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Studies In The Guinea-pig With ICI 185,282: A Thromboxane A_2 Receptor Antagonist

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Abstract—The effects of ICI 185,282 (5(Z)-7-([2,4,5-cis]-4-*O*-hydroxyphenyl-2-trifluoromethyl-1,3-dioxan-5-yl)heptenoic acid) have been studied on guinea-pig platelets and pulmonary smooth muscle in-vitro and in-vivo. When tested on guinea-pig lung parenchyma in-vitro, ICI 185,282 (1×10^{-7} M) produced a significant shift in U-46619 response curves (concentration ratio of 13·3); the antagonist (1×10^{-5} M) did not modify histamine responses. When tested on guinea-pig trachea in-vitro ICI 185,282 (1×10^{-7} M) caused significant inhibition of U-46619 and PGD_2 responses (concentration ratios of 8·3 and 14·1, respectively); the antagonist (1×10^{-5} M) proved less effective against contractions of $PGF_{2\alpha}$, LTD_4 and histamine (concentration ratios of 7·0, 1·5 and 1·6). When added to guinea-pig platelet rich plasma in-vitro, ICI 185,282 ($\times 10^{-6}$, 1×10^{-5} M) caused concentration-dependent parallel shifts to the right of U-46619 aggregation curves, yielding concentration ratios of 13·6 and 141·9, respectively. In-vitro, addition of ICI 185, 282 ($\times 10^{-5}$M) to indomethacin-treated pulmonary smooth muscle did not modify resting tone, neither did it induce aggregation or swelling in platelet-rich plasma preparations. When administered orally to guinea-pigs ICI 185,282 (0·1, 0·5 mg kg^{-1}) caused a significant inhibition of U-46619-induced platelet aggregation ex-vivo which persisted ≥ 8 h. In-vivo, a single oral dose of ICI 185,282 (1 mg kg^{-1}) inhibited bronchospasm induced by U-46619, PGD_2, $PGF_{2\alpha}$, arachidonic acid, LTD_4 and PAF; responses to histamine were unaffected. When dosed intravenously to lightly anaesthetized spontaneously breathing guinea-pigs ICI 185,282 (25 mg kg^{-1}) failed to modify C_{dyn} and R_{aw}. We conclude that ICI 185,282 is a potent, selective, orally active antagonist, which expresses activity at platelet and pulmonary TXA_2 receptors.

Despite intensive research the role of cyclo-oxygenase products of arachidonic acid metabolism in human bronchial asthma remains contentious. Animal experimentation has revealed that eicosanoids stimulate mucous secretion (Marom et al 1981), modify tracheal neurotransmitter release (Shore et al 1987), modulate bronchial tone (Hyman et al 1978) and induce pulmonary oedema formation (Carpenter & Roth 1987) and airway hyperresponsiveness (Fuller et al 1986). Prostanoids are known to occur in abundance in the human lower respiratory tract (Ozaki et al 1987), and asthmatic subjects are hypersensitive to inhaled cyclo-oxygenase products (Mathe et al 1973). Furthermore, analysis of bronchoalvolar lavage fluid obtained from human asthmatics during acute antigen challenge reveals a significant increase in constrictor prostanoid release (Murray et al 1986). Such findings support the premise that intervention with a thromboxane A_2 (TXA_2) receptor antagonist may prove beneficial in human bronchial asthma.

We have previously described the pharmacological properties of a novel series of 1,3-dioxane TXA_2 receptor antagonists typified by ICI 159,995 (Jessup et al 1985), ICI 180080 (Jessup et al 1986) and ICI 185,282 (Byland et al 1987; Jessup et al 1987). We now describe the activity of ICI 185,282 (5(Z)-7-([2,4,5-cis]-4-*O*-hydroxyphenyl-2-trifluoromethyl-1,3-dioxan-5-yl)heptenoic acid) in models of lung function in the guinea-pig.

Materials and Methods

Smooth muscle

Male Dunkin Hartley guinea-pigs (250–350 g) were killed by cervical dislocation and the lungs and trachea removed. Strips of lung parenchyma (25 × 3 × 3 mm approx.) were immersed in oxygenated (95% O_2, 5% CO_2) Krebs Henseleit solution containing indomethacin (10^{-5} M), maintained at 37°C and subjected to a resting tension of 0·5 g. Chains consisting of 5 rings of trachea were similarly treated. Agonist concentration—response curves were obtained using a cumulative dose schedule. Antagonist potency was calculated by determining the agonist EC50 in the absence, and 60 min after addition of antagonist to the bathing Krebs-Henseleit solution and expressed as concentration ratios. The EC50 was defined as the concentration of agonist producing 50% of the maximum control response. Responses were recorded isotonically throughout.

Guinea-pig platelets

Fasted, conscious, male Dunkin Hartley guinea-pigs (250–350 g) were orally dosed with either vehicle or ICI 185,282. Animals were subsequently anaesthetized (anaethetic ether) and bled from the abdominal aorta. Blood was collected into 3·8% (w/v) trisodium citrate (1 part to 9 parts whole blood), centrifuged at 200 *g* for 10 min, and platelet-rich plasma harvested. Agonist induced aggregation, measured in terms of extent using a Payton aggregometer, was expressed as a percentage of the maximum control response.

Konzett Rossler method

Fasted, male Dunkin Hartley guinea-pigs (250–350 g) were anaesthetized with pentobarbitone (60 mg.kg^{-1} i.p.). A jugular vein was cannulated to permit administration of anaesthetic (pentobarbitone, 6 mg mL^{-1}) and agonists. A tracheal cannula was inserted to allow measurement of air overflow according to the method of Konzett & Rossler

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(1940). Maximum bronchoconstriction in this model was determined by clamping off all airflow to the animal; agonist-induced bronchospasm was expressed as a percentage of this theoretical maximum.

When bronchospasm was induced with U-46619, an agonist dose-response curve was obtained in each animal before, and at 30 min intervals after, oral administration of ICI 185,282 or vehicle. To investigate the effects of ICI 185,282 on changes in pulmonary function induced by intravenous administration of arachidonic acid, leukotriene D_4 (LTD_4), platelet activating factor (PAF), prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), PGD_2 and histamine, guinea-pigs were surgically prepared as above, and dosed orally with antagonist or vehicle. After an interval of 60 min a cumulative agonist dose-response curve was obtained in each animal.

Spontaneously breathing guinea-pig

Fasted, male Dunkin Hartley guinea pigs (250–350g) were anaesthetized with alphaxalone (5 mg.kg^{-1} i.v., ear vein), the jugular vein was cannulated and anaesthesia was maintained by infusion. The trachea was cannulated and airflow measured by a pneumotachograph and differential pressure transducer. A cannula was inserted into the pleural cavity to permit measurement of pleural pressure. Airway resistance (R_{aw}) and dynamic compliance (C_{dyn}) were monitored on a breath basis (Amdur & Mead 1958).

The following drugs and chemicals were used: histamine diphosphate, prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), prostaglandin D_2 (PGD_2), arachidonic acid, indomethacin, L-α-phosphatidylcholine, β-acetyl-γ-*O*-alkyl (PAF) (Sigma Chemical Co.). U-46619 ((15S)-hydroxy-11α-,9α-(epoxymethano)-prosta-5Z,13E-dienoic acid, Upjohn Co.). Leukotriene D_4 was a gift from P.Bernstein (ICI Americas, Wilmington).

All except the following compounds were prepared as stock solutions in saline or distilled water. ICI 185,282 (Brewster et al 1986) was dissolved in dimethyl sulphoxide or either 10 or 100 mM Na_2CO_3 and subsequently neutralised to pH 7–8 with HCl. Arachidonic acid was dissolved in an appropriate volume of 100 mM Na_2CO_3. Dilutions of PGD_2 and LTD_4 were prepared fresh daily from an ethanolic stock solution stored at −80°C. Further dilutions of the above, made using saline or Krebs-Henseleit solution, were stored on ice as appropriate.

Statistical analysis was performed on a log dose ratio values using Student's *t*-test; comparisons were made between treated and vehicle dosed groups.

Results

Smooth muscle

When added cumulatively to the lung parenchyma preparations in-vitro both the stable endoperoxide analogue U-46619 ($3\times10^{-9}-3\times10^{-6}$ M) and histamine ($8\times10^{-8}-5\times10^{-5}$ M) caused reproducible, concentration-dependent contractions with EC50) values (mean ± s.e.) of $1{\cdot}3\pm0{\cdot}6\times10^{-7}$ M, n = 6 and $3{\cdot}2\pm0{\cdot}6\times10^{-6}$ M, n = 4, respectively. ICI 185,282 ($1\times10^{-7}-1\times10^{-5}$ M), when added as a bolus to tissue baths containing lung parenchyma preparations did not itself alter resting tone. However, these antagonist additions did cause a significant shift to the right of subsequent U-46619, but not histamine, response curves (Fig. 1).

ICI 185,282 was tested as an antagonist of the contractions of tracheal chain preparations induced by U-46619, histamine, LTD_4 $PGF_{2\alpha}$ and PGD_2. The relative potencies of the agonists were $LTD_4 > U\text{-}46619 = PGF_{2\alpha} >$ histamine $> PGD_2$. Addition of ICI 185,282 ($1\times10^{-7}-1\times10^{-5}$ M) to the preparations did not modify resting tone, but did cause inhibition of U-46619, PGD_2 and $PGF_{2\alpha}$ responses; contractions induced by LTD_4 and histamine were unaffected (Table 1).

Guinea-pig platelets

When added to guinea-pig citrated platelet-rich plasma in-vitro, U-46619 ($1{\cdot}14\times10^{-7}-5\times10^{-7}$ M) caused reproducible, concentration-dependent platelet aggregation. ICI 185,282 (1×10^{-6}, 1×10^{-5} M), when added to the platelets did not initiate either platelet swelling or aggregation, but did cause concentration-dependent parallel shifts to the right of subsequent U-46619 aggregation curves, yielding concentration ratios (mean ± s.e., n = 4) of $13{\cdot}6\pm1{\cdot}0$ and $141{\cdot}9\pm22$, respectively.

When dosed orally to groups (n = 6) of conscious, fasted male Dunkin Hartley guinea-pigs, ICI 185, 282 (0·1 and 0·5 mg kg^{-1}) caused dose-dependent inhibition of U-46619-induced platelet aggregation ex-vivo (Fig. 2). Significant ($P<0{\cdot}005$) platelet thromboxane A_2 receptor antagonist activity was evident 1 h after dosing and persisted for 8 h.

Pulmonary models

Cumulative intravenous doses of ICI 185,282 (0·156-40 mg kg^{-1}, n = 8), when administered to spontaneously breathing,

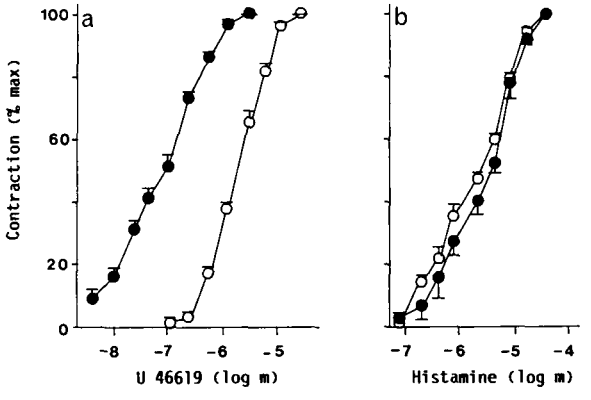

FIG. 1. In-vitro response (mean ± s.e., n = 4) of guinea-pig lung parenchyma to a) U-46619 in the absence (—●—) and presence of ICI 185,282 (1×10^{-7} M, —○-) and b) histamine in the absence (—●—) and presence of ICI 185,282 (1×10^{-5} M, —○—).

Table 1. In-vitro antagonist activity of ICI 185,282 on guinea-pig trachea

Agonist	EC50(M)	Conc of ICI 185,282 (M)	Conc ratio (mean ± s.e. n ≥ 4)
U-46619	$6{\cdot}1\pm0{\cdot}6\times10^{-7}$	1×10^{-7}	$8{\cdot}3\pm1{\cdot}9$
PGD_2	$1{\cdot}5\pm0{\cdot}1\times10^{-5}$	1×10^{-7}	$14{\cdot}1\pm1{\cdot}1$
$PGF_{2\alpha}$	$6{\cdot}1\pm0{\cdot}5\times10^{-7}$	1×10^{-5}	$7{\cdot}0\pm1{\cdot}5$
LTD_4	$1{\cdot}6\pm0{\cdot}1\times10^{-9}$	1×10^{-5}	$1{\cdot}5\pm0{\cdot}3$
Histamine	$8{\cdot}7\pm0{\cdot}1\times10^{-7}$	1×10^{-5}	$1{\cdot}6\pm0{\cdot}4$

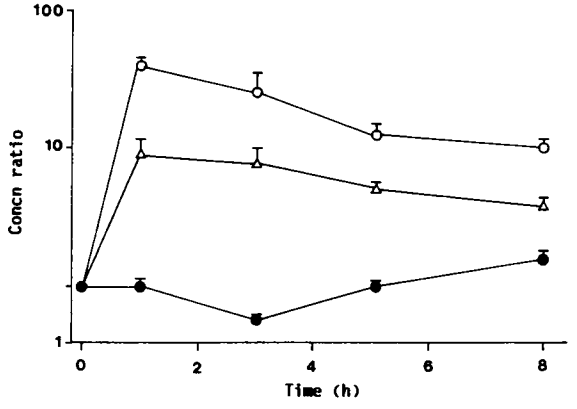

FIG. 2. Effect of orally dosed ICI 185,282: 0·5 mg kg^{-1} (—○—, n=6); 0·1 mg kg^{-1} (—△—, n=6) and vehicle (—●—, n=6) on U-46619 induced platelet aggregation ex vivo in the guinea-pig.

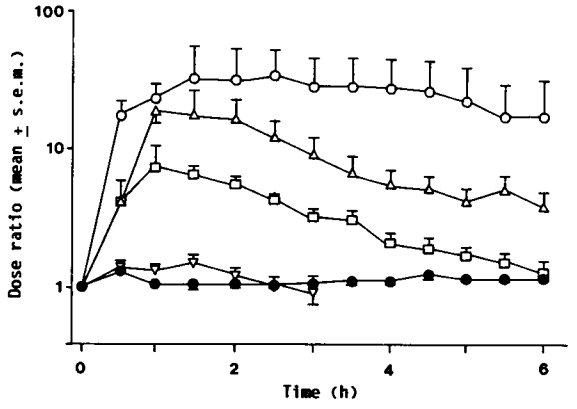

FIG. 3. U-46619 induced bronchospasm in the guinea-pig following oral administration of ICI 185,282, 0·1 mg kg^{-1} (—○—, n=9), 0·05 mg kg^{-1} (—△—, n=6), 0·025 mg kg^{-1} (—□—, n=6), 0·01 mg kg^{-1} (—▽—, n=6) and vehicle (—●—, n=6).

lightly anaesthetized guinea-pigs, did not significantly modify resting values of C_{dyn} or R_{aw} (Table 2). Furthermore, (25 mg kg^{-1}, n=6) failed to modify resting respiratory function in this model over 10 min when dosed intravenously as a single bolus injection.

When administered at 30 min intervals, cumulative intravenous doses of U-46619 (0·1–4 μg kg^{-1}) caused reproducible bronchoconstriction in anaesthetized guinea-pigs when measured by the method of Konzett & Rossler (1940). When administered orally, ICI 185,282 (0·01–0·1 mg kg^{-1}) caused dose-dependent parallel shifts to the right of subsequent U-46619 response curves with maximum inhibition generally occurring within 60–90 min (Fig. 3). Results obtained with a larger oral dose of the antagonist (1 mg kg^{-1}) indicated a more rapid onset of activity with a peak dose ratio (mean ± s.e., n=5) of 292 ± 122 occurring within 30 min.

Cumulative intravenous doses of arachidonic acid (0·01–2 mg kg^{-1}), PGD_2 (0·001–0·25 mg kg^{-1}), $PGF_{2\alpha}$ (0·008–2 mg kg^{-1}), LTD_4 (0·03–0·5 μg kg^{-1}) and histamine (0·001–0·128 mg kg^{-1}), when administered to anaesthetized guinea-pigs, caused dose-related bronchospasm. Pretreatment with a single oral dose of ICI 185,282 (1 mg kg^{-1}) effectively inhibited subsequent arachidonic acid, PGD_2, $PGF_{2\alpha}$, and LTD_4, but not histamine responses (Fig. 4 a,b,c,d,e).

PAF (0·0001 mg kg^{-1}), when dosed intravenously to anaesthetized guinea-pigs caused profound bronchospasm measured by the method of Konzett & Rossler (1940), which persisted for at least 16 min. Pretreatment of animals with a single oral dose of ICI 185,282 (1 mg kg^{-1}) significantly inhibited subsequent PAF-induced pulmonary responses (Fig. 5).

Table 2. Effect of ICI 185,282 on resting pulmonary function in the guinea-pig.

Cumulative dose of ICI 185,282 (mg kg^{-1}, i.v., n=8)	ΔR_{aw} % (mean ± s.e.)	ΔC_{dyn} % (mean ± s.e.)
0·156	0·6 ± 0·6	−0·8 ± 0·8
0·313	0·4 ± 0·4	0·1 ± 2·2
0·625	−1·2 ± 0·8	1·9 ± 3·0
1·25	−1·8 ± 1·4	2·9 ± 3·1
2·5	−2·6 ± 2·1	3·4 ± 2·9
5	−2·1 ± 2·1	2·3 ± 2·8
10	−1·4 ± 1·4	4·1 ± 5·1
20	−1·8 ± 1·4	6·1 ± 5·3
40	−1·6 ± 3·3	7·2 ± 3·5

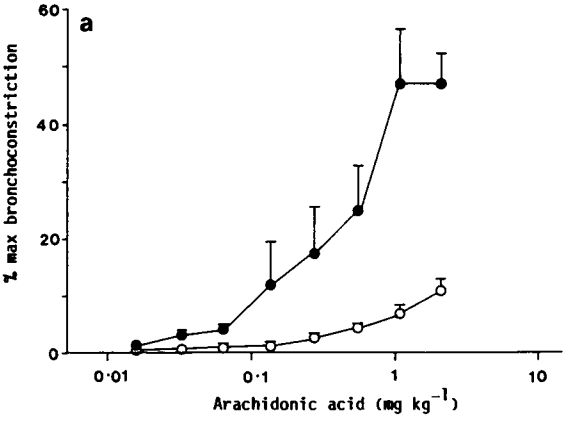

FIG. 4a. Arachidonic acid-induced bronchospasm in the guinea-pig 1 h after oral administration of ICI 185,282, 1 mg kg^{-1} (—○—, n=6) and vehicle (—●—, n=6).

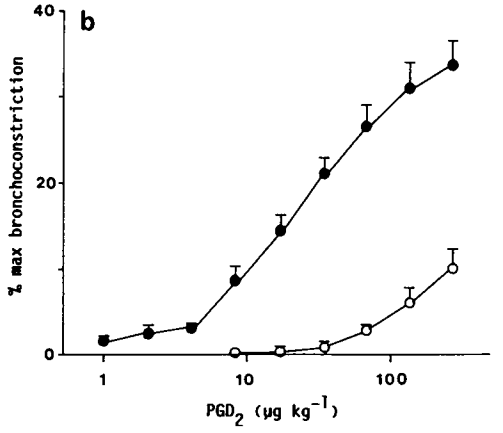

FIG. 4b. PGD_2-induced bronchospasm in the guinea-pig 1 h after oral dosing with ICI 185,282, 1 mg kg^{-1} (—○—, n=6) and vehicle (—●—, n=6).

