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The effects of an oral thromboxane TP receptor antagonist BAY u 3405, on prostaglandin D_2- and histamine-induced bronchoconstriction in asthma, and relationship to plasma drug concentrations

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1 The potent bronchoconstrictors prostaglandin (PG) D_2, PG $F_{2\alpha}$ and thromboxane A_2 are thought to have a role in the pathogenesis of asthma, mediated via the thromboxane (TP) receptor.
2 BAY u 3405 is a new potent selective competitive TP receptor antagonist.
3 The effect of single oral doses of 20 mg and 50 mg BAY u 3405 was examined against histamine and PG D_2 bronchial provocation at 90 min after drug ingestion and, for the 20 mg dose alone, at 60 min after ingestion, in randomised, double-blind placebo controlled crossover studies. A time course study was performed with the 20 mg dose.
4 BAY u 3405 protected against PG D_2 bronchial provocation. The 20 mg dose increased the amount of PG D_2 required to produce a fall of 20% in the forced expiratory volume in 1 s by 6-fold and 16-fold at 60 min and 90 min after ingestion respectively, and the 50 mg dose by 14-fold at 90 min after ingestion.
5 The specificity of the drug was confirmed *in vivo* in that there was no significant protection against histamine bronchial provocation at either dose or at either time point.
5 The time course study showed significant protection against PG D_2 bronchial provocation at 1 h and at 3 h after a single 20 mg oral dose.
7 There was no correlation between subjects in plasma BAY u 3405 concentration and drug effect. Within the subjects performing the time course study there was a strong correlation in time between drug effect and plasma BAY u 3405 concentration.
8 BAY u 3405 may be useful in preventing prostanoid mediated bronchoconstriction in clinical asthma.

Keywords thromboxane receptor antagonist prostaglandin D_2 histamine bronchial provocation asthma

Introduction

The potent bronchoconstrictors prostaglandin (PG) D_2, its principal metabolite 9α,11β-PG F_2, PG $F_{2\alpha}$ and thromboxane (TX) A_2 have been suggested as effector mediators in the pathogenesis of asthma. Prostaglandin $F_{2\alpha}$ was one of the first prostanoids to demonstrate a constrictor response in the airways probably by both direct and reflex actions (Beasley *et al.*, 1987). Prostaglandin D_2 is the predominant prostanoid released from human pulmonary mast cells on immunological challenge (Lewis *et al.*, 1982), and along with its major metabolite 9α,11β-PG F_2 produces bronchoconstriction when inhaled by asthmatic subjects at a potency approximately 30 times greater than histamine on a molar basis (Hardy *et al.*, 1984). Inhaled PG D_2

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also potentiates airway responsiveness to both inhaled histamine and methacholine (Fuller *et al.*, 1986), but this effect is not observed with higher doses (Hardy *et al.*, 1986). Prostaglandin D_2 may also have other pro-inflammatory actions, for example, eosinophil accumulation in trachea of dogs has been shown to be increased by aerosolised PG D_2 (Emery *et al.*, 1989).

In addition to PG D_2 whose effects are mostly observed in relation to the allergen-induced early asthmatic response (EAR), there is indirect evidence to incriminate cyclo-oxygenase products in broncho-constriction observed during the late asthmatic response (LAR) (Fairfax *et al.*, 1983; Shephard *et al.*, 1985). Similar indirect evidence suggests that this mediator class also contributes to airway narrowing provoked by inhaled hypertonic saline (Finnerty *et al.*, 1990), isocapnic hyperventilation (Finnerty *et al.*, 1992) and exercise-induced asthma (Finnerty & Holgate, 1990). PG D_2, 9α,11β-PG F_2 and TX are all found in increased quantities in the airways of atopic asthmatic subjects following allergen challenge (Dworski *et al.*, 1988; Murray *et al.*, 1986; Wenzel *et al.*, 1989), and levels of both PG D_2, and 9α,11β-PG F_2 have been found to be increased in the airways of asymptomatic asthmatics when compared with both rhinitic and normal subjects (Liu *et al.*, 1990).

Prostanoids exert their contractile effects on airway smooth muscle by interacting with the thromboxane (TP) receptor (Coleman & Sheldrick, 1989; McKenniff *et al.*, 1988). Recently antagonists directed to this receptor such as GR 32191 and ICI 192,605 have shown partial inhibition of the EAR (Beasley *et al.*, 1989; Singh *et al.*, 1990), thereby confirming the potential contribution of this class of mediator to allergen-provoked bronchoconstriction in asthma. Thus there is sufficient basis for proposing a role for these prostanoids in the pathogenesis of asthma, and for possible future therapeutic manipulation in asthma and other allergic diseases.

BAY u 3405 (3(**R**)-[[(4-fluorophenyl) sulphonyl] amino]-1, 2, 3, 4-tetrahydro-9H-carbazole-9-propanoic acid) is a potent selective competitive TP receptor antagonist, which belongs to the group of cyclo-alkano-indolesulphonamides and is free of significant adverse effects. It inhibits the contractile responses of the TXA_2 mimetic U-46619, PG D_2 and 9α,11β-PG F_2 in guinea-pig (McKenniff *et al.*, 1991), and of U46619, PG D_2 and PG $F_{2\alpha}$ in human and ferret (McKenniff *et al.*, 1991; Norel *et al.*, 1991), airway smooth muscle preparations *in vitro*, with pA_2 values of between 8.0 and 8.9. This potency is of a similar magnitude to two other reported TP receptor antagonists GR 32191 and AA-2414, which both inhibit U46619 contractile responses in guinea pig trachea with pA_2 values of 7.7 (Fujimura *et al.*, 1991). When given orally, i.v. or by aerosol in guinea pigs, BAY u 3405 inhibits both U46619 and PG D_2 induced bronchoconstriction while having no effect on histamine, 5-hydroxytryptamine or leukotriene D_4 induced bronchoconstriction (Francis *et al.*, 1991).

This drug therefore offers the potential for further evaluating the role of contractile prostanoids in asthma. We have examined its ability to antagonise inhaled PG D_2- and histamine-induced bronchoconstriction in asthmatic subjects, the duration of any protective effect and its relationship with circulating drug concentrations.

Methods

This study was performed in two centres. Study 1 was carried out in Southamptom and examined the effect of a single 20 mg dose of BAY u 3405 PG D_2- and histamine-induced fall in forced expiratory volume in 1 s (FEV_1) 60 min after ingestion of the medication. In this study the duration of protection was also studied. Study 2 was conducted in Cape Town, South Africa and examined the effect of single 20 mg and 50 mg doses of BAY u 3405 on PG D_2- and histamine-induced bronchoconstriction 90 min after ingestion.

Subjects

Thirteen non-smoking male asthmatic subjects aged between 22–64 (mean age 38.8) years participated in Study 1, of whom six also participated in the time course study (Table 1). Eleven non-smoking asthmatic subjects (five female and six male) aged between 20–39 (mean age 26.5) years participated in the second study (Table 1). All subjects had a baseline FEV_1 of >65% of predicted, and a provocative concentration of histamine causing a 20% fall in FEV_1 (PC_{20} histamine) of <2 mg ml^{-1}. All were atopic as judged by a wheal >3 mm diameter on skin prick testing to one or more of *Dermatophagoides pteronnyssinus*, house dust, mixed grass pollens and cat and dog dander (Bencard, Brentford, UK). Their regular treatment consisted of either inhaled β_2-adrenoceptor agonists alone, or in combination with inhaled corticosteroids. Inhaled bronchodilators were withheld for at least 6 h prior to challenge, while inhaled corticosteroids were withheld for a minimum of 12 h. All subjects' asthma was stable for at least 4 weeks prior to entry. They were asked not to take any aspirin or non-steroidal anti-inflammatory drugs in the 2 weeks prior to or during the studies. Written informed consent was obtained from each subject and the protocol was approved by the Combined Southampton University and Hospitals Ethical Subcommittee (Study 1) and by the Ethical Committee of the Medical Faculty of the University of Stellenbosch (Study 2).

Bronchial provocation

Histamine (BDH Chemicals, Poole, Dorset, UK) was diluted in 0.9% sodium chloride (saline) from a stock solution of 64 mg ml^{-1} (stored at −20° C), to produce a range of doubling concentrations of 0.03–32 mg ml^{-1}. Prostaglandin D_2 (Salford Ultrafine Chemicals and Research Ltd, Manchester, UK) was stored at −20° C as a stock solution in methanol at a concentration of 25 mg ml^{-1}. The identity, purity and concentration of PG D_2 was confirmed by high performance liquid chromatography (h.p.l.c.). Solutions were prepared freshly immediately before use by dilution in saline to produce a range of doubling concentrations from 0.004–4 mg ml^{-1}.

Table 1 Characteristics of asthmatic subjects studied

Subject	*Age (years)*	*Sex*	*Baseline FEV_1 (l)*	*% predicted FEV_1 (%)*	*Baseline PC_{20} histamine (mg ml^{-1})*	*Treatment**
Study 1						
1°	38	M	3.7	100	0.15	V
2°	60	M	2.58	92	0.65	V, B
3°	64	M	2.2	90	0.2	V, B
4	57	M	2.6	81	0.25	V
5	44	M	2.7	66	0.9	V, B
6	37	M	2.73	67	0.4	V
7	31	M	3.99	91	0.3	V, B
8°	34	M	4.2	102	0.3	V
9°	27	M	3.42	86	0.6	V
10	31	M	3.0	77	0.2	V, B
11	28	M	3.95	101	0.45	V, B
12°	22	M	3.78	91	0.04	–
13	33	M	3.86	92	0.15	V
Mean ± s.e. mean	38.9 ± 3.7		3.3 ± 0.2	87.4 ± 3.3	†0.275	
Study 2						
1	20	F	2.42	77	0.18	V, B
2	21	F	2.05	73	0.09	V
3	32	F	2.35	83	0.16	V, B
4	30	F	3.05	109	0.13	V, B
5	39	F	2.2	100	0.24	V, B
6	27	F	1.1	65	1.38	V, B
7	24	M	2.25	74	1.04	V
8	23	M	3.2	102	0.6	V
9	30	M	3.02	96	0.98	V, B
10	25	M	3.67	97	0.18	V
11	31	M	2.15	68	0.38	V, B
Mean ± s.e. mean	27.4 ± 1.7		2.5 ± 0.2	85.5 ± 4.6	†0.327	

* V = inhaled β_2-adrenoceptor agonist; B = inhaled corticosteroids.
† Geometric mean.
° Took part in time course study.

The solutions were administered as aerosols generated from a starting volume of 2 ml in a disposable Inspiron Mini-nebulizer (CR Bard International, Sunderland, UK) driven by compressed air at a pressure of 20 psi triggered by a dosimeter with no delay and a delivery time of 1 s. Subjects were instructed to take five consecutive breaths from functional residual capacity to total lung capacity via a mouthpiece (Chai *et al.*, 1975). Baseline FEV_1 was recorded as the highest of three measurements. Subjects then inhaled 5 breaths of saline and FEV_1 was recorded as the higher of two measurements made after 1 and 3 min. Provided the FEV_1 did not fall by ≥10% from the baseline value, provocation with either PG D_2 or histamine was undertaken. Increasing doubling concentrations of agonist were inhaled at 5 min intervals and FEV_1 measured at 1 and 3 min after each inhalation. The challenge was terminated when the FEV_1 fell ≥20% of the higher of the two post-saline values. The percentage fall in FEV_1 from the post saline value was plotted against the concentration of agonist on a logarithmic scale and that concentration producing a 20% decrease (PC_{20}) derived by linear interpolation.

Study protocols

Study 1 The study was conducted in a placebo-controlled randomised double-blind crossover manner. Subjects attended the laboratory on four separate occasions, at least 1 week apart, to undertake bronchial provocation with increasing inhaled concentrations of histamine and PG D_2 on each of 2 visits, after pretreatment either with BAY u 3405 20 mg or matched placebo administered as a single tablet on an empty stomach. The challenges were performed at the same time of day for each subject, and the treatments were administered in random order for each set of provocation studies. Having fasted for 4 h, baseline recordings of FEV_1 were made, followed by further measurements at 5, 10, 15, 20, 25, 30, 40, 50 and 60 min thereafter. At 60 min 10 ml venous blood was withdrawn for assay of the plasma concentration of BAY u 3405. Bronchial provocation with either histamine or PG D_2 then proceeded as described above.

Six of the 13 subjects (1, 2, 3, 8, 9 and 12, Table 1) returned for two further visits to determine the time course of the protective effect of BAY u 3405. A

baseline FEV_1 was recorded, and if this was within 15% of that measured during the concentration-response studies, bronchial provocation with PG D_2 was undertaken. Once FEV_1 had fallen $\geq$20% of the post saline value, FEV_1 was allowed to recover to within 15% of the starting baseline and either BAY u 3405 20 mg or placebo administered in random order. Prostaglandin D_2 challenge was then undertaken to obtain a PC_{20} value at 1, 3, 5 and 7 h after drug dosing, with FEV_1 being allowed to return spontaneously to within 10% of the starting baseline after each PG D_2 challenge. At the same time points venous blood was also withdrawn for measurement of plasma BAY u 3405 concentration.

Study 2 This was conducted as a three period, randomised placebo controlled crossover study. Subjects attended for six visits, on three of which BAY u 3405 20 or 50 mg or placebo were administered in random order, followed 90 min later by PG D_2 provocation to obtain a PC_{20} value. On the remaining three visits subjects followed the same drug dosing protocol, but on these occasions they were challenged with increasing concentrations of inhaled histamine. Blood was taken for determination of the plasma drug concentrations at 0, 1.5, 2.5 and 24 h after administration.

BAY u 3405 assay

The plasma concentrations of BAY u 3405 were determined by RP-h.p.l.c. with u.v. detection set at 230 nm, giving a detection limit of 5 ng ml^{-1}. Imprecision was less than 2%, and inaccuracy less than 3% (Ritter, 1990). The assay was performed at Bayer AG, Institute of Clinical Pharmacology (Study 1) and at the Department of Pharmacology, University of Orange Free State, Bloemfontein, RSA (Study 2).

Statistical analysis

For the bronchial provocation studies, standard two-period crossover analyses were carried out according to Hills & Armitage, 1979. The PC_{20} values were logarithmically transformed and compared using Student's *t*-test for paired data and geometric means were calculated for each group. The baseline and post-drug FEV_1 recordings were compared using single factor analysis of variance. For each subject, and for each dose and time point studied, the efficacy of BAY u 3405 in inhibiting bronchial responsiveness to PG D_2 was described as a drug activity ratio, being the PC_{20} for the active treatment divided by the PC_{20} for the placebo treatment. The relationship between the drug activity ratio and plasma BAY u 3405 concentration was examined by Spearman's Rank Order Correlation. The null hypothesis was rejected at $P < 0.05$.

Results

In both studies histamine and PG D_2 caused dose related bronchoconstriction enabling PC_{20} values for each agonist to be derived. BAY u 3405 produced no detectable adverse reactions in any of the subjects.

Study 1

Twelve subjects completed both paired visits for each of the constrictor agonists, subject 13 failing to complete the PG D_2 visits, and subject 3 failing to complete the histamine visits, in both cases due to upper respiratory tract infections.

Repeatability of PG D_2 bronchial provocation Five subjects successfully completed both baseline PG D_2 challenges 2 weeks apart during the time course study. The geometric mean PC_{20} PG D_2 for this subgroup was 0.04 mg ml^{-1}. The coefficient of repeatability of PG D_2 bronchial provocation was 0.92 doubling dilutions (Bland & Altman, 1986).

PG D_2 bronchial provocation There was no significant difference in baseline FEV_1 between the treatment and placebo groups, nor was there any significant difference in either group between baseline FEV_1 and FEV_1 recordings at any time point up to 60 min after ingestion of BAY u 3405 20 mg.

Inhaled PG D_2 caused dose related bronchoconstriction in all subjects studied with a geometric mean PC_{20} value after drug placebo of 0.04 mg ml^{-1}. When compared with oral placebo, BAY u 3405 produced an increase in the PC_{20} PG D_2 in 11 of the 12 subjects (Figure 1). For the group as a whole the PC_{20} PG D_2 increased from a geometric mean value of 0.04 to 0.19 mg ml^{-1} ($P < 0.001$). The protection afforded by BAY u 3405 was highly variable ranging from a calculated drug activity ratio of 0.8 in subject 12 to 51.3 in subject 5, the geometric mean of the calculated drug activity ratios was 6.1.

Histamine bronchial provocation There was no significant difference in baseline FEV_1 between the treatment and placebo groups, nor was there any significant difference in either group between baseline FEV_1 and FEV_1 recordings at any time point up to 60 min after drug ingestion.

There was a suggestion of a period effect for log PC_{20} histamine ($P = 0.058$), therefore the treatment effect was calculated allowing for this. There was no significant difference between active and placebo groups in the log PC_{20} histamine, with the geometric means being 0.52 (range 0.13–11.0) and 0.28 (range 0.08–1.82) mg ml^{-1} respectively (P = NS).

Time course study Six subjects entered this phase of the study, completing PG D_2 challenge procedures for both active and placebo treatments at baseline and 3 h post treatment, while five subjects satisfactorily completed both challenge procedures at 1, 5 and 7 h post treatment. No significant differences were observed in baseline values of FEV_1, between groups, or between baseline and post treatment FEV_1 for either group.

There was significant protection afforded against the PG D_2 provoked fall in FEV_1 by the active drug at both the 1 and 3 h post dosing time points ($P < 0.03$, $n = 5$ and $P < 0.01$, $n = 6$ respectively), and a trend ($P = 0.08$, $n = 5$) towards protection at 5 h. However at 7 h post dosing there was no difference between the placebo or active treatment (Figure 2).

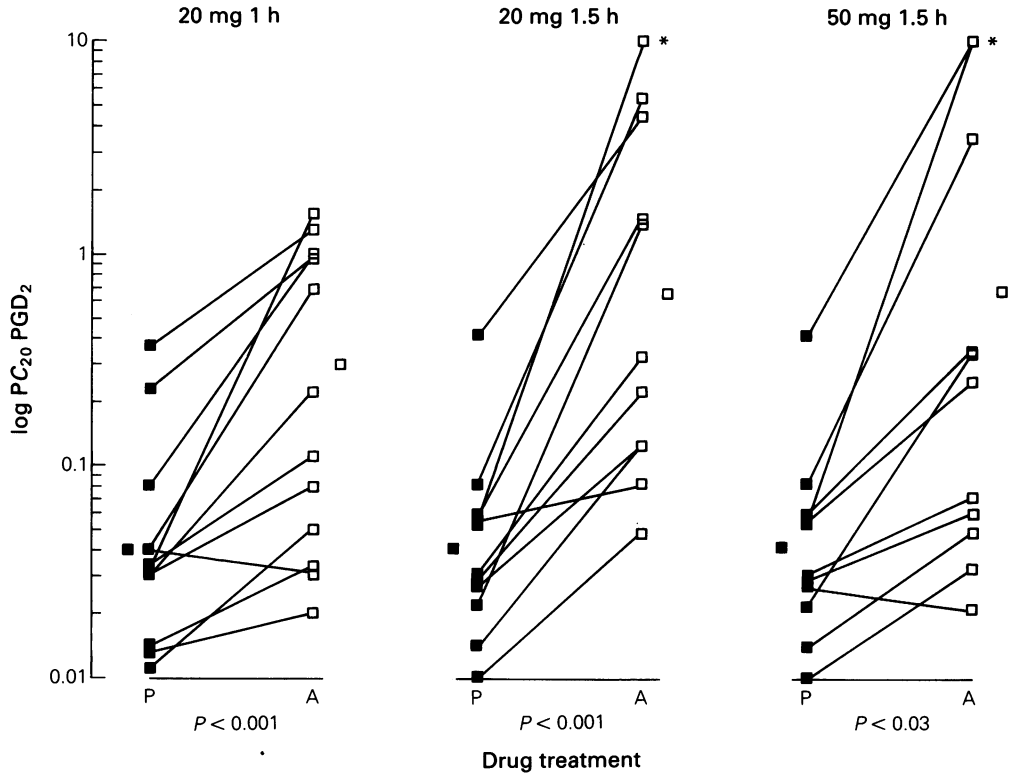

Figure 1 Individual plots on a logarithmic scale of the PC_{20} PG D_2 against BAY u 3405 (open squares, A) and placebo (closed squares, P) treatments for, from left to right, the 20 mg dose at 60 min, the 20 mg dose at 90 min, and the 50 mg dose at 90 min. Alongside are the corresponding squares to represent the geometric means. Statistical analysis was performed using Student's paired *t*-test on logarithmically transformed data. * Greater than 4 mg ml^{-1}.

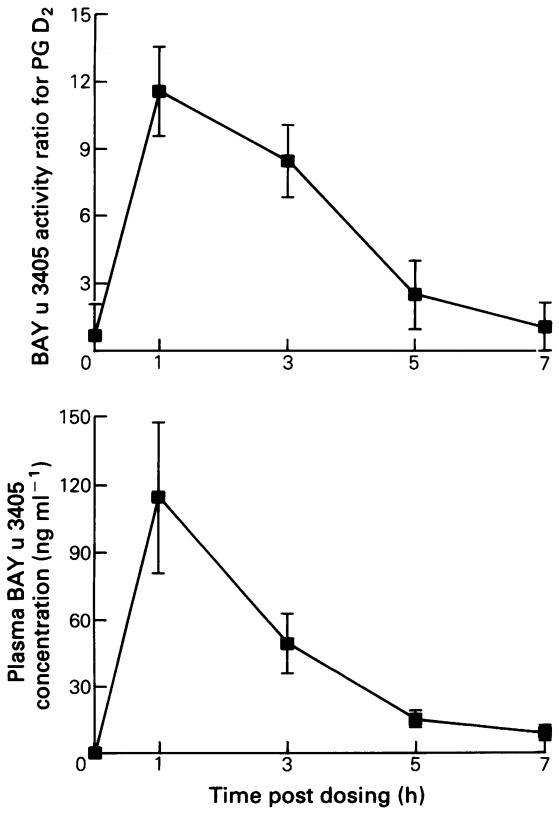

Figure 2 Graphs of the drug activity ratios for PG D_2 bronchial provocation (upper graph), and plasma BAY u 3405 concentrations (lower graph) plotted against time for the time course of action of BAY u 3405 study. Squares in the upper graph represent geometric means and bars the geometric standard error of the mean, while squares in the lower graph represent the mean and bars the standard error of the mean.

Study 2

Eleven subjects (Table 1) completed both paired visits for the bronchial provocation studies for each of the agonists.

PG D_2 bronchial provocation There was no significant difference in baseline FEV_1 between the two treatment and placebo groups, nor was there any significant difference for each group between baseline FEV_1 and FEV_1 recordings at any time point up to 90 mins after drug ingestion.

BAY u 3405 at both the 20 and 50 mg doses afforded significant protection against PG D_2 induced bronchoconstriction, with the PC_{20} PG D_2 increasing in all 11 subjects for the 20 mg dose, and 10 of the 11 subjects for the 50 mg dose (Figure 1). For the group as a whole the geometric mean PC_{20} PG D_2 increased from 0.04 mg ml^{-1} (placebo) to 0.59 mg ml^{-1} for 20 mg BAY u 3405 ($P < 0.001$) and 0.54 mg ml^{-1} for 50 mg BAY u 3405 ($P < 0.03$). The geometric means of the calculated drug activity ratios were 15.9 (range 1.5–628.3) for the 20 mg dose, and 13.7 (range 0.8–24897.5) for the 50 mg dose.

Histamine bronchial provocation There was no significant difference in baseline FEV_1 between the treatment and placebo groups, nor any significant difference in either group between baseline FEV_1 and FEV_1 recordings at any time point up to 60 min after drug ingestion. In contrast to the protection afforded against PG D_2, BAY u 3405 at the 20 mg and 50 mg doses failed to protect the airways against the constrictor effects of histamine, the geometric mean values

being 0.32 (range 0.24–22.5) mg ml^{-1} for the 20 mg dose, 0.35 (range 0.1–33.9) mg ml^{-1} for the 50 mg dose, and 0.15 (range 0.02–3.9) mg ml^{-1} for placebo (P = NS).

Plasma concentrations of BAY u 3405

BAY u 3405 was not detected in the plasma of any subject after placebo treatment. From the results pooled from both studies median BAY u 3405 levels at the time of PG D_2 bronchial provocation were 98.8 (range 20–399) ng ml^{-1} for the 20 mg dose and 223.8 (24.5–921.5) ng ml^{-1} for the 50 mg dose. No significant correlations could be established between the protection afforded by the drug against PG D_2-induced bronchoconstriction and plasma concentrations obtained after either the 20 or 50 mg dose. Plasma drug concentrations on the histamine challenge days were similar, with median plasma drug concentrations for the low and high dose being 70 (10–456) and 300 (86.9–543.6) ng ml^{-1} respectively. However in the time course study, a close correlation was found between the plasma concentrations of BAY u 3405 and the peak protection afforded against PG D_2 induced bronchoconstriction when expressed as drug activity ratios (r = 1, $P < 0.0001$ Spearman's Rank Order Correlation), (Figure 2).

Discussion

This study demonstrates that the TP receptor antagonist BAY u 3405, produces a 6-fold protection against PG D_2 induced bronchoconstriction at 60 min after ingestion (20 mg dose), while at 90 min after ingestion, protection was 16-fold for the 20 mg dose and 14-fold for the 50 mg dose. In the time course study the peak effect occurred between 1 and 3 h after the 20 mg dose, with a trend towards a significant effect still being detectable at 5 h. This study has clearly shown that BAY u 3405, while not being a bronchodilator, produced appreciable protection of asthmatic airways against the constrictor action of inhaled PG D_2 but not histamine. These *in vivo* observations in human asthma confirm *in vitro* and guinea pig studies indicating that this orally active drug is a potent TP receptor antagonist. Although peak protection coincided with peak plasma concentrations, the extent of protection failed to exhibit a dose-response relationship between the 20 and 50 mg doses. Prostaglandin D_2 is a potent bronchoconstrictor when inhaled by asthmatic patients. In the present study PC_{20} values for PG D_2 challenge on the placebo days range from 0.01 to 0.42 mg ml^{-1} (geometric mean 0.04 mg ml^{-1}), confirming that this agonist is approximately 10-fold more potent than histamine in molar terms. The ability to construct linear dose-response curves with inhaled PG D_2 enables the potency of a given dose of an antagonist to be assessed in terms of a shift of the curve to the right. In almost all the subjects BAY u 3405 produced a large displacement of the PG D_2 dose-response curve but did not increase baseline airway calibre. This protective effect could be due to specific receptor antagonism or functional antagonism. Since the drug has no significant effect on the airways response to histamine, clinically significant functional antagonism seems unlikely.

The specificity of the TP receptor blockade induced by BAY u 3405 has been shown *in vitro*, with no effect being observed on other prostanoid receptor subtypes such as DP, EP_1, EP_2, FP or IP. On isolated guinea pig, ferret or human airways the behaviour of BAY u 3405 suggests competitive antagonism against a number of prostanoid contractile agonists including PG D_2, its metabolite 9α,11β-PG F_2, PG $F_{2\alpha}$, the thromboxane mimetic U46619 and 16,16-dimethyl-PG E_2 (McKenniff *et al.*, 1991). No activity was detected against the effects of histamine or leukotriene (LT) D_4 (Francis *et al.*, 1991). The failure of this study to demonstrate any significant activity of BAY u 3405 against histamine induced bronchoconstriction *in vivo*, provides good evidence that the protective efficacy of this compound cannot be explained on the basis of functional antagonism. It is not possible to undertake a Schild analysis for competitive antagonism (under non-steady state conditions), however, taking into account the *in vitro* pharmacology of BAY u 3405, competitive antagonism seems the most plausible mechanism of action.

Both selective H_1 (Rafferty & Holgate, