Effects of Quinotolast, a New Orally Active Antiallergic Drug, on Experimental Allergic Models

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ABSTRACT—The effects of a new antiallergic drug, quinotolast [sodium 5-(4-oxo-1-phenoxy-4H-quinolizine-3-carboxamido)tetrazolate monohydrate], were studied and compared with those of tranilast, amlexanox, pemirolast, repirinast and disodium cromoglycate (DSCG) in experimental allergic models. Quinotolast potently inhibited such type I allergic reactions as passive cutaneous anaphylaxis (PCA) and anaphylactic bronchoconstriction in rats by both intravenous and oral dosing. All of these effects were stronger than those of the reference drugs tested. Quinotolast inhibited histamine release from rat peritoneal cells, but it had no antagonistic effect on histamine-, serotonin-, platelet activating factor- or bradykinin-induced cutaneous reactions in rats. Moreover, it was clearly demonstrated that quinotolast and DSCG had a cross tachyphylaxis to inhibit PCA in rats, suggesting that these drugs, at least in part, share the same mechanism of action. Furthermore, quinotolast potently inhibited PCA in guinea pigs in which DSCG and other reference drugs showed poor inhibitory activity. Quinotolast also showed stronger inhibitory effects on histamine and peptide leukotrienes release from guinea pig lung fragments or mouse cultured mast cells than the other drugs tested. Thus, the effect of quinotolast on type I allergic reaction would seem to be based on an inhibition of mediator release from inflammatory cells including mast cells. The results suggest that quinotolast will be beneficial in the treatment of type I allergy-related diseases.

Keywords: Quinotolast, Antiallergics, Mediator release inhibitor

The pathogenesis of asthma is complicated, but there is no doubt that allergic reaction is one of the main triggers of asthmatic attack. Disodium cromoglycate (DSCG), which has an inhibitory activity against the type I allergic reaction (1), has been used for the treatment of asthma in the clinic, where it is effective in 60 to 70% of the patients with mild to moderate asthma (2).

The clinical effect of DSCG is regarded as based on the inhibition of mediator release from the mast cells (3). In experimental allergic models, DSCG shows an obvious inhibitory effect on the type I allergic reaction, especially in rats. However, it has been revealed that many compounds with potent inhibitory effects on the type I reaction in rats had no clinical effects (4–6). Therefore, efficacy in rats does not always warrant effectiveness in humans. Thus, we assumed that a drug which showed inhibitory effects on type I reaction not only in rats but in other species might, more reliably, be expected to be effective in humans. On the other hand, from the view of medication compliance, the delivery route of DSCG, i.e., inhalation, poses difficulties, especially for children. Therefore, efforts have been made to find new orally active drugs with strong antiallergic activity and less species specificity.

In our research laboratories, various series of compounds have been synthesized chemically and tested for development as antiallergic drugs, and some quinolizine derivatives have been found to have potential as antiallergics. One of these compounds, quinotolast [sodium 5-(4-oxo-1-phenoxy-4H-quinolizine-3-carboxamido)tetrazolate monohydrate], was found to have strong antiallergic effects when it was given orally and intravenously.

The purpose of this study was to examine the antiallergic effects of quinotolast and to compare them with those of DSCG and other orally active antiallergic drugs, tranilast (7), amlexanox (8), pemirolast (9) and repirinast (10), in experimental allergic models using not only rats but guinea pigs and mice as well.
MATERIALS AND METHODS

Animals
Male Sprague-Dawley rats were purchased from Japan SLC, Inc. (Hamamatsu) and Clea Japan, Inc. (Tokyo). Male Hartley guinea pigs and male ICR mice were from Japan SLC. Female BDF1 mice were from Charles River Japan, Inc. (Atsugi) and Japan SLC.

Drugs
Quinotolast, tranilast, amlexanox, pemirolast, repirinast and MY-1250 (an active metabolite of repirinast (10)) were prepared in our research laboratories. DSCG was provided by Fisons Co., Ltd. (Loughborough, UK). The chemical structure of quinotolast is shown in Fig. 1. For oral dosing, all drugs were dissolved or suspended in 0.5% methylcellulose. For i.v. dosing, quinotolast was dissolved in 0.12 mM Na2CO3 and diluted with 0.1% NaHCO3 containing saline or was dissolved in saline. Tranilast was dissolved in 0.1 M Na2HPO4; amlexanox was dissolved in saline with appropriate amounts of NaOH. DSCG, pemirolast and MY-1250 were dissolved in saline. In the in vitro experiments, quinotolast was dissolved in dimethyl sulfoxide (for 1 pg/ml and over) or purified water (for under 1 ng/ml) and diluted with reaction buffers. DSCG, pemirolast and MY-1250 were dissolved in reaction buffers, and amlexanox and tranilast were dissolved in the reaction buffers with appropriate amounts of NaOH and NaHCO3, respectively.

Type I allergic reactions
Passive cutaneous anaphylaxis (PCA) in rats: Rats (8 week-old) were sensitized intradermally on their shaved backs with 0.1 ml of 32-fold diluted homologous antiserum containing anti-egg albumin IgE (PCA titer 1:64), and 48 hr later, the rats were challenged i.v. with 1 ml of saline containing 5 mg of egg albumin (EA) and 5 mg of Evans blue. One hour after the challenge, the rats were killed, and the skin of the back was removed. The severity of PCA was assessed by measuring the diameter of the blued spot or quantifying the extravasated dye according to the method of Katayama et al. (11). To study the presence of tachyphylaxis by quinotolast and DSCG, each drug was given i.v. in a large dose 30 min before challenge, and again at a smaller dose simultaneously with the antigen challenge. Additionally, to examine cross tachyphylaxis between quinotolast and DSCG, either drug was given as above in reverse sequence.

PCA in guinea pigs: Guinea pigs (349 – 580 g) were sensitized intradermally on their shaved backs with 0.1 ml of 16-fold diluted homologous anti-EA serum containing IgE (PCA titer 1:128), and 8 days later, the guinea pigs were challenged with 1 ml of saline containing 10 mg of EA and 10 mg of Evans blue. Thirty minutes after the challenge, the guinea pigs were killed, and the skin of the back was removed. The severity of PCA was assessed by quantifying the extravasated dye.

Anaphylactic bronchoconstriction in rats: Rats (6 week-old) were adrenalectomized under pentobarbital anesthesia. After recovery from the shock of the operation, the rats were sensitized i.v. with 1 ml of mouse monoclonal IgE antibody against dinitrophenyl (DNP) epitope (PCA titer 1:500). One day later, the rats were challenged i.v. with 0.5 mg of trinitrophenylated bovine serum albumin (TNP-BSA) under pentobarbital anesthesia (25 mg/kg, i.p.), and airway resistance was measured according to a procedure based on the method of Konzett and Rössler (12), with modifications. Briefly, the trachea was cannulated for artificial respiration (3.3 ml/stroke, 60 strokes/min), and the side arm of the cannula was connected to a transducer to measure the pressure of superfluous air. The bronchoconstriction was estimated as a percentage of the maximal increase of the pressure achieved by clamping-off the trachea (%increase).

Histamine release from rat peritoneal cells: Rats (372 – 446 g) were killed by decapitation and the abdominal cavity was washed with phosphate-buffered salts solution (154 mM NaCl, 2.7 mM KCl, 0.9 mM CaCl2, 6.7 mM phosphate, 7.5 U/ml heparin, 0.1% BSA, pH 7.1). The peritoneal cells contained about 9 – 15% mast cells when measured by toluidine blue staining. The cells were sensitized with homologous anti-EA IgE serum (PCA titer 1:128) for 30 min at 37°C and resuspended with reaction medium (154 mM NaCl, 2.7 mM KCl, 1 mM CaCl2, 1 mM MgCl2, 10 mM Tris-acetate, 1% normal rat serum, pH 7.4). The cells (5 x 10⁶ cells) were incubated for 5 min at 30°C and challenged with EA (3 ng/ml). Drugs were added to the reaction tube simultaneously with the antigen. Five minutes later, the reaction was stopped by chilling the tube on ice. Histamine content in the supernatant was measured fluorometrically by the method of Shore et al. (13).