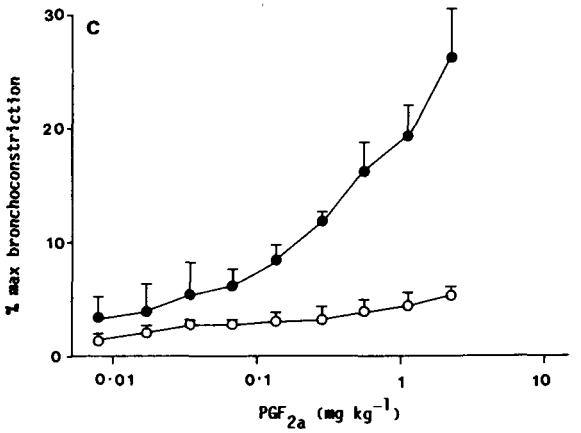

FIG. 4c. $PGF_{2\alpha}$-induced bronchospasm in the guinea-pig 1 h after oral dosing with ICI 185,282, 1 mg kg^{-1} (—○—, n = 6) and vehicle (—●—, n = 6).

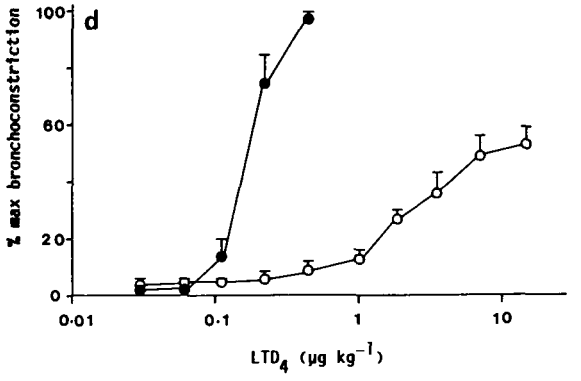

FIG. 4d. LTD_4 induced-bronchospasm in the guinea-pig 1 h after oral dosing with ICI 185,282, 1 mg kg^{-1} (—○—, n = 5) and vehicle (—●—, n = 5).

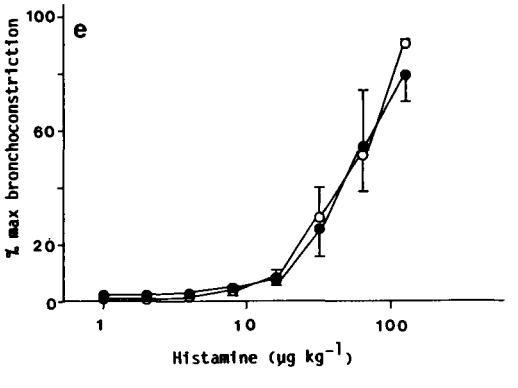

FIG. 4e. Histamine induced-bronchospasm in the guinea-pig 1 h after oral dosing with ICI 185,282, 1 mg kg^{-1} (—○—, n = 5) and vehicle (—●—, n = 5).

Discussion

This study confirms our previous observations that ICI 185,282 is a potent selective antagonist (Byland et al 1987; Jessup et al 1987), and demonstrates that the compound expresses its activity, both in-vitro and in-vivo, at guinea-pig platelet and pulmonary TXA_2 receptors.

