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Antiulcerogenic Effect of Pentacaine, Chlorpromazine and Stobadine on Ethanol- and Indomethacin-Induced Stomach Lesions in Rats

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Summary

The aim was to compare the antiulcerogenic effect of pentacaine, chlorpromazine and stobadine on indomethacin- and ethanol-induced stomach lesions in rats. Pentacaine effectively inhibited the formation of ethanol lesions, but in the given dose and under the given experimental conditions it was ineffective against indomethacin-induced damage. Chlorpromazine and stobadine effectively inhibited indomethacin erosions, but did not affect ethanol lesions significantly. The similarity of the effect of chlorpromazine and stobadine as compared with pentacaine, in the two stomach injury models, allows the assumption that stobadine has properties typical for an indirectly acting antiulcerogenic substance. This newly discovered property of stobadine extends the possibilities of its utilization to a further set of indications.

Key words:
Pentacaine – Chlorpromazine – Stobadine – Antiulcerogenic effect

Introduction

Ethanol- and indomethacin-induced ulcerations of the gastric mucosa differ fundamentally from each other, because ethanol necrotizes the gastric mucosa if administered perorally in a high concentration, whereas the effect of indomethacin does not require direct contact with the gastric mucosa. Its necrotizing effect is generally attributed to inhibition of cyclooxygenase and thus to inhibition of prostaglandin synthesis in the gastric mucosa, with resultant depression of its defence. Antiulcerogenic substances are divided – according to whether they inhibit these necrotic effects directly or indirectly – into cytoprotective substances and substances with an indirect protective effect mediated mainly by inhibition of acid secretion (Robert *et al.* 1984).

This study compares the protective effect of pentacaine (P), chlorpromazine (CPZ) and stobadine (S) in two gastric lesion models, since pentacaine is a cytoprotective substance (Nosálová *et al.* 1986) and chlorpromazine is only indirectly antiulcerogenic (Mirossay *et al.* 1987), while stobadine is included among

the potential scavengers of free radicals (Šantrůček and Křepelka 1988), but has not yet been tested.

Material and Methods

The experimental animals were male Wistar rats (Velaz, Prague) weighing 220–260 g, which were deprived of food 24 h before the experiment, but had free access to water. Acute gastric lesions were induced with an ulcerogenic dose of indomethacin (20 mg/kg) (Sigma, St. Louis, Mo.), administered subcutaneously in a volume of 0.5 ml/100 g, and with absolute ethanol, administered orally in 0.5 ml/100 g volume.

Pentacaine, chlorpromazine and stobadine were administered in single doses adopted from data in the literature and shown by our own preceding results to be reliably antiulcerogenic (Mirossay *et al.* 1987, Nosálová *et al.* 1987). Pentacaine and stobadine (substances synthesized and kindly provided by Dr. L. Beneš, Physiological Science Centre of the Slovak Academy of Sciences, Bratislava, stobadine in the hydrochloride form) were administered in a dose of 20 mg/kg whereas chlorpromazine (Plegomazin, Egyt, Hungary) in a dose of 10 mg/kg. All these drugs were administered directly by stomach tube as aqueous solutions in 0.5 ml/100 g volume. The control group was given distilled water in the same volume. All the substances were administered preventively 30 min before administering indomethacin or ethanol.

The animals were killed 4 h after indomethacin administration and 1 h after ethanol. The number and length of the lesions were evaluated. The results are expressed as the mean values ± S.D. for 9–24 animals. Statistical significance of the differences was evaluated by Student's unpaired t-test with a significance of $p<0.01$.

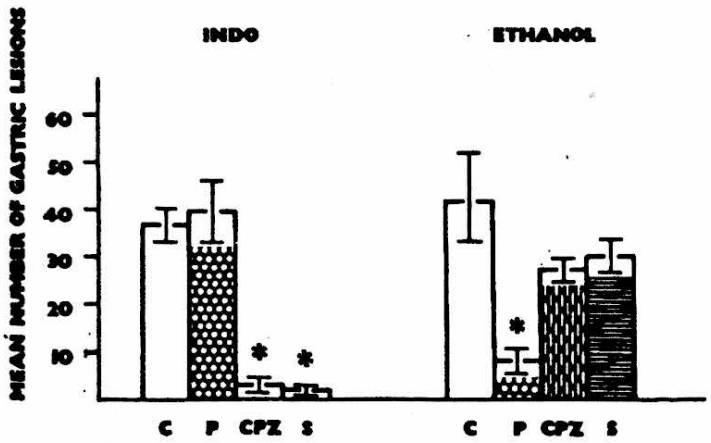

Fig. 1
Mean number of stomach lesions induced by indomethacin or ethanol in rats pretreated with distilled water (C), pentacaine (P), chlorpromazine (CPZ) and stobadine (S), * $p<0.01$.

