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Gastrointestinal Ulcerogenic Activity of Tolmetin Sodium in Rats in Comparison with Those of Indomethacin and Aspirin

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The gastrointestinal (GI) ulcerogenicity of tolmetin sodium was compared with those of aspirin and indomethacin, as representative non-steroidal anti-inflammatory drugs, in rats. Ulcerogenic activity of tolmetin sodium administered orally was more potent in the stomach of the fasted rat than in the intestines of the fed rat, whereas indomethacin was more ulcerogenic in the intestines than in the stomach. Aspirin was ulcerogenic only in the stomach. In the gastric mucosa, tolmetin sodium, like aspirin but not indomethacin, produced far fewer lesions by the intravenous than by the oral route. However, tolmetin sodium, unlike aspirin, did not reduce the gastric acidity of the pylorus-ligated rat and was less ulcerogenic in the pylorus-ligated rat than in the intact rat. Consequently, the GI ulcerogenicity of tolmetin sodium appeared to be different in character from those of aspirin and indomethacin.

Keywords——ulcerogenic activity; tolmetin sodium; aspirin; indomethacin; stomach; intestines; rat

Gastrointestinal (GI) ulceration is a common adverse effect of non-steroidal anti-inflammatory drugs (NSAIDs).[1] Ulcerogenic activity of NSAIDs in the GI tract has been studied by many investigators using rats. Although various kinds of activity of NSAIDs are considered to be due to their capacity to inhibit prostaglandin biosynthesis, it is probable that NSAIDs do not necessarily cause GI ulcers through a common mechanism such as inhibition of prostaglandin biosynthesis. NSAIDs could, therefore, have characteristic GI ulcerogenicities. Tolmetin sodium as well as zomepirac sodium has a pyrrole ring different from that of any other NSAID. The GI ulcerogenic activity of tolmetin sodium in rats has been studied by several investigators.[2–5] Most of their reports, however, have assessed the potency of ulcerogenic activity and the safety index, and the character of GI ulcerogenicity of tolmetin sodium has not been clarified. In the present work, we show that tolmetin sodium has some different features from aspirin and indomethacin as regards GI ulcerogenicity in rats.

Methods

Male Wistar rats (90—180 g) were used. Each drug was suspended or dissolved in a 0.5% gum tragacanth aqueous solution for oral administration and dissolved in 0.1 M phosphate buffer (pH 7.0) for intravenous administration.

Ulcerogenic Activity in the Stomach of Fasted Rats——Each drug was administered orally or intravenously to rats fasted for 24 h prior to the experiment. Six hours later, the rats were sacrificed and the stomach was removed. The stomach was opened along the greater curvature and macroscopically examined. The severity of lesions for each stomach was graded according to the following scale; normal, 0; bleeding and/or erosions of mucosa, 1; 1—4 small ulcers (<2 mm in diameter or length), 2; 5 small ulcers or more, or one large ulcer (≥ 2 mm in diameter or length), 3; 2 large ulcers or more, 4. The SUD50, the dose at which the mean gastric score was equal to 2.0 (SUD-grade 2), was calculated from the regression equation computed from the doses and their scores.

Ulcerogenic Activity in the Intestines of Fed Rats——Each drug was administered orally or intravenously to fed rats. Twenty-four hours later, the rats were sacrificed 10 min after an intravenous injection of 1 ml/kg body weight of

4% pontamine sky blue, and the intestines were removed. The intestinal mucosa was macroscopically examined after immersing it in a 10% formalin solution for fixation. The severity of lesions was scored and the IUD50, the dose at which the mean intestinal score was equal to 2.0 (IUD-grade 2), was calculated as described above.

Gastric Ulcerogenic Activity in Pylorus-Ligated Rats——The pylorus of rats fasted for 24 h was ligated under hexobarbital sodium anesthesia. Immediately after the operation, each drug was administered orally in a volume of 5 ml/kg. Six hours later, the rats were sacrificed and the stomach was examined for lesions of the mucosa. The gastric contents were collected, centrifuged and titrated for acidity to pH 7.0 with 0.1 N NaOH.