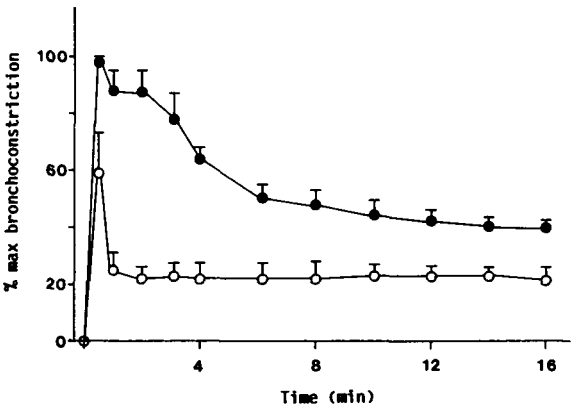

FIG. 5. PAF-induced bronchospasm in the guinea-pig 1 h after oral dosing with ICI 185,282, 1 mg kg^{-1} (—○—, n = 5) and vehicle (—●—, n = 5). Significant inhibition ($P < 0.05$) of the response was seen at all time points.

In-vitro ICI 185,282 effectively blocked contractions of guinea-pig trachea induced by U-46619, PGD_2 and $PGF_{2\alpha}$; the drug did not affect histamine or LTD_4 responses. Similar in-vitro selectivity was observed on guinea-pig lung parenchyma preparations where contractions to U-46619, but not histamine, were inhibited by the antagonist. ICI 185,282 was also a potent antagonist at guinea-pig platelet TXA_2 receptors in-vitro.

The potent, selective $T \times A_2$ antagonist activity exhibited in-vitro by ICI 185,282 was also evident following oral administration of the drug to guinea-pigs. The spectrum of activity of ICI 185,282 in-vivo was such that changes in pulmonary function induced by the intravenous injection of U-46619, $PGF_{2\alpha}$ and, PGD_2, agonists known to activate TXA_2 receptors (Ogletree et al 1985), and LTD_4, arachidonic acid and PAF, but not histamine, were effectively blocked by the antagonist. The results indicate that ICI 185,282 is rapidly and efficiently absorbed from the gastrointestinal tract of the guinea-pig and has a prolonged duration of action in this species.

Intravenous administration of arachidonic acid (Barrett et al 1986), LTD_4 (Hamel et al 1982) and PAF (Vargaftig et al 1982) to guinea-pigs is associated with cyclo-oxygenase product release and attendent bronchospasm. The degree of inhibition of LTD_4 and PAF induced changes in pulmonary function seen following pretreatment of animals with ICI 185, 282 suggests, that in the guinea-pig, a major proportion of the bronchospasm is a function of cyclo-oxygenase product release. The role of cyclo-oxygenase products as mediators of LTD_4 and PAF induced bronchospasm is not confined to this species of pig; a similar situation exists in the pulmonary system of cats (Graybar et al 1986) and dogs (Chung et al 1986).

In allergic asthmatic subjects inhalation of PGD_2 results in bronchospasm, a component of which is cholinergically mediated and probably reflects stimulation of nonmyelinated C-fibre nerve endings and myelinated rapidly adapting irritant receptors (Beasley et al 1987). In addition, inhalation of this prostanoid by asthmatics leads to the onset of bronchial hypersensitivity (Fuller et al 1986), whereas $PGF_{2\alpha}$ stimulates human mucoid sputum production (Lopez-Vid-

riero et al 1977). A significant stimulation of prostanoid release into the airways has been documented in chronic stable asthmatics following antigen provocative challenge with Dermatophagoides pteronyssinus (Murray et al 1986). Furthermore, studies using the technique of bronchoalveolar lavage have revealed that in man, the epithelial surface of the lower respiratory tract represents a specialized compartment with high local levels of cyclo-oxygenase products evident (Ozaki et al 1987). Prostaglandins and TXA_2 are further implicated in the control of human pulmonary function by the observations that non-steroidal anti-inflammatory drugs are known to inhibit the late asthmatic response to house dust mite (Fairfax 1982), and TXA_2 synthase inibition modifies bronchial responsiveness to inhaled acetylcholine in asthmatic subjects (Fujimura et al 1986).

ICI 185,282 is a potent, selective, orally active antagonist whose activity is expressed at platelet and pulmonary TXA_2 receptors in the guinea-pig. A compound with a profile of activity similar to that exhibited by ICI 185,282 should prove a useful tool for evaluating the role of arachidonate metabolites in human bronchial asthma.

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