menguy and Desbaillets (4) have demonstrated the ulcerogenic action of the drug in the dog. We have obtained dose-response and time-response curves for gastric ulceration in rats following administration of indomethacin by intraperitoneal route (5). The responses reached a peak five hours after injection of 20 mg/Kg of indomethacin. Previousely, we have demonstrated the inhibitory effect of acetazoleamide on histamine-induced gastric ulcer in guinea pig and restraint ulcer in the rat (6,7).

In the present work the effect of acetazoleamide on indomethacin-induced gastric ulceration in the rat is studied.

METHODS

Subjects. Subject were 80 guinea pigs of both sexes. weighing270-390 g. They lived in the animal room in large home cages. They had not been used as subjects in pharmacological experiments before. They were fed with food and water ad libitum.

Drugs. Acetazoleamide as sodium salt was dissolved in saline solution (0.8.5%) at the concentration of 25 mg/ml. Indomethacin was dissolved in saline solution at the concentration of 2 mg/l.

Experimental program The animals were divided into four groups of 20 guinea pigs and starved for 24 hours. The first group was used

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as control. They were injected with 1 ml/100g body weight of saline solution. The third group were injected with 20 mg/Kg of indomethacin. The fourth group were injected with the same dose of acetazoleamide and 30 minutes later they were injected with 20 mg/Kg of indomethacin. All injections were made by intraperitoneal route. Five hours later the animals were killed by a blow on the head, the stomachs were immediately removed, opened along the greater curvature, washed with water and carefully examined by direct lighting. Necrohemorrhagic spots were considered as evidence of ulcer formation. In the positive casses, the frequency of these necrohemorrhagic spots, found in the glandular part of the stomach, ranged form 3 to 8 per stomach.

RESULTS

The results are presented in the table 1. It shows that:

1. Acetazoleamide has significantly prevented the occurrence of indomethacin-induced gastric ulcer.

2. The percentage of indomethacin - induced gastric ulcer confirms our previous results (5).

3. In the saline injected animals and acetazoleamide-injected guinea pigs there was no ulcer formation.

Table 1

The incidence of gastric ulcer in guinea pigs treated with acetazoleamide and indomethacin.

group	Drugs and Doses (mg/Kg body weight)	Number of guinea pigs	Number with ulcers	Percentage
I	Saline (control group)	20	0	0
II	Indomethacin 20	20	20	100*
III	Acetazoleamide 250	20	0	0
IV	Acetazoleamide 250 + Indomethacin 20	20	5	25*

DISCUSSION

Davenport and Fisher (8) found a high concentration of carbonic anhydrase in the parietal cells of the gastric mucosa and suggested that it was a part mechanism responsible for the secretion of hydrochloric acid. The failure of earlier carbonic anhydrase inhibitors, such as thiocyanate and sulfonamide, to inhibit gastric acid secretion prompted Davenport to withdraw his theory. However, subsequent discovery of more

* P. 0.001 comparing groups II and IV.

potent carbonic anhydrase inhibitdrs, acetazoleamide, revived the carbonic anhyrase theory of Davenport. It is demonstrated that acetazoleamide produced a marked inhibition of histamine stimulated acid secretion in pouch dogs by as much as 97% (9). It is also demonstrated that acetazoleamide prevented occurrence of gastric ulcers produced by restraint in the rat (7), pylorus ligation in the rat (10), histamine in the guinea pig (6) and phenylbutazone in the rat (11).

In the present work, the fact that indomethacin-ulcers are inhibited by pretreatment of animals with acetazolemide and, the prevention of indomethaein-induced gastric ulcer by an alpha blocking agent, phentolamine (12), suggest the combined role of the genesis of this kind of ulcer.

Summary

Experimental acute gastric ulcer is produced by the intraperitoneal injection of a single dose of indomethacin. Acetazoleamide, a potent carbonic anhydrase inhibitor, has significantly prevented the occurrence of these ulcers. Its probable mechanism is discussed.

Résumé

L'ulcère gastrique aigu expérimental est produit par l'injection intrapéritonéale d'une dose unique de l'indomèthacin. L'acétazoleamide, un puissant inhibiteur de l'anhydrase carbonique, a significativement prévenu l'apparition de ces ulcéres. Le mécanisme possible de cet effet préventif est discutè.

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