Intestinal Ulcerogenic Activity in Bile-Duct Ligated Rats——The common bile duct of fed rats was ligated under hexobarbital sodium anesthesia according to the method of Brodie *et al.*[7] More than 4 h after surgery, both the operated and sham-operated rats were given each drug. Twenty-four hours later, the rats were sacrificed and the intestines were examined.

Drugs Used——Drugs used were as follows: tolmetin sodium (tolmetin sodium dihydrate), aspirin and indomethacin.

Statistical Analysis——The Mann-Whitney U-test and Student's *t*-test were used for statistical analyses of ulcerogenic score and gastric acidity, respectively.

Results

Ulcerogenic Activity in the Stomach of Fasted Rats

Tolmetin sodium produced long and narrow ulcers (score; 2 or more) in the glandular portion of the stomach at doses of 40 mg/kg *p.o.* or more. The shape of lesions was similar to that produced by aspirin, but not indomethacin, which produced dotted or short ulcers. The ulcerogenic activity of tolmetin sodium was approximately as potent as that of aspirin and about 3 times less potent than that of indomethacin (Table I).

Table II shows the incidence of rats with gastric ulcers and the ulcerogenic score after intravenous administration of each drug. With tolmetin sodium and aspirin, the incidence was apparently higher by the oral than by the intravenous route, whereas indomethacin administered intravenously gave a similar or somewhat weaker result as compared with the oral route.

TABLE I. Ulcerogenic Activities of Tolmetin Sodium, Aspirin and Indomethacin in the Stomach of Fasted Rats

Drug	Dose mg/kg *p.o.*	No. of rats	No. of rats with ulcers[a]	Ulcerogenic lesions mean score ± S.E.	SUD50[b] in mg/kg (95% confidence limits)
Vehicle		10	(2)	0.8 ± 0.3	
Tolmetin sodium	20	6	(0)	0.8 ± 0.2	
	40	6	(3)	1.5 ± 0.4	
	60	6	(3)	1.5 ± 0.2	51.7
	80	6	(5)	3.0 ± 0.5	(41.7—64.1)
	160	6	(6)	4.0 ± 0.0	
Aspirin	20	6	(0)	0.8 ± 0.2	
	40	6	(3)	1.3 ± 0.3	
	60	6	(5)	2.3 ± 0.4	45.3
	80	6	(5)	3.3 ± 0.5	(36.1—57.0)
	160	6	(6)	4.0 ± 0.0	
Indomethacin	4	6	(0)	0.5 ± 0.2	
	8	6	(2)	1.3 ± 0.4	16.9
	16	6	(5)	2.3 ± 0.6	(9.2—30.8)
	32	6	(4)	2.3 ± 0.6	

a) Score; 2 or more.
b) SUD50 values, the doses required to produce lesions with the score of 2, were calculated from the regression equation for each drug.

Table II. Ulcerogenic Activities of Tolmetin Sodium, Aspirin and Indomethacin Administered Intravenously in the Stomach of Fasted Rats

Drug	Dose mg/kg *i.v.*	No. of rats	No. of rats with ulcers[a]	Ulcerogenic lesions mean score ± S.E.
Vehicle		6	(0)	0.0 ± 0.0
Tolmetin sodium	160	6	(0)	0.0 ± 0.0
Aspirin	160	6	(0)	0.2 ± 0.2
Indomethacin	32	6	(3)	1.7 ± 0.3

a) Score; 2 or more.

Table III. Ulcerogenic Activities of Tolmetin Sodium, Indomethacin and Aspirin in the Intestines of Fed Rats

	IUD50[a] in mg/kg (95% confidence limits)			
	p.o.		*i.v.*	
Tolmetin sodium	150 (134—168)	30[b]	151 (134—169)	18
Indomethacin	3.63 (3.30—4.01)	30	3.77 (3.51—4.04)	18
Aspirin	>1280	18	Not tested	

a) IUD50 values, the doses required to produce lesions with the score of 2, were calculated from the regression equation for each drug.
b) No. of rats used.

