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Effect of Stobadine on Indomethacin- and Ethanol-Induced Stomach Lesions and Gastric Secretion

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Summary

Stobadine was found to inhibit the ulcerogenic activity of indomethacin in relation to the dose but was ineffective against the direct necrotizing action of ethanol. It also inhibited gastric acid secretion when administered intraduodenally. Although stobadine is considered to be a scavenger of free radicals, our results indicate that, under the given experimental conditions, it is rather the inhibition of gastric acid secretion that is responsible for its antiulcerogenic effect. The preliminary results do not allow the exclusion of other mechanisms for explaining its antiulcerogenic effect.

Key words:
Stobadine – Indomethacin – Ethanol – Gastric ulcers – Rat

Introduction

A new substance – stobadine, (–)-cis-2,8-dimethyl-2,3,4,4a,5,9b-hexahydro-1H-pyrido-(4,3b)-indole dihydrochloride, has the antiarrhythmic (Štolc *et al.* 1982), α-adrenolytic (Lukovič and Machová 1984) and antihistaminic effects (Lukovič and Machová 1984). It also acts protectively on myocardial ischaemia in the dog (Styk *et al.* 1985) and on hypoxia-induced brain tissue damage (Štolc and Horáková 1988). These protective effects of stobadine on different tissues prompted us to verify whether it also has a gastroprotective effect.

The aim of this study was to analyze the effect of stobadine administered *in vivo* on lesions of the gastric mucosa caused by indomethacin and ethanol and its effect on gastric acid secretion.

Material and Methods

Male Wistar rats (Velaz, Prague), weighing 200–240 g, were used in all the experiments. They were deprived of food 24 h before the experiment, but had free access to water. Acute stomach lesions were induced with an ulcerogenic dose of indomethacin (20 mg/kg, administered subcutaneously in 0.5 ml/100 g volume) or with absolute ethanol (administered perorally in 0.5 ml/100 g volume). Stobadine dissolved in distilled water (2, 10 and 20 mg/kg) or plain distilled water were administered by stomach tube 30 min before administering the ulcerogens. The animals were killed under ether

anaesthesia 4 h after administering indomethacin and 1 h after administering ethanol. The number and length of the stomach lesions were expresses in mm, counting the length of spot lesions as 1 mm.

Gastric secretion was measured 4 h after ligating the pylorus under ether anaesthesia. The contents of the stomach were analyzed and their volume and pH were recorded. Acid output was expressed in μmol . (h . 100 g)$^{-1}$ (using titration with 0.1 N NaOH up to pH 7.0). The mean output values per hour, computed from 4 hours' output, are given. Stobadine was administered perorally or intraduodenally immediately after ligating the pylorus. Each experiment was carried out in 7–10 animals.

The results are expressed as means ± S.E.M. and they were evaluated by Student's unpaired t-test; $p<0.05$ and $p<0.01$ being considered as significant.

Table 1

Effect of stobadine (2, 10, 20 mg/kg) on gastric lesions induced by indomethacin or ethanol in rats

Stobadine (mg/kg)	Lesion induction	Number of lesions per rat	Mean lesions length per rat (mm)
Control		37.3 ± 4.0	52.2 ± 5.6
2.0	Indomethacin	38.1 ± 6.9	58.7 ± 11.4
10.0	Indomethacin	15.5± 3.0[a]	18.9± 3.7[a]
20.0	Indomethacin	0.7± 0.4[a]	0.7± 0.4[a]
Control		42.2 ± 8.9	110.4 ± 15.0
2.0	Ethanol	34.7 ± 4.4	106.3 ± 17.4
10.0	Ethanol	39.5 ± 6.0	113.3 ± 20.7
20.0	Ethanol	33.8 ± 3.2	99.3 ± 14.9

Stobadine was given 30 min before the administration of indomethacin or ethanol. Mean values ± S.E.M. from 10 rats. a – significantly different from the controls ($p<0.01$)

