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Potentiation of gastric toxicity of ibuprofen by paracetamol in the rat

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Abstract—A fixed dose combination of ibuprofen (400 mg) and paracetamol (325 mg) is by far the most extensively prescribed medicament for a variety of musculoskeletal disorders in India. Following clinical observations that this drug combination induces significant adverse effects, its gastric toxicity was investigated in rats. Ibuprofen (25 mg kg^{-1} p.o., twice daily × 5 days), paracetamol (20 mg kg^{-1} p.o, twice daily × 5 days), and a combination of the two, had no significant effect on free and total gastric acidity in pylorus-ligated rats. Ibuprofen induced visible gastric ulceration whereas paracetamol did not. However, the combination of these two drugs had an additive effect inducing severe gastric erosions, ulcerations and bleeding. The augmented toxicity of this drug combination appeared to be a consequence of attenuated gastric mucin activity and reduction in the gastric muco-protective barrier. This investigation indicates the likely hazard of an irrational fixed dose drug combination.

The fixed dose combination of ibuprofen (400 mg) and paracetamol (325 mg) is the most popular analgesic-anti-inflammatory medication in India, prescribed extensively for rheumatoid arthritis, osteoarthritis, cervical spondylosis, ankylosing spondylitis, acute musculo-skeletal disorders and infective inflammations. This combination appears to be promoted exclusively in India (MIMS 10;91,1990). Clinical observations, though subjective, indicated that complaints of epigastric distress, abdominal pain, nausea and vomiting were substantially more in patients taking this drug combination than in those prescribed ibuprofen alone. This observation prompted us to undertake an experimental investigation as a prelude to a more comprehensive study.

Materials and methods

Male Charles Foster rats, 150-180 g, obtained from the Institute animal house, were kept in colony cages at an ambient temperature of 25 ± 1°C and 45-55% relative humidity, with a 12 h light/12 h dark cycle. The cages had wide wire mesh floors to obviate coprophagy. The rats were fed a standard pellet diet (Hind Lever) and tap water was freely available. Food was withheld 24 h before and water 1 h before experimentation, which was conducted under similar ambient conditions, between 0900 and 1400 h.

Forty rats were randomly allocated into four equal groups which received the following treatments: group 1, 0·9% NaCl (saline) 1 mL p.o. twice daily for 5 days. Group 2, ibuprofen (Boots, India) 25 mg kg^{-1} p.o. twice daily for 5 days. Group 3, paracetamol (Sigma, USA) 20 mg kg^{-1} p.o. twice daily for 5 days. Group 4, ibuprofen (25 mg kg^{-1}) plus paracetamol (20 mg kg^{-1}) p.o. twice daily for 5 days.

The drugs were suspended in 1 mL saline. On the 6th day, all the rats were subjected to pylorus ligation (Shay et al 1945) under ether anaesthesia and were decapitated 4 h after ligation. The stomach was removed and its contents were collected for biochemical estimations. The stomach was then cut open along the greater curvature and examined for the presence of erosions, bleeding spots and ulcers. The ulcer index was calculated from the number of ulcers and their severity, as confirmed by histopathological examination (Goel et al 1985). Apart from free and total acid, the gastric mucin activity (total hexoses, hexosamine, fucose and sialic acid) (Sanyal et al 1982, 1983), peptic activity (Debnath et al 1974) and protein content (Lowry et al 1951) of gastric juice was also estimated. The ratio of the total carbohydrate (sum of total hexoses, hexosamine, fucose and sialic acid) to protein was taken as the index of mucin activity (Sanyal et al 1983).

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Results

Ibuprofen, paracetamol, and their combination, had no significant effects on free and total acidity, and peptic activity. Paracetamol by itself did not induce visible gastric ulceration whereas ibuprofen produced gastric erosions and ulceration. However, the combination induced marked and severe gastric erosions, ulcerations and bleeding. While the effect of paracetamol on gastric mucin and protein remained minimal, that of ibuprofen was statistically significant and the combination produced reduction in gastric mucin activity and an increase in gastric juice protein content, leading to a reduction in the carbohydrate/protein ratio. However, when compared with the ibuprofen group, the data remained statistically insignificant except for the decrease in total carbohydrates. The results are summarized in Tables 1, 2.

Discussion

Paracetamol has been reported to exert a protective effect against gastric mucosal injury induced by aspirin or ethanol, both in man and animals (Stern et al 1984; Poon et al 1989). However, it did not induce a similar protective effect when combined with ibuprofen in volunteers (Lanza et al 1986). While the ulcerogenic effect of ibuprofen, like that of other NSAIDs is due to reduction in the synthesis of gastroduodenal cytoprotective prostaglandins (PGs) (Hawkey & Daneshmend 1989), the gastroprotective effect of paracetamol does not appear to be mediated through mucosal PGs (Van Kolfschoten & Van Noordiwijk 1987). On the contrary, there are reports that paracetamol reduces the levels of PGs in inflammatory exudate and exerts a significant anti-inflammatory action (Higgs et al 1976). Paracetamol has also been reported to be more effective than aspirin in reducing pain and swelling in inflammatory conditions other than arthritis (Cooper 1981).

The effect of paracetamol on the offensive acid-pepsin and defensive mucin factors was minimal. Ibuprofen, and the combination of paracetamol and ibuprofen, had little effect on acid-pepsin output, and, therefore, this is unlikely to be the cause of the observed gastric toxicity. Paracetamol was also found to have little effect on either gastric mucin activity or the protein content of the gastric juice. Ibuprofen, on the other hand, reduced significantly the markers of gastric mucin, and increased the protein leading to a significant reduction in the carbohydrate/protein ratio. A similar feature has been reported earlier with a number of NSAIDs, including aspirin (Menguy & Masters 1965; Menguy & Desbaillets 1968). The reduction in gastric mucin activity has been related to the inhibition of PG synthesis (Hawkey & Daneshmend 1989), while the increase in gastric juice protein reflects mucosal injury (Menguy & Desbail-

Table 1. Effect of paracetamol, ibuprofen and their combination on gastric acidity and ulceration in rats.

Treatment	pH	Free acidity mEq L^{-1}/100 g	Total acidity mEq L^{-1}/100 g	Peptic activity (μmol tyrosine mL^{-1}	Ulcer index
Saline	2·12±0·2	34·9±9·8	71·6±13·6	239·2±34·6	6·2±0·9
Paracetamol	2·09±0·3	39·4±6·9	72·6±11·2	254·0±26·9	8·3±2·0
Ibuprofen	2·02±0·3	42·2±7·4	79·9±11·8	287·3±39·2	18·3±3·8
Paracetamol +ibuprofen	1·84±0·2	46·8±7·2	89·9±18·6	302·0±38·6	23·8±4·4

n = 10 in each group; values represent mean ± s.e.m. The pylorus of the rats were ligated for 4 h. None of the data of the Paracetamol + ibuprofen group was significantly different from the corresponding Ibuprofen group.

Table 2. Effect of paracetamol, ibuprofen and their combination on gastric mucin activity in rats.

	Carbohydrate (μg mL^{-1}) (C)					Protein (μg mL^{-1})	
Treatment	Hexoses	Hexosamine	Fucose	Sialic acid	Total	(P)	C/P ratio
Saline	736±62	246·4±28·2	45·7±3·8	34·4±4·9	1062±92	288±32	3·68±0·4
Paracetamol	672±78	202·6±18·9	36·6±6·3	29·7±5·0	941±68	316±22	2·98±0·9
Ibuprofen	524±44*	166·2±17·0*	23·9±4·2*	20·6±3·3*	733±54*	398±29*	1·84±0·6*
Paracetamol +ibuprofen	415±52**	132·8±13·6**	16·0±3·9**	14·4±2·9*	577±42**[a]	446±39*	1·29±0·4**

n = 10 in each group; values represent mean ± s.e.m. The pylorus of the rats were ligated for 4 h. * $P < 0·05$, ** $P < 0·01$, *** $P < 0·001$ compared with saline-treated control (Student's t-test). [a] $P < 0·05$ compared with Ibuprofen.

lets 1968). A decrease in the carbohydrate/protein ratio is, thus, an indicator of breakdown of the gastric mucosal barrier.

The results indicate that paracetamol does not afford a protective effect against ibuprofen-induced gastric toxicity but may induce additive effects.

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