Ulcerogenic Activity in the Intestines of Fed Rats

Tolmetin sodium produced ulcers in the jejunum and ileum of the fed rat at doses of 160 mg/kg or more by both the oral and intravenous routes. The shape of the lesions was similar to that produced by indomethacin. The ulcerogenic potency of tolmetin sodium as well as that of indomethacin was substantially the same by the oral and intravenous routes (Table III). Aspirin produced no intestinal ulcers at doses of up to 1280 mg/kg *p.o.*

Each drug was given orally once a day for 5 d and the intestinal lesions were examined 24 h after the last administration. The IUD50 values of tolmetin sodium and indomethacin were 138 (120—158, $n=24$) and 2.19 (1.88—2.55, $n=24$) mg/kg/d *p.o.*, respectively. There was not much difference in the potency of tolmetin sodium between single and repeated administrations, whereas the potency of indomethacin given repeatedly was nearly twice that of a single dose.

Gastric Ulcerogenic Activity in Pylorus-Ligated Rats

As can be seen in Fig. 1, tolmetin sodium produced significantly fewer gastric lesions in the pylorus-ligated rat than in the intact rat, while aspirin induced severe gastric lesions in both. Ulcerogenic activity of indomethacin was less potent in the pylorus-ligated rat than in the intact rat, though the difference was not statistically significant. Tolmetin sodium and indomethacin, unlike aspirin, did not reduce the gastric acidity in the pylorus-ligated rat. These three drugs did not influence the volume of gastric contents.

Intestinal Ulcerogenic Activity in Bile Duct-Ligated Rats

Bile duct ligation was found to be effective in preventing the intestinal ulcerogenicity of

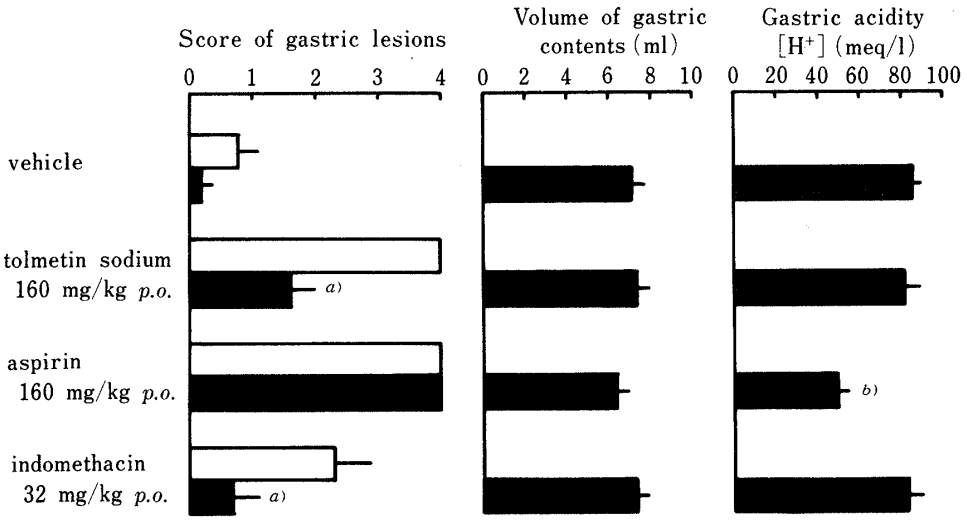

Fig. 1. Effects of Tolmetin Sodium, Aspirin and Indomethacin on Gastric Mucosa and Secretion in Pylorus-Ligated Rats

a) $p<0.01$; significantly different from each intact group in the Mann-Whitney U-test.
b) $p<0.01$; significantly different from the vehicle control group in Student's *t*-test.
□, intact rat $N=6$; ■, pylorus-ligated rat $N=7$.

TABLE IV. Effect of Bile Duct Ligation on the Intestinal Ulcerogenic Activities of Tolmetin Sodium and Indomethacin in Rats

Drug	Route	Dose mg/kg	Ulcerogenic lesions (mean score ± S.E.)[a]	
			Sham-operation	Bile duct ligation
Tolmetin sodium	*p.o.*	320	3.5 ± 0.3	0.0 ± 0.0[b]
Indomethacin	*p.o.*	8	3.7 ± 0.3	0.0 ± 0.0[b]
Tolmetin sodium	*i.v.*	320	3.2 ± 0.4	0.0 ± 0.0[b]
Indomethacin	*i.v.*	8	3.7 ± 0.3	0.0 ± 0.0[b]

a) Each group consisted of 6 rats.
b) $p<0.01$; significantly different from each sham-operated group in the Mann-Whitney U-test.

tolmetin sodium as well as indomethacin by both the oral and intravenous routes (Table IV).