Peptide leukotrienes (pLTs) release from cultured
mouse mast cells: Mast cells were obtained after the culture of bone marrow cells from the femurs of female BDF1 mice in the presence of conditioned medium from WEHI-3 cells containing interleukin 3 (14). The cells were suspended with Tyrode's buffer (137 mM NaCl, 2.7 mM KCl, 1.8 mM CaCl2, 1 mM MgCl2, 0.4 mM NaH2PO4, 11.9 mM NaHCO3, 5.6 mM glucose) containing 0.1% gelatin and were sensitized with mouse monoclonal anti-DNP IgE (50 μg/10⁶ cells). Then the cells were washed and resuspended with Tyrode's buffer containing 0.25% BSA. The cells (2×10⁶ cells) were incubated for 5 min at 37°C and challenged with TNP-BSA (2 ng BSA/ml). Drugs were added to the reaction tube simultaneously with the antigen. Ten minutes later, the reaction was stopped by the addition of EDTA (2.7 mM). pLTs in the cell supernatant were quantified as immunoreactive leukotriene C4 (iLTC4) with a leukotriene C4/D4/E4[3H] assay system (Amersham International plc, Amersham, UK).

Histamine and pLTs release from guinea pig chopped lungs: Guinea pigs were sensitized i.v. with 0.5 ml of homologous anti-EA IgG serum (PCA titer 1:9850). Twenty-four hours later, the guinea pigs were killed, and the lungs were removed and chopped into fragments (1×1×1 mm) with a McIlwain tissue chopper (Mickle Lab. Eng. Co., Gomshall, UK). The lung fragments (200 mg wet weight) were placed in a polystyrene tube with Krebs-Henseleit buffer (118 mM NaCl, 4.7 mM KCl, 2.6 mM CaCl2, 1.2 mM MgSO4, 1.2 mM KH2PO4, 25 mM NaHCO3, 5.6 mM glucose) and incubated for 10 min at 37°C and challenged with EA (300 μg/ml). Drugs were added to the reaction tube simultaneously with the antigen. Fifteen minutes later, the reaction was stopped by chilling the tube on ice. Histamine and pLTs in the supernatant were quantified as above.

Type II allergic reaction

Forssman antiserum-induced bronchoconstriction in guinea pigs: Guinea pigs (285–435 g) were anesthetized with pentobarbital (25 mg/kg, i.p.), and the trachea was cannulated for artificial respiration (5 ml/stroke, 60 strokes/min). Bronchoconstriction (15) was induced by i.v. injection of 20-fold diluted rabbit anti-sheep red blood cells (SRBC) serum (Forssman antiserum; Cappel, Inc., West Chester, PA, USA), and airway resistance was measured as described above. Quinotolast, tranilast and amlexanox were given intraduodenally 15, 60 and 15 min, respectively, before the challenge; and DSCG was given i.v. 2 min before the challenge.

Type III allergic reaction

Arthus type paw edema in rats: Rats (6-week-old) were used. Paw edema was induced according to the method described previously (16). Immediately after EA was injected i.v. to rats, homologous anti-EA IgG antiserum was injected into the subplantar region of the right hind paw of the animals. The volume of the hind paw was measured before and at 1 and 3 hr after the antiserum challenge.

Type IV allergic reaction

Hypersensitivity contact dermatitis in mice: ICR strain mice (6-week-old) were sensitized by application of 7% picryl chloride (Nacalai Tesque, Inc., Kyoto) in ethanol solution to the shaved abdominal skin twice at an interval of 1 week. One week after the second sensitization, the thickness of the ears was measured with a dial thickness gauge (Citizen Watch Co., Tokyo), then both ears of the mice were painted with 1% picryl chloride olive oil solution. Twenty-four hours later, the thickness of the ears was measured again, and the increase of thickness was taken as an indication of hypersensitivity (17).

Chemical mediator induced cutaneous reaction

Rats (8-week-old) were used in groups of 5. Evans blue (5 mg in 1 ml of saline) was given i.v. to rats; and immediately, 0.05 ml of phosphate-buffered saline containing 10 μg of histamine dihydrochloride (Nacalai Tesque, Inc.), 2.5 μg of serotonin creatinine sulphate (E. Merck AG, Darmstadt, FRG), 100 ng of platelet activating factor (PAF; Avanti Polar Lipids, Inc., Alabaster, AL, USA) or 5 μg of bradykinin triacetate (BK; Sigma Chem., Co., St. Louis, MO, USA) was given intradermally into the shaved back. One hour later, the rats were killed by decapitation, and the skin of the back was removed. Evans blue in the skin was extracted and measured as above. Quinotolast, tranilast, amlexanox and pemirolast were given p.o. 15, 60, 15 and 15 min, respectively, before the mediator injection; and DSCG was given i.v. just before the mediator.

Statistical analyses

Data were expressed as the mean±S.E. Statistical significance of differences were assessed by Dunnett’s or Tukey’s multiple comparison test following the analysis of variance (ANOVA). P values less than 0.05 were considered statistically significant. ED50, IC50 and IC30 values were calculated by the probit method.

RESULTS

Type I allergic reactions

PCA in rats: When drugs were given i.v. to rats, quinotolast, amlexanox, pemirolast, MY-1250 and DSCG dose-dependently inhibited PCA (Fig. 2A). The doses of quinotolast, amlexanox, pemirolast, MY-1250 and DSCG
required to inhibit the reaction by 50% (ED50) were 0.0063, 0.021, 0.012, 0.15 and 1.3 mg/kg, respectively. Tranilast showed no apparent inhibitory effect at doses up to 10 mg/kg. Given p.o., quinotolast, tranilast, amlexanox, pemirolast and repirinast inhibited the reaction, but DSCG had no effect at doses up to 100 mg/kg. ED50 values for quinotolast, tranilast, amlexanox, pemirolast and repirinast were 0.0081, 81, 0.20, 0.014 and 177 mg/kg, respectively. Although almost complete inhibition was observed with quinotolast at a dose of 0.32 mg/kg, its effect was slightly attenuated at a dose of 1 mg/kg (Fig. 2B).

To study the tachyphylaxis by quinotolast and DSCG in PCA, quinotolast or DSCG was given i.v. to rats at a dose of 0.1 or 20 mg/kg, respectively, 30 min before challenge; and the second doses were injected i.v. simultaneously with the antigen challenge. As shown in Table 1, pretreatment with quinotolast markedly decreased the inhibition of the reaction by the second dose of this drug or by DSCG. Furthermore, pretreatment with DSCG attenuated the effects of the second dose of either drug, suggesting that quinotolast has a tachyphylactic effect by itself and that cross-tachyphylaxis between quinotolast and DSCG does exist.

Table 1. Tachyphylactic effects of quinotolast and DSCG on PCA in rats

| Drug       | 1st*  | 2ndb | Diameter of | %Inhibition |
|------------|-------|------|-------------|-------------|
|            | 1st*  | 2ndb | blued spot (mm) | %Inhibition |
| Saline     | — (control) | | 9.4 ± 0.4 | 6.4 |
| Quinotolast| —     | Quinotolast | 0.4 ± 0.4** | 95.7 |
| Quinotolast| 0.0 ± 0.4** | Quinotolast | 5.6 ± 1.0** | 31.9 |
| Saline     | DSCG  | DSCG | 0.5 ± 0.5** | 94.7 |
| Saline     | —     | —    | 10.0 ± 0.5  | 9.0 |
| Saline     | —     | —    | 9.1 ± 0.4   | 9.0 |
| DSCG       | —     | Quinotolast | 0.3 ± 0.3** | 97.0 |
| DSCG       | Quinotolast | Quinotolast | 5.6 ± 1.0** | 44.0 |
| Saline     | DSCG  | DSCG | 0.4 ± 0.4** | 96.0 |
| Saline     | DSCG  | DSCG | 4.6 ± 1.1** | 54.0 |

