STUDIES ON THE MECHANISM OF ACTION OF CETRAXATE
[4'- (2-CARBOXYETHYL)PHENYL TRANS-4-AMINOMETHYL CYCLOHEXANECARBOXYLATE HYDROCHLORIDE],
A NEW ANTI-ULCER AGENT

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Abstract—To elucidate mechanisms involved in the anti-ulcer action of cetraxate, the effects of this agent on the ulcer index (UI), fibrinolytic activity (FA) and contents of several connective tissue components in ulcer tissue were examined using aspirin- and acetic acid ulcers in rats. In aspirin ulcer, cetraxate (100 and 300 mg/kg p.o.), like tranexamic acid (500 mg/kg p.o.), L-aminocaproic acid (500 mg/kg p.o.) and gefarnate (200 mg/kg p.o.), inhibited both the UI and FA. However, aluminum sucrose sulfate (1000 mg/kg p.o.) was effective only against the UI and L-glutamine (500 mg/kg p.o.) failed to inhibit both parameters. In acetic acid ulcer, following oral, daily × either 5 or 8 administrations, cetraxate (200 and 300 mg/kg), gefarnate (200 mg/kg), aluminum sucrose sulfate (1000 mg/kg) and L-glutamine (500 mg/kg) were effective on both the UI and FA. Tranexamic acid (500 mg/kg) and L-aminocaproic acid (500 mg/kg) were ineffective on the UI, although both agents inhibited FA. In acetic acid ulcer, cetraxate induced increases in hexosamine and uronic acid, that is, acid mucopolysaccharides (AMPS), especially chondroitin sulfate A and -C, whereas L-glutamine and aluminum sucrose sulfate resulted in increases in hexosamine and sialic acid, that is, glycoproteins. From these results, cetraxate may mainly accelerate the ulcer healing by increasing AMPS in ulcer tissue. Moreover, the local anti-FA property of this agent may be also beneficial in treating bleeding ulcers.

We previously reported that cetraxate, 4'- (2-carboxyethyl)phenyl trans-4-aminomethyl cyclohexanecarboxylate hydrochloride, had marked anti-ulcer effects in various acute and chronic types of experimental gastric ulcers, but only slightly inhibitory effects on aggressive factors such as HCl and pepsin in gastric juice (1). These effects were thereafter confirmed by Hashizume et al. (2). This compound is chemically a β-hydroxyphenyl propionic ester of tranexamic acid and has been shown in vitro to possess more potent antiplasmin action than that seen with tranexamic acid (3).

In the present study, we attempted to elucidate the mechanism of the anti-ulcer effect of cetraxate and examined the effects of this compound on the ulcer index (UI) and fibrinolytic activity (FA) in ulcer tissue using aspirin- and acetic acid-induced ulcers in rats. Furthermore, we also examined the effects of cetraxate on the contents of several connective tissue components in the rat acetic acid ulcer tissue to determine whether or not this drug has accelerative actions on ulcer healing by increasing tissue components in that region.
Drugs

The drugs used were as follows: cetraxate (Daiichi Seiyaku), tranexamic acid (Daiichi Seiyaku), L-aminocaproic acid (Daiichi Seiyaku), gefarnate (gefanil, Sumitomo Kagaku), aluminum sucrose sulfate (ulcerimin, Chugai Seiyaku) and L-glutamine (Kyowa Hakko).

Production of experimental gastric ulcers and drug treatment

Aspirin ulcer (acute ulcer): Female Wistar rats, weighing approx. 180 g, were fasted for 24 hr and then each test drug, dissolved or suspended in 1% gum arabic solution, was given orally. The control animals were given 1% gum arabic solution orally. An hour later, gastric ulcers were induced by oral administration of aspirin 200 mg/kg suspended in 1% gum arabic solution. Six hr after aspirin dosing, the animals were sacrificed under deep ether anesthesia and the stomachs were removed. The UI and FA in the ulcer region were determined.

Acetic acid ulcer (chronic ulcer): Female Wistar rats, weighing approx. 180 g at the beginning of the experiment were used and the ulcer was induced as described in our previous report (4). Each test drug, dissolved or suspended in 1% gum arabic solution, was given orally daily x 5 or 8 starting from the day of the operation. The control animals were given 1% gum arabic solution. Twenty-four hr after the last administration of drugs, the animals were given an overdose of ether and the stomachs were removed. After the estimation of the UI, the FA in the ulcer region was determined. Moreover, the contents of several connective tissue components in ulcer tissue were determined in other groups of animals than those used for determination of FA and UI.