Discussion

Shriver *et al.*[3] have classified the ulcerogenic activities of NSAIDs into two groups; one consists of drugs affecting the gastric mucosa and submucosa, and the other consists of drugs affecting the gastric mucosa and submucosa and the small bowel. In their classification, aspirin is included in the former group, while indomethacin and tolmetin sodium are included in the latter group. In the present study, tolmetin sodium produced the same shape of lesions as indomethacin in the intestinal mucosa of the fed rat, and aspirin produced almost no intestinal lesions. Tolmetin sodium, however, produced long and narrow lesions in the glandular portion of the stomach in the fasted rat and the shape of the lesions was similar to that produced by aspirin but not indomethacin; indomethacin produced dotted or short lesions. Furthermore, tolmetin sodium was about 3 times more ulcerogenic in the stomach of fasted rats than in the intestines of fed rats, which is in contrast with the finding that indomethacin was about 3.5 times more ulcerogenic in the intestines than in the stomach.

Thus, it appears that the ulcerogenic properties of tolmetin sodium differ not only from those of aspirin but also from those of indomethacin.

The existence of a direct contact mechanism has been suggested in the production of gastric lesions by some NSAIDs, based on the findings that they are more ulcerogenic by oral than by parenteral administration.[8,9] Tolmetin sodium as well as aspirin caused apparently fewer gastric lesions by the intravenous than by the oral route, whereas indomethacin administered intravenously gave a similar or somewhat weaker result than that given orally. These results suggest that the direct contact mechanism is a much more important factor in the gastric ulcerogenicity of tolmetin sodium and aspirin than in the ulcerogenicity of indomethacin. A back-diffusion of gastric acid has been proposed as one of the mechanisms in the gastric ulcerogenicity of asprin,[10] and Brodie and Chase[11] have shown aspirin-induced reduction of gastric acidity in the pylorus-ligated rat. Okabe *et al.*[6] have reported that pylorus ligation did not increase the severity of indomethacin-induced gastric lesions, although aspirin-induced lesions were aggravated by pylorus ligation. They suggested a difference in the mechanism of gastric ulcerogenicity between aspirin and indomethacin. As can be seen in Fig. 1, tolmetin sodium did not reduce the gastric acidity in the pylorus-ligated rat and, like indomethacin, caused fewer gastric lesions in the pylorus-ligated rat than in the intact rat. Thus, the mode of gastric ulcerogenicity of tolmetin sodium seemed to be different from that of indomethacin or aspirin.

On the other hand, the intestinal ulcerogenicity of NSAIDs has been thought to be related to the enterohepatic circulation.[7,12] Tolmetin sodium, like indomethacin, produced intestinal ulcers when given by the intravenous route as well as the oral route. The bile duct ligation prevented the intestinal ulcerogenicity of tolmetin sodium as well as indomethacin. Thus, the mode of intestinal ulcerogenicity of tolmetin sodium seems to be similar to that of indomethacin.

The GI ulcerogenicity of NSAIDs has been considered to be related to a common phenomenon, that is the withdrawal of prostaglandins.[1] As described above, however, the mode of ulcerogenicity of tolmetin sodium seemed to be different from that of indomethacin or aspirin, though it is not clear yet what causes the difference. Therefore, it seems that NSAIDs do not always cause GI ulcers through a common mechanism, and that they have their own character of GI ulcerogenicity. Thus, the character of GI ulcerogenicity of NSAIDs should be clarified as well as the potency.

In conclusion, the GI ulcerogenicity of tolmetin sodium appeared to be different in character from that of aspirin or indomethacin. It seems likely that NSAIDs should be divided into more categories than those in the classification of Shriver *et al.*,[3] as regards ulcerogenicity in rats.

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