Table 2

The influence of stobadine on gastric secretion in rats

Stobadine (mg/kg)	Route of administration	Basal gastric secretion Volume (ml per rat)	μmol H^+. (h . 100 g)$^{-1}$	pH
Control	p.o.	9.8 ± 0.9	117.3 ± 15.0	1.7 ± 0.3
2.0	p.o.	8.2 ± 0.7	83.7 ± 11.9	1.5 ± 0.2
10.0	p.o.	10.3 ± 1.1	125.1 ± 15.2	1.3 ± 0.02
20.0	p.o.	8.0 ± 0.7	84.6 ± 12.3	1.8 ± 0.3
Control	i.d.	8.7 ± 1.3	90.4 ± 18.3	1.7 ± 0.3
2.0	i.d.	6.6 ± 0.9	62.4 ± 14.0	1.9 ± 0.4
10.0	i.d.	1.8 ± 0.4[a]	10.2 ± 0.8[a]	4.2 ± 0.2[a]
20.0	i.d.	1.3 ± 0.1[a]	6.6 ± 0.6[a]	4.4 ± 0.2[a]

Mean values ± S.E.M. from 7–10 rats. Stobadine was given perorally (p.o.) or intraduodenally (i.d.) immediately after pylorus ligation. a – significantly different from the controls ($p<0.01$)

Results

Stobadine inhibited the ulcerogenic activity of indomethacin in correlation to the dose. Significant reduction of stomach lesions was recorded after doses of 10 and 20 mg/kg ($p < 0.01$). After 20 mg/kg, 40 % of the rats were completely free from any macroscopically detectable lesions. In a dose of 2 mg/kg stobadine did not inhibit the formation of lesions (Tab. 1). Unlike indomethacin, ethanol-induced lesions of the gastric mucosa were not influenced by any of the given doses of stobadine (Tab. 1).

Tab. 2 shows that perorally administered stobadine did not significantly affect either the volume or the acidity of the gastric juice. When administered intraduodenally in doses of 10 and 20 mg/kg, it significantly inhibited volume of the gastric juice and acid output and raised the pH. A dose of 2 mg/kg mildly reduced basal gastric secretion but the results were not significant (Tab. 2).

Discussion

Certain antioxidative substances and free radical scavengers are known to reduce both indomethacin-induced intestinal ulceration (Del Soldato 1984) and ethanol-induced stomach lesions (Evangelista and Meli 1985). Stobadine is a promising antiarrhythmic substance with a cardioprotective effect. Štolc and Horáková (1988) found that it also acted protectively on brain tissue and that this effect was associated with the ability to extinguish free oxygen radicals.

The results show that stobadine, in doses of 10 and 20 mg/kg, effectively prevented indomethacin-induced ulcers, but not ethanol-induced stomach lesions. This is contrary to the results of Evangelista and Meli (1985) who demonstrated that free radical scavengers effectively prevented ethanol lesions. Since indomethacin requires an acid pH in the stomach lumen for the induction of stomach lesions (Guth *et al.* 1979), but ethanol does not, we also studied the effect of stobadine itself on gastric secretion. It was found to have an inhibitory effect on gastric acid secretion, but only when it was administered intraduodenally – an effect which correlated directly with the inhibition of ulcer formation after indomethacin.

The above results draw the attention to following points: (1) stobadine appears to be not a "cytoprotective", but only on "antiulcerogenic" substance in the rat stomach (in accordance with the hypothesis of Robert *et al.* 1984), (2) its antisecretory activity appears to be rather responsible for its antiulcerogenic effect although stobadine was described as a scavenger of free radicals (Šantrůček and Křepelka 1988), and (3) its inability to inhibit gastric secretion when administered locally after ligation of the pylorus demonstrates that it is resorbed from the lower parts of the gastrointestinal tract and transported to the parietal cells in the blood stream.

In conclusion, this paper draws the attention to new, hitherto unknown properties of stobadine in its antiulcerogenic effect on the gastric mucosa. This effect seems to be modified by inhibition of gastric secretion, but other mechanisms, e.g. its antihistaminic effect (Lukovič and Machová 1984), which might be associated with its antisecretory effect, cannot be ruled out. These considerations will require further study.

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