Measurement of UI

In both types of ulcers, excised tissue was placed flat on a board without making creases. In the aspirin ulcer, maximal diameter of each ulcer was measured with a caliper under the observation of a magnifying glass and the UI was expressed as the sum of the following scores: score 1, the diameter of 1-3 mm; score 2, the diameter of 4-6 mm; score 3, the diameter of 7-9 mm; score 4, the diameter of 10-13 mm; score 5, the diameter of over 13 mm. On the other hand, the UI of acetic acid ulcer was expressed in the same manner as in the previous report (4).

Determination of FA in ulcer tissue

The FA in ulcer tissue was determined by the fibrin plate method, a modification of the method described by Astrup and Müllertz (5). The stomach tissue in the ulcer area was punched out with a metabolic cylinder of 5 mm in diameter and the tissue was then put on the standard fibrin plate at 37°C. The FA was expressed as the multiplied product (mm²) of the longitudinal and abscissal lengths (mm) of lysis area around the tissue piece in the fibrin plate after 18 hr.

Extraction and determination of the contents of connective tissue components in ulcer tissue

The extraction and determination of the contents of several components in ulcer tissue were performed as previously reported (4) and the tissue components, hexosamine, sialic acid, uronic acid and hydroxyproline contents were determined as indices of total mucos-
polysaccharides, glycoproteins (GP), acid mucopolysaccharides (AMPS) and collagen (CL), respectively.

**Fractionation and determination of AMPS**

The fractionation and determination of AMPS were also carried out as in a previous report (4).

The results were statistically evaluated using Student's t-test.

RESULTS

**Effects of cetraxate on UI and FA in ulcer tissue of aspirin ulcer (Table 1)**

Cetraxate had a significant inhibitory effect on UI; the inhibition was 48.8 and 69.7% at 100 and 300 mg/kg, respectively. Tranexamic acid, the parent compound of cetraxate, an antiplasmin agent, also showed a significant inhibition of 37.2% at 500 mg/kg on the UI.

The FA in ulcer tissue (control group) was 44.8% higher than that in normal tissue (normal group). As expected, cetraxate and tranexamic acid remarkably inhibited the FA in ulcer tissue at a dose lower than that required to inhibit the UI. ε-aminocaproic acid, another antiplasmin agent, at 500 mg/kg was also effective in inhibiting both the UI and FA. Of known anti-ulcer agents, gefarnate 200 mg/kg and aluminum sucrose sulfate 1000 mg/kg were effective on the UI, whereas L-glutamine 500 mg/kg was ineffective. Among these anti-ulcer agents, only gefarnate (200 mg/kg) was significantly active in inhibiting the FA.

### Table 1. Effects of cetraxate and other drugs on ulcer index and fibrinolytic activity in ulcer tissue of aspirin ulcer in rats

| Drugs         | Dose (mg/kg p.o.) | Ulcer index | % inhibition | Fibrinolytic activity (mm²) | % inhibition |
|---------------|-------------------|-------------|--------------|-----------------------------|--------------|
| Normal        |                   | 0           |              | 396.5 ± 40.0               |              |
| Control       | 4.3 ± 0.3         | 14.0        | 547.1 ± 5.9  |                            |              |
| Cetraxate     | 50                | 3.7 ± 0.4   | 40.4 ± 20.7  | 95.0                        |
|               | 100               | 2.2 ± 0.5** | 48.8 ± 38.1  | 122.9                       |
|               | 300               | 1.3 ± 0.2***| 69.7         | 159.4                       |
| Tranexamic acid| 100              | 3.3 ± 0.3   | 23.7         | 103.3                       |
|               | 500               | 2.7 ± 0.5*  | 37.2         | 124.8                       |
| ε-aminocaproic acid | 100       | 3.7 ± 0.3   | 14.0         | 78.8                        |
|               | 500               | 2.5 ± 0.4** | 41.9         | 88.0                        |
| Gefarnate     | 100               | 3.0 ± 0.6   | 30.2         | 33.5                        |
|               | 200               | 2.3 ± 0.2***| 46.9         | 85.7                        |
| Aluminum sucrose sulfate | 500    | 2.7 ± 0.5   | 37.2         | 28.1                        |
|               | 1000              | 2.0 ± 0.4***| 53.5         | 76.6                        |
| L-glutamine   | 200               | 3.5 ± 0.4   | 18.6         | 10.6                        |
|               | 500               | 3.2 ± 0.6   | 25.6         | 77.1                        |

Results are mean ± S.E. obtained from 8 rats.