Results

Fig. 1 illustrates the number of gastric mucosal lesions after the administration of indomethacin and ethanol. The effect of the test substances on the two ulceration models differed. Chlorpromazine and stobadine were found to be very effective when administered preventively before indomethacin. The mean number of lesions fell significantly to 2.9±1.5 after chlorpromazine and to 2.2±1.2 after stobadine as against 36.3±3.4 in the controls. After pentacaine, the number of

indomethacin-induced lesions did not change significantly and remained at the same level as in the control group (39.4±6.4).

Unlike indomethacin, reduction of the number of lesions in ethanol-induced damage of the gastric mucosa after chlorpromazine and stobadine pretreatment was non-significant; it fell from 42.2±8.9 in the control group to 27.0±2.7 after chlorpromazine and to 30.0±3.6 after stobadine. Only pentacaine lowered the number of defects significantly to 7.8±2.7 (Fig. 1).

Parallel changes also occurred in the mean total length of the lesions. The values for indomethacin-induced lesions were as follows: controls: 48.2±4.9 mm, P: 50.6±8.6 mm, CPZ: 3.7±1.9 mm, S: 2.3±1.1 mm, i.e. significant results were obtained after chlorpromazine and stobadine. The necrotizing effect of ethanol was influenced as follows: controls: 110.4±15.0 mm, P: 10.5±3.0 mm, CPZ: 70.2±21.3 mm, S: 92.0±15.2 mm (Fig. 2), i.e. in this case only pentacaine had a significant effect.

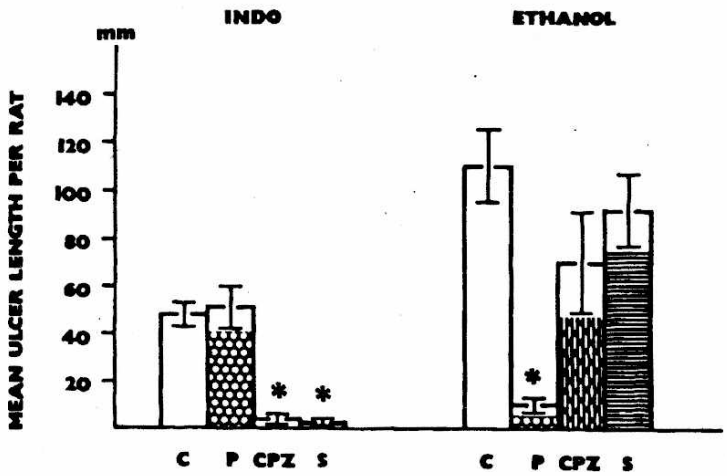

Fig. 2
Mean lesion length after the administration of indomethacin or ethanol to rats pretreated with distilled water (C), pentacaine (P), chlorpromazine (CPZ) and stobadine (S), * $p<0.01$.

Discussion

Pentacaine is an effective inhibitor of the formation of various experimental gastric lesions and accelerates the process of the healing of chronic defects (Nosálová *et al.* 1987). Since it is able to protect the gastric mucosa from the direct necrotizing action of ethanol, it is ranked among the potential cytoprotective substances (Robert 1984). Although the mechanism of the gastroprotective effect of pentacaine is not known exactly, it is assumed that it stimulates the synthesis of endogenous prostaglandins, as also demonstrated by a partial block of the favourable effect of pentacaine on ethanol-induced lesions after indomethacin pretreatment (Nosálová *et al.* 1986). Inhibition of cyclooxygenase – and hence of endogenous prostaglandin synthesis also – is therefore possibly the reason why pentacaine is also ineffective against indomethacin-induced stomach lesions.

Chlorpromazine is a powerful inhibitor of stomach lesions when given intraperitoneally (Mirossay *et al.* 1987) or perorally prior to the administration of indomethacin, but it does not significantly inhibit ethanol-induced injury to the gastric mucosa.

In our experiments, stobadine acted similarly to chlorpromazine. Stobadine is a new substance which has been shown to be able to extinguish free radicals, with a protective after-effect in various organs and tissues (Šantrůček and Křepelka 1988). Since stobadine proved ineffective in the ethanol-induced ulceration model, it is possible that it influences gastric acid secretion in the same way as chlorpromazine; this is a typical property of antiulcerogenic substances which do not have a direct cytoprotective effect (Robert *et al.* 1984). The beneficial effect of stobadine on indomethacin-induced defects of the gastric mucosa is a new property which draws attention to further possibilities for the utilization of this substance.

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