*Quinotolast (0.1 mg/kg), DSCG (20 mg/kg) or saline was given i.v. 30 min before the antigen challenge. **Quinotolast (0.032 mg/kg) or DSCG (3.2 mg/kg) was given i.v. simultaneously with the antigen. The diameter of the blued spot is expressed as the mean ± S.E. of the values in 5 rats. Significantly different at *P<0.05, **P<0.01 from the control, and *P<0.05, **P<0.01 from the respective saline-pretreated group (Tukey's test).

Anaphylactic bronchoconstriction in rats: The results are shown in Fig. 4. When drugs were given i.v. to the
rats, quinotolast, amlexanox, MY-1250 and DSCG dose-dependently inhibited the reaction, and their respective ED$_{50}$ values were 0.0084, 0.032, 0.32 and 0.24 mg/kg. Given p.o., quinotolast, tranilast, amlexanox and pemirolast also inhibited the reaction, and the respective ED$_{50}$ values were 0.016, 101, 0.23 and 0.023 mg/kg.

Repirinast, however, showed no apparent inhibitory effect in doses up to 100 mg/kg.

Histamine release from rat peritoneal cells: Figure 5 shows that all of the drugs concentration-dependently inhibited histamine release from rat peritoneal cells. The IC$_{50}$ values for quinotolast, tranilast, amlexanox,
pemirolast and DSCG were 0.018, 46, 0.018, 0.020 and 4.2 pg/ml, respectively.

**pLTs release from cultured mouse mast cells**: As shown in Fig. 6, quinotolast concentration-dependently inhibited pLTs release from cultured mast cells. Tranilast, amlexanox, pemirolast and MY-1250 also inhibited pLTs release from cultured mast cells. Tranilast, amlexanox, pemirolast and MY-1250 were added simultaneously with the antigen.
release, but their effects were much weaker than that of quinotolast. The IC\textsubscript{50} values for quinotolast, tranilast, amlexanox, pemirolast and MY-1250 were 0.72, 41, 27, 35 and 1.9 \textmu g/ml, respectively. DSCG showed no inhibitory effects in concentrations up to 100 \textmu g/ml.

**Histamine and pLTs release from guinea pig chopped lungs:** Further experiments were performed to study the effects of drugs on the release of histamine and pLTs from the lungs of guinea pigs sensitized with anti-EA serum after challenge with EA. The results are shown in Fig. 7. Quinotolast and amlexanox slightly inhibited histamine release from the lung, and quinotolast was more active than amlexanox. Tranilast, MY-1250 and DSCG had no effect in concentrations up to 100 \textmu g/ml, and pemirolast had no effect in concentrations up to 3.2 \textmu g/ml. Quinotolast and amlexanox also significantly inhibited iLTC\textsubscript{4} release from the lung. The IC\textsubscript{50} value for quinotolast was 4.7 \textmu g/ml, and the inhibition by amlexanox was less than 30% even at a concentration of 100 \textmu g/ml. Tranilast, pemirolast, MY-1250 and DSCG showed no effect in concentrations up to 100 \textmu g/ml.

### Type II allergic reaction

**Forssman antiserum-induced bronchoconstriction in guinea pigs:** Rabbit anti-SRBC serum caused a biphasic bronchoconstriction in guinea pigs. Quinotolast (up to 100 mg/kg, p.o.), tranilast (up to 320 mg/kg, p.o.), amlexanox (up to 100 mg/kg, p.o.), pemirolast (up to 100 mg/kg, p.o.) and DSCG (up to 100 mg/kg, i.v.) showed no inhibitory effect on either phase of bronchoconstriction (data not shown).

### Type III allergic reaction

**Arthus type paw edema in rats:** The animals were observed for edema 1 and 3 hr after challenge with anti-EA

| Drug        | Dose (mg/kg) | 1 hr after challenge | 3 hr after challenge |
|-------------|-------------|----------------------|----------------------|
|             |             | Increase of paw volume (ml) | %Inhibition | Increase of paw volume (ml) | %Inhibition |
| Quinotolast (p.o.) | 0 (control) | 0.96±0.08 | 22.9 | 0.92±0.09 |
|             | 0.1         | 0.74±0.05∗ | 27.1 | 0.84±0.05 |
|             | 1           | 0.70±0.04∗∗ | 29.2 | 0.78±0.02 |
|             | 10          | 0.68±0.04∗∗ | 27.1 | 0.74±0.05 |
|             | 100         | 0.70±0.04∗∗ | 19.6 | 0.74±0.05 |
| Tranilast    | 0 (control) | 1.12±0.07 | 7.1 | 1.18±0.07 |
| (p.o.)       | 2           | 1.04±0.04 | 14.3 | 1.10±0.03 |
|             | 100         | 1.04±0.05 | 14.3 | 1.10±0.06 |
|             | 320         | 0.96±0.02 | 14.3 | 0.98±0.04∗ |
| Amlexanox    | 0 (control) | 1.00±0.03 | 4.2 | 1.00±0.07 |
| (p.o.)       | 1           | 0.78±0.04 | 18.8 | 0.88±0.02 |
|             | 10          | 0.64±0.07∗∗ | 33.3 | 0.70±0.05 |
|             | 100         | 0.72±0.05* | 25.0 | 0.78±0.05 |
| DSCG         | 0 (control) | 1.12±0.04 | -3.6 | 1.06±0.07 |
| (i.v.)       | 0.1         | 1.16±0.05 | -3.6 | 1.06±0.07 |
|             | 1           | 0.98±0.05 | 12.5 | 0.96±0.05 |
|             | 10          | 1.00±0.03 | 10.7 | 0.96±0.02 |
|             | 100         | 0.88±0.06** | 21.4 | 0.84±0.04* |

Quinotolast, tranilast and amlexanox were given p.o. 15, 60 and 15 min, respectively, before the antigen challenge, and DSCG was given i.v. just before the challenge. Increase of ear thickness is expressed as the mean±S.E. of the values from 10 mice. Significantly different at *P<0.05, **P<0.01 from the control (Dunnett’s test).
serum. Quinotolast (p.o.) and amlexanox (p.o.) slightly inhibited the edema at 1 hr but not at 3 hr after challenge, whereas DSCG (i.v.) had a slight effect at both observation times. Tranilast (p.o.), on the other hand, slightly inhibited the reaction only at 3 hr (Table 2).

**Type IV allergic reaction**

**Hypersensitivity contact dermatitis in mice:** As shown in Table 3, quinotolast (up to 100 mg/kg, p.o.), tranilast (up to 320 mg/kg, p.o.), amlexanox (up to 100 mg/kg, p.o.) and DSCG (up to 10 mg/kg, i.v.) showed no inhibitory effects on the reaction.

**Chemical mediator induced cutaneous reaction in rats**

Quinotolast (up to 100 mg/kg, p.o.), tranilast (up to 320 mg/kg, p.o.), amlexanox (up to 100 mg/kg, p.o.), pemirolast (up to 100 mg/kg, p.o.) and DSCG (up to 100 mg/kg, i.v.) produced no suppressive effects on histamine-, serotonin-, PAF- or BK-induced cutaneous reactions (data not shown).

**DISCUSSION**

The effects of drugs on such type I allergic reactions as PCA and anaphylactic bronchoconstriction were examined in rats. Quinotolast, pemirolast, amlexanox and DSCG potently inhibited type I allergic reactions, but the effects of tranilast and repirinast were slight. Given i.v. to rats, quinotolast was about 300 times more active than DSCG, and when given p.o. to rats, quinotolast as well as tranilast, pemirolast and amlexanox showed effects, with quinotolast being almost as active as pemirolast and more active than amlexanox or tranilast. DSCG had no effect. Thus, quinotolast was one of the most active of the test drugs.