C: Control, T: Test drug, N: Normal.

Asterisk indicates a significant difference from control (**: P < 0.001, *: P < 0.01, #: P < 0.05).
in ulcer tissue.

Effects of cetraxate on UI and FA in ulcer tissue following oral, daily \( \times 8 \) administrations beginning day 0 after ulcers were induced by acetic acid (Table 2)

The FA in ulcer tissue (control group) was 75\% higher than that in normal tissue (normal group). Cetraxate at 100 mg/kg/day showed a significant inhibitory effect of 31.9\% on the UI and a significant inhibitory effect of 71.2\% on the FA in ulcer tissue. This compound at 300 mg/kg/day induced further potent effects. Gefarnate 200 mg/kg/day, aluminum sucrose sulfate 1000 mg/kg/day and L-glutamine 500 mg/kg/day were also effective on both the UI and FA in ulcer tissue. On the other hand, tranexamic acid and \( \varepsilon \)-amino-caproic acid at 500 mg/kg/day were ineffective on the UI, although both agents significantly inhibited the FA in ulcer tissue.

Effects of cetraxate on UI and contents of connective tissue components in ulcer tissue following oral, daily \( \times 5 \) administrations beginning day 0 after the operation in acetic acid ulcer

Effects on UI (Table 3): Against the UI, a significant inhibition of 44.0\% was evident with the treatment of cetraxate 300 mg/kg/day, the effect of which was comparable to that of gefarnate 500 mg/kg/day, aluminum sucrose sulfate 1000 mg/kg/day and L-glutamine 500 mg/kg/day. Tranexamic acid 500 mg/kg/day and \( \varepsilon \)-amino-caproic acid 500 mg/kg/day were also effective, albeit not significantly.

| Drugs                  | Dose (mg/kg/day p.o.) | Ulcer index (mm\(^2\)) | \% inhibition | Fibrinolytic activity (mm\(^2\)) | \% inhibition |
|------------------------|-----------------------|-------------------------|---------------|----------------------------------|---------------|
| Normal                 |                       | 355.6 \( \pm \) 23.8    |               |                                  |               |
| Control                |                       | 622.3 \( \pm \) 71.4    |               |                                  |               |
| Cetraxate              | 50                    | 23.7 \( \pm \) 3.5      | 26.8          | 463.1 \( \pm \) 73.9            | 59.7          |
|                        | 100                   | 22.1 \( \pm \) 3.0*     | 31.9          | 432.4 \( \pm \) 49.2*           | 71.2          |
|                        | 300                   | 15.4 \( \pm \) 2.0**    | 52.6          | 405.5 \( \pm \) 59.7*           | 81.0          |
| Tranexamic acid        | 100                   | 22.8 \( \pm \) 3.0      | 29.9          | 447.4 \( \pm \) 70.3            | 65.6          |
|                        | 500                   | 23.0 \( \pm \) 2.8      | 29.2          | 415.5 \( \pm \) 40.1*           | 77.5          |
| \( \varepsilon \)-amino-caproic acid | 100           | 30.0 \( \pm \) 2.4      | 5.2           | 458.3 \( \pm \) 36.4            | 61.5          |
|                        | 500                   | 30.5 \( \pm \) 4.2      | 6.2           | 433.9 \( \pm \) 41.9*           | 70.6          |
| Gefarnate              | 100                   | 22.4 \( \pm \) 4.4      | 31.0          | 489.9 \( \pm \) 50.2            | 49.6          |
|                        | 200                   | 17.0 \( \pm \) 2.0**    | 47.8          | 434.0 \( \pm \) 69.2*           | 70.3          |
| Aluminum sucrose sulfate | 500                | 26.0 \( \pm \) 3.6      | 26.0          | 476.3 \( \pm \) 49.1            | 54.7          |
|                        | 1000                  | 20.5 \( \pm \) 2.8**    | 36.9          | 404.7 \( \pm \) 40.8*           | 81.9          |
| L-glutamine            | 200                   | 23.3 \( \pm \) 5.0      | 28.3          | 453.2 \( \pm \) 90.0            | 63.4          |
|                        | 500                   | 16.5 \( \pm \) 3.3*     | 49.2          | 411.4 \( \pm \) 91.0*           | 79.1          |

