Thus, although reactive blue was able to antagonize the responses to ATP in the guinea-pig detrusor, these concentrations of the antagonist also inhibited responses to ACh, although the latter appears to be inhibited in a non-competitive manner. It is not possible to equate the degree of blockade produced following electrical stimulation to the dose-ratio shifts obtained following agonist drug. However, the lack of complete inhibition of the responses to electrical stimulation of the guinea-pig detrusor strips (20–25% of maximal response still remaining) even at low frequencies of stimulation by a concentration of reactive blue (100 μM) capable of producing a 70 fold shift in the dose-response curve to ATP, would suggest that even if ATP is involved in the non-cholinergic, non-adrenergic excitatory response, it cannot be the only transmitter involved. One method of comparison would be to examine the effects of reactive blue on matching responses to electrical stimulation, ATP and ACh. However, this is not always possible, For example, in the rat bladder, where the sensitivity of the tissue to nerve stimulation and ACh is much greater that its sensitivity to ATP (Choo & Mitchelson 1980b), comparable responses cannot be obtained. In rat bladder, reactive blue (100 μM) showed only a very slight inhibitory effect against ATP and is thus not a useful tool for resolving the problem of whether ATP is involved in atropine resistance in the rat urinary bladder. Furthermore, the inhibition of responses to ACh by reactive blue also limits its usefulness in resolving whether the innervation of the bladder is entirely cholinergic as suggested by Carpenter 1977; Chesher 1970; Huković et al 1965; Ursillo & Clark 1956.

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Comparison of the effects of sodium salicylate with anti-ulcer agents in preventing indomethacin-induced intestinal ulcer

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In 1976, Ezer et al first described how the marked gastrointestinal ulcerogenic effect of indomethacin can be prevented by the simultaneous administration of sodium salicylate. The detailed results (Ezer et al 1979) were confirmed by others (Hayden et al 1978; Goburdhun et al 1978; Kyuki et al 1978; Rosenbaum et al 1979; Corell & Jensen 1979). The 1:10 combination of indomethacin with sodium salicylate (RGH-6705, Pelsonin) shows promising results clinically (Torgyán et al 1979).

Although the gastric ulcerogenic effect of non-steroidal anti-inflammatory drugs has been intensively studied the intestinal ulcerogenic effect has received much less attention possibly because the intestinal ulcers are more difficult to evaluate than gastric ulcers, and also because non-steroid inflammatory drugs bring about mainly gastric ulcers. Indomethacin, however, is an exception, it causes intestinal ulcers that can lead to peritonitis. We have examined the intestinal ulcerogenic effect of indomethacin and its prevention by sodium salicylate

Female Wistar rats, 120–150 g, *not* fasted before the treatments, were allowed free access to food and water during experiments. Under these conditions it requires at least 48 h for the intestinal ulcers to develop. To ensure the full expression of the ulcerogenic activity of indomethacin the animals were mostly killed 72 h after the drug was given. To evaluate the development of small intestinal ulcers, the tensile strength of intestinal wall was determined, by the inflation technique of Ezer et al (1976), because the erosion caused by ulcerogenesis leads to the weakening of the strength of the intestinal wall. The small intestine from pylorus to caecum was removed and the end was ligated, and a

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Table 1. Action of different anti-ulcer drugs on the indomethacin-induced intestinal ulcers (rats killed 72 h after the treatment).

Treatment	n	Dose* mg kg^{-1} oral	T.S.†	% deaths
Indomethacin (Ind.)	30	15	40 ± 8	40
Ind. + Na salicylate	10	15 + 150	161 ± 6	—
Ind. + Propantheline	10	15 + 20	48 ± 10	20
Ind. + Gastrixon	10	15 + 20	57 ± 15	10
Ind. + Cimetidine	10	15 + 75	49 ± 12	20
Ind. + Cimetidine	10	15 + 150	18 ± 10	20
Ind. + Cimetidine	10	15 + 300	12 ± 5	30
Value of untreated animals	20	—	168 ± 4	—

* First dose = indomethacin, second dose is that of the anti-ulcer drug.
† T.S. = tensile strength of small intestine in mm Hg ± s.e. 72 h after indomethacin treatment.

polyethylene tube connected with a mercury manometer and a 3-valve Griffin rubber ball was inserted and ligated onto the other end. The entire small intestine was placed into 0·9% NaCl (saline) at 37 °C and the pressure increased until air bubbles appeared from the weakened sites in intestinal wall. This pressure, expressed in mm Hg, is the tensile strength of the wall. Animals that died from peritonitis during treatment were rated of 0 value tensile strength.

Statistical analysis of the results was by Student's *t*-test.

Indomethacin and Propontelin were purchased from Chinoin (Budapest), Gastrixon (tropine-xanthene-9-carbonic acid ester-Br-methylate) from EGYT (Budapest) and sodium salicylate from Polfa (Warsaw). Cimetidine was the product of Chemical Works of G. Richter Ltd (Budapest).

In Table 1, the effects of known anti-ulcerogenic compounds and of sodium salicylate on the indomethacin-induced small intestinal ulcer are summed. Propanthelin and gastrixon (parasympatholytics) when administered simultaneously with indomethacin did not influence the intestinal ulcerogenesis, the tensile strength of the small intestinal wall being similar to that in the indomethacin-treated group. Cimetidine (an H_2 receptor antagonist) in different doses did not prevent indomethacin-induced ulcers, and in higher doses promoted them. The tensile strength after cimetidine, 300 mg kg^{-1}, was 12 mm Hg,

Table 2. Action of sodium salicylate (150 mg kg^{-1}) on intestinal ulcer induced by indomethacin (15 mg kg^{-1}) as a function of post-treatment time in groups of 10 animals.

Indomethacin dose mg kg^{-1} oral	Time (h)* of NaSal. dose	Tensile strength†
15	0	161 ± 8
15	4	150 ± 10
15	8	142 ± 6
15	24	64 ± 12
15	no treatment	40 ± 10

* time Na salicylate given after indomethacin.
† see Table 1.

Table 3. Action of sodium salicylate, administered 4 h after indomethacin (15 mg kg^{-1}), treatment on indomethacin-induced intestinal ulcers as function of dose in groups of 10 animals (controls 20 animals).

Treatment	Dose* mg kg^{-1} oral	Tensile strength†	% deaths
Indomethacin	15	40 ± 10	45
+ Na salicylate	15 + 15	45 ± 8	40
" "	15 + 37	106 ± 8*	—
" "	15 + 75	158 ± 6*	—
" "	15 + 150	160 ± 5*	—
Value of untreated animals	—	168 ± 4	—

* $P < 0{\cdot}01$ related to indomethacin treatment.
† see Table 1.

whereas that after indomethacin treatment was 48 mm Hg. A 150 mg kg^{-1} dose of simultaneously administered sodium salicylate prevented the intestinal ulcerogenic effect of indomethacin.

Table 2 shows that simultaneous treatment with sodium salicylate and indomethacin is not essential. It is apparent that sodium salicylate protects the intestinal mucosa from damage when administered up to 8 h after indomethacin, the ulcers being determined 72 h after drug dosage. When sodium salicylate was given 24 h after indomethacin however, it did not prevent indomethacin ulcerogenesis.

Table 3 shows that varying doses of sodium salicylate administered 4 h after indomethacin in proportion of 1:1 to 1:10 by weight with respect of indomethacin treatment prevented ulcer formation in the small intestine.

The mechanism(s) of the intestinal ulcerogenic effect of non-steroid anti-inflammatory drugs is not yet known. Compounds inhibiting gastric ulcer formation (propantheline, gastrixon, cimetidine) were unable to prevent ulcerogenesis in the wall of small intestine. The results show, that the mechanism of ulcerogenesis in the wall of stomach and small intestine may differ essentially. This supposition is supported especially by the preventative action of sodium salicylate administered 4–8 h after indomethacin treatment.

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