The inhibitory effects of DSCG on type I reactions in rats are reported to derive from inhibition of mediator release from the mast cells (1, 3, 18). In the present study, quinotolast, pemirolast, amlexanox and DSCG potently inhibited histamine release from the peritoneal mast cells; and quinotolast was the most active. However, quinotolast, tranilast, pemirolast, amlexanox and DSCG had no effect on histamine-, serotonin-, PAF- or BK-induced cutaneous reactions, suggesting that these drugs do not block all histamine, serotonin, PAF and BK receptors which are concerned with the vascular permeability in the skin. The results do demonstrate that quinotolast potentially inhibits the type I allergic reaction in rats, and suggest that the activity may be due to the inhibition of release of such mediators as histamine from the mast cells. Additionally, we further studied the presence of cross tachyphylaxis between quinotolast and DSCG to examine the mode of action of quinotolast, and found that quinotolast clearly exhibited cross tachyphylaxis with DSCG. The results support the concept that quinotolast, as well as DSCG, inhibits the type I reaction by the inhibition of mediator release and that these drugs, at least in part, share the same mechanism of action.

In animal experiments, DSCG is known to be ineffective in guinea pigs and mice (18-20). In this study, DSCG had no effect on PCA in guinea pigs, anaphylactic histamine release from guinea pig lung fragments or anaphylactic release of pLTs from guinea pig lung fragments and mouse cultured mast cells. It is well-known that mast cells are heterogeneous among tissues and species with respect to histochemical and functional properties and drug responsibility (21-24), and DSCG is ineffective on mucosal type mast cells, even in rats (19, 22-24). This may be one reason why DSCG could not show any inhibitory effect in guinea pigs and mice. Furthermore, several additional pharmacological actions of DSCG, in which mast cells are not necessarily involved, have been proposed (25-27), but many of the details remain to be clarified. On the contrary, quinotolast inhibited the type I allergic reaction in guinea pigs, and it also inhibited the release of histamine and pLTs from guinea pig lung fragments and cultured mouse mast cells. The inhibitory effect of quinotolast on the release of pLTs was greater than its inhibitory effect on the release of histamine in guinea pigs. Since pLTs, a series of newly-generated mediators, are present in the mast cells and other inflammatory cells such as eosinophils and macrophages, it is still not clear which cells quinotolast acts on to inhibit the release of pLTs. Further studies are needed to clarify the mechanism. Our findings, however, suggest that quinotolast has effects on the type I allergic reaction in guinea pigs, which could be attributed to its inhibition of release of histamine and pLTs from inflammatory cells.

Recently, a pLTs antagonist, ONO-1078, was reported to be useful for treating adult bronchial asthma (28). Although the fact that quinotolast acts also in guinea pigs does not necessarily give a clear clinical correlation, it is possible that quinotolast, which has an inhibitory effect on pLTs release, is a drug with a wide spectrum of anti-allergic action.

Quinotolast also showed a significant, though slight inhibition of a type III allergic reaction, Arthus type paw edema, in rats. The mechanism for this inhibition is not clear, but the inhibition of release of chemical mediators such as histamine and pLTs from inflammatory cells may be relevant (29).

The type II allergic reaction, which was thought to derive from the complement system (15), was not inhibited by the drugs tested. From the results, quinotolast appears to have no effect on this system.

In this study, quinotolast was shown to have inhibitory
effects on the type I reaction not only in rats but in guinea pigs and mice as well, and it was much more active in this respect than DSCG and the other reference drugs. Furthermore, quinotolast by both the p.o. and i.v. routes showed these effects, although DSCG elicited these effects only when given i.v. In summary, our findings indicate that quinotolast will be beneficial in clinical use.

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