Asterisk indicates a significant difference from control (**: \( P<0.01 \), *: \( P<0.05 \)). Other explanations as in Table 1.
TABLE 3. Effects of cetrazate and other drugs on ulcer index and hexosamine and sialic acid contents in ulcer tissue following oral, daily × 5 administrations beginning day 0 after the operation in acetic acid ulcer of rats

| Drugs                  | Dose (mg/kg/day p.o.) | Ulcer index (mm²) | % inhibition | Hexosamine (µg glucosamine HCl/100 mg dry tissue) | % increase | Sialic acid (µg N-acetylneuraminic acid/100 mg dry tissue) | % increase |
|------------------------|-----------------------|-------------------|--------------|-----------------------------------------------|------------|-------------------------------------------------------------|------------|
| Control                |                       | 41.4 ± 3.7        |              |                                               |            |                                                            |            |
| Cetrazate              | 300                   | 23.2 ± 3.9*       | 44.0         | 2588.0 ± 18.2**                              | 21.5       | 2790.7 ± 254.1                                              | 13.8       |
| Tranexamic acid        | 500                   | 28.2 ± 4.7        | 31.9         | 2386.7 ± 27.3                                | 12.1       | 2952.7 ± 35.9                                              | 20.4       |
| e-aminocaproic acid   | 500                   | 35.2 ± 5.2        | 15.0         | 2138.0 ± 71.1                                | 0.4        | 2463.1 ± 164.6                                              | 0.4        |
| Control                |                       | 38.3 ± 3.0        |              |                                               |            |                                                            |            |
| Gefarnate              | 300                   | 24.4 ± 1.2*       | 36.3         | 2871.6 ± 30.6**                              | 28.0       | 2098.3 ± 205.2                                              | -1.6       |
| Aluminum sucrose sulfate | 1000                | 20.5 ± 3.7*       | 46.5         | 2811.9 ± 27.9**                              | 25.4       | 2912.8 ± 236.4*                                             | 36.6       |
| L-glutamine            | 500                   | 22.3 ± 3.8*       | 41.8         | 2731.1 ± 18.5**                              | 21.8       | 3758.4 ± 54.1**                                             | 76.2       |

Results of ulcer index are mean ± S.E. obtained from 10 rats.
Results of hexosamine and sialic acid contents are mean ± S.E. obtained from 6 samples (a sample consists of gastric tissue from 5 rats).

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\% \text{ inhibition} = \frac{C-T}{C} \times 100 \quad (C: \text{Control}, \ T: \text{Test drug}).
\]

Asterisk indicates a significant difference from control (**: P < 0.01, *: P < 0.05).
Effects on hexosamine content (Table 3): The hexosamine content in ulcer tissue was increased by all drugs which exhibited the effectiveness on the UI. The increases were 22–28% with these drugs.

Effects on sialic acid content (Table 3): The sialic acid content in ulcer tissue was increased by 76.2 and 36.6%, respectively with L-glutamine 500 mg/kg/day and aluminum sucrose sulfate 1000 mg/kg/day. No significant increments in this component were noted with any other test drugs.

Effects on uronic acid content (Table 4): Of test drugs, only cetraxate increased the uronic acid content in ulcer tissue, the increase being 30.3% at 300 mg/kg/day.

Effects on hydroxyproline content (Table 4): Significant increases in hydroxyproline content in ulcer tissue were not seen with any drug used herein.

Effects on hexosamine content (Table 5): Unlike effects following daily x 5 administrations as shown already in Table 3, a significant increase (23.5%) in the hexosamine content in ulcer tissue was observed only with cetraxate (300 mg/kg/day).

Effects on sialic acid content (Table 5): Of test drugs, only L-glutamine at 500 mg/kg/day led to a significant increase of 36.8% in the sialic acid content in ulcer tissue, while other test drugs were ineffective in increasing this component.

Effects on uronic acid content (Table 6): As in the case of daily x 5 administrations, cetraxate was the only drug which significantly increased the uronic acid content in ulcer tissue, the increase being 36.2% at 300 mg/kg/day. Of comparative drugs, aluminum sucrose sulfate 1000 mg/kg/day produced some increase (approx. 20%) in this component, but such was not significant.

Effects on hydroxyproline content (Table 6): The hydroxyproline content in ulcer tissue was not significantly increased by any drug used in this study.

### Table 4. Effects of cetraxate and other drugs on uronic acid and hydroxyproline contents in ulcer tissue following oral, daily x 8 administrations beginning day 0 after the operation in acetic acid ulcer

| Drugs               | Dose (mg/kg/day) p.o. | Uronic acid µg glucuronic acid/100 mg dry tissue | % increase | Hydroxyproline µg hydroxyproline/100 mg dry tissue | % increase |
|---------------------|-----------------------|-----------------------------------------------|-------------|---------------------------------------------------|-------------|
| Control             |                       | 252.0 ± 12.0                                 |            | 558.7 ± 90.6                                     |            |
| Cetraxate           | 300                   | 328.4 ± 18.9*                                | 30.3        | 577.7 ± 24.1                                     | 3.4         |
| Trasexamic acid     | 500                   | 271.0 ± 3.6                                  | 7.5         | 532.9 ± 9.1                                     | -5.2        |
| ε-aminocaproic acid | 500                   | 255.2 ± 26.8                                 | 1.3         | 533.1 ± 38.8                                     | 1.0         |
| Control             |                       | 266.4 ± 11.4                                 |            | 592.3 ± 48.7                                     |            |
| Gefarnate           | 300                   | 302.0 ± 22.4                                 | 13.4        | 507.6 ± 24.2                                     | 14.3        |
| Aluminum sucrose    | 1000                  | 288.0 ± 18.9                                 | 8.1         | 518.0 ± 50.9                                     | 12.5        |
| L-glutamine         | 500                   | 273.4 ± 60.2                                 | 2.6         | 542.2 ± 59.9                                     | -8.5        |

Results are mean ± S.E. obtained from 6 samples (a sample consists of gastric tissue from 5 rats). Asterisk indicates a significant difference from control at P ≤ 0.05.
### Table 5. Effects of cetraxate and other drugs on hexosamine and sialic acid contents in ulcer tissue following oral, daily \( \times 8 \) administrations beginning day 0 after the operation in acetic acid ulcer of rats

| Drugs             | Dose \( \text{mg/kg/day p.o.} \) | Hexosamine \( \mu g \) glucosamine HCl/100 mg dry tissue | \% increase | Sialic acid \( \mu g \) N-acetylmuramic acid/100 mg dry tissue | \% increase |
|-------------------|----------------------------------|--------------------------------------------------------|-------------|--------------------------------------------------------|-------------|
| Control           |                                  | 1403.3 ± 26.8                                          |             | 1538.9 ± 21.7                                          |             |
| Cetraxate         | 100                              | 1479.3 ± 68.1                                          | 5.3         | 1600.5 ± 127.6                                          | 4.0         |
|                   | 300                              | 1735.5 ± 34.4**                                        | 23.5        | 1660.1 ± 114.6                                          | 7.9         |
| Control           |                                  | 1419.6 ± 78.9                                          |             | 1288.0 ± 38.9                                          |             |
| Tranexamic acid   | 500                              | 1497.2 ± 128.6                                         | 5.5         | 1366.8 ± 93.0                                          | 6.1         |
| Control           |                                  | 1435.0 ± 72.9                                          |             | 1819.4 ± 66.3                                          |             |
| \( \epsilon \)-aminocaproic acid | 500 | 1269.0 ± 140.4                                         | -11.7       | 1770.0 ± 20.9                                          | -2.7        |
| Control           |                                  | 1609.0 ± 82.2                                          |             | 1188.9 ± 39.6                                          |             |
| Gefarnate         | 200                              | 1600.0 ± 48.1                                          | -0.6        | 1152.8 ± 29.6                                          | -3.6        |
| Control           |                                  | 1342.0 ± 66.2                                          |             | 1547.2 ± 12.1                                          |             |
| Aluminum sucrose sulfate | 1000 | 1524.0 ± 28.5                                         | 14.9        | 1569.4 ± 32.5                                          | 1.4         |
| Control           |                                  | 1132.5 ± 62.7                                          |             | 1265.0 ± 94.5                                          |             |
| L-glutamine       | 500                              | 1297.0 ± 19.1                                          | 14.5        | 1458.3 ± 55.3*                                         | 36.8        |

Results are mean ± S.E. obtained from 6 samples (a sample consisted of gastric tissue from 5 rats). Asterisk indicates a significant difference from control (**: \( P < 0.01 \), *: \( P < 0.05 \)).

### Table 6. Effects of cetraxate and other drugs on uronic acid and hydroxyproline contents in ulcer tissue following oral, daily \( \times 8 \) administrations beginning day 0 after the operation in acetic acid ulcer of rats

| Drugs             | Dose \( \text{mg/kg/day p.o.} \) | Uronic acid \( \mu g \) glucuronic acid/100 mg dry tissue | \% increase | Hydroxyproline \( \mu g \) hydroxyproline/100 mg dry tissue | \% increase |
|-------------------|----------------------------------|--------------------------------------------------------|-------------|--------------------------------------------------------|-------------|
| Control           |                                  | 264.4 ± 20.5                                           |             | 500.0 ± 60.2                                           |             |
| Cetraxate         | 100                              | 298.3 ± 12.9                                           | 12.8        | 476.6 ± 18.6                                           | -4.0        |
|                   | 300                              | 360.1 ± 15.7*                                          | 36.2        | 504.1 ± 24.8                                           | 0.8         |
| Control           |                                  | 238.8 ± 31.8                                           |             | 602.8 ± 5.5                                            |             |
| Tranexamic acid   | 500                              | 267.5 ± 15.2                                           | 12.0        | 508.3 ± 70.8                                           | -15.7       |
| Control           |                                  | 274.9 ± 60.9                                           |             | 645.0 ± 75.0                                           |             |
| \( \epsilon \)-aminocaproic acid | 500 | 254.0 ± 27.0                                         | 2.5         | 630.0 ± 10.0                                           | -2.7        |
| Control           |                                  | 246.0 ± 44.9                                           |             | 569.0 ± 36.0                                           |             |
| Gefarnate         | 200                              | 244.0 ± 50.6                                           | -0.8        | 552.4 ± 52.5                                           | -2.9        |
| Control           |                                  | 239.5 ± 17.2                                           |             | 626.6 ± 17.6                                           |             |
| Aluminum sucrose sulfate | 1000 | 295.8 ± 11.7                                         | 23.5        | 815.0 ± 85.0                                           | 15.8        |
| Control           |                                  | 245.0 ± 19.8                                           |             | 561.5 ± 1.5                                            |             |
| L-glutamine       | 500                              | 234.0 ± 7.0                                            | -4.5        | 687.2 ± 118.8                                          | 22.4        |

Results are mean ± S.E. obtained from 6 samples (a sample consisted of gastric tissue from 5 rats). Asterisk indicates a significant difference from control at \( P < 0.05 \).
tissue was not significantly affected by any of test drugs.

**Effects of cetraxate on the percentage and content of each AMPS in ulcer tissue following daily, oral × 8 administrations beginning day 0 after the operation in acetic acid ulcer of rats**

| Groups          | HA Percentage | HS Percentage | ChS-A | ChS-B | ChS-C | Hep Percentage |
|-----------------|---------------|---------------|-------|-------|-------|----------------|
| Control         | 45.6          | 10.5          | 26.2  | 9.8   | 7.3   | 0.6            |
| Cetraxate 300 mg/kg | 42.1          | 7.3           | 30.9  | 8.3   | 11.2  | 0.2            |
| Control         | 60.3          | 13.9          | 34.6  | 13.0  | 9.7   | 0.8            |
| Cetraxate 300 mg/kg | 72.5          | 12.6          | 53.2  | 14.3  | 19.3  | 1.4            |

Results are mean of 3 determinations.
HA: Hyaluronic acid. HS: Heparitin sulfate. ChS-A: Chondroitin sulfate A. ChS-B: Chondroitin sulfate B. ChS-C: Chondroitin sulfate C. Hep: Heparin.

**DISCUSSION**

It has been confirmed by many investigators that in experimental animals or humans, FA in circulating blood and ulcer tissue is elevated with the development of ulcer (6-8). In the present experiment, we also demonstrated a marked elevation of FA in ulcer tissue using aspirin- and acetic acid induced ulcer models in rats. This local FA is considered to be due to plasminogen activators, because in the preliminary experiment, the specimens obtained from the gastric tissues in normal and ulcer regions had the ability to lyse the standard fibrin plate, but not the heated fibrin plate. Cetraxate showed an excellent effect in inhibiting both the UI and FA in ulcer tissue on the acutely produced gastric lesions by oral administration of aspirin to rats. Furthermore, it is noteworthy that tranexamic acid and z-aminocaproic acid, antiplasmin agents, also were effective in the case of aspirin-induced ulcer. The gastric lesions induced by anti-inflammatory agents such as aspirin, phenylbutazone and indomethacin appear to be more like an acute hemorrhagic erosive gastritis. Therefore, the mechanism of anti-ulcer action of cetraxate on experimental acute gastric ulcers such as aspirin ulcer may be mainly due to anti-FA effect, that is, anti-hemorrhagic nature of this drug. On the other hand, in rat acetic acid ulcer which is said to resemble the human chronic ulcer, like gefarnate, aluminum sucrose sulfate and L-glutamine, cetraxate was effective on both the UI and FA. However, tranexamic acid and z-
aminocaproic acid were ineffective on the UI, although both drugs remarkably inhibited the FA. From these findings, it is unlikely that in acetic acid ulcer, the anti-FA effect of drugs is directly related to their anti-ulcer effect.

Fukawa et al. (9) reported that drugs which are known to promote mucous regeneration and granuloma formation in gastric tissue showed a significant acceleration on the healing in acetic acid ulcer. In the next experiment, therefore, in order to clarify a possible mechanism of anti-ulcer action of cetraxate on the acetic acid ulcer, we investigated the effect of this drug on the contents of several connective tissue components. We (4) have already shown that in the healing process of the rat acetic acid ulcer, the levels of hexosamine and sialic acid in ulcer tissue reached a maximum on the 5th day after the operation and thereafter decreased rapidly as the level of uronic acid increased. In this experiment, drug effects were evaluated on the 5th day when the hexosamine and sialic acid levels showed their peaks and on the 8th day when their levels began to fall. From the data in the present experiments, it is clear that drug effects on the contents of hexosamine and sialic acid are more remarkable with a 5 day than 8 day administration (Tables 3 and 5), whereas effects on uronic acid are more potent with a 8 day treatment (Tables 4 and 6). As a result, cetraxate induced significant increases in hexosamine and uronic acid in ulcer tissue. On the other hand, the treatment of L-glutamine or aluminum sucrose sulfate resulted in increases in hexosamine and sialic acid contents. These observations suggest that cetraxate may mainly promote the regeneration of gastric mucosa and the granuloma formation in the ulcer floor by increasing the AMPS, while the latter comparative drugs do so by increasing the GP. The increase in hexosamine content in the ulcer region was further observed also by gefarnate, that is, this increase was found by all drugs which exhibited the effectiveness on the UI. Takagi and Yano (10) also reported that in rats subjected to the water immersion and restraint form of stress, the hexosamine content in pyloric tissue was increased by L-glutamine and gefarnate. In view of the above findings and the fact that hexosamine in tissues is always a main component of AMPS and GP, the hexosamine content in ulcer tissue is considered to be the best indicator of the ulcer healing.

We also studied the kinds of AMPS in the ulcer portion of acetic acid ulcer. In this experiment, cetraxate brought about increases in the contents of ChS-A and ChS-C in ulcer tissue, although this drug affected only slightly the percentage of each AMPS to total AMPS. Concerning the relationship between AMPS and CL, it has been demonstrated that of AMPS, ChS may participate in the formation of CL fibrils (11–13). Therefore, cetraxate may contribute to reinforcement of the ulcer floor by increasing ChS-A and ChS-C in the granuloma formed on the ulcer floor and then promoting the formation of CL fibrils.

The results of our earlier report (1) taken together with our present data suggest that the anti-ulcer action of cetraxate contributes to the acceleration of ulcer healing based on the increment of AMPS in ulcer tissue rather than the protective effect of this drug on aggressive factors such as HCl and pepsin in gastric juice. In addition, the anti-FA effect of this drug is considered to be beneficial in treating bleeding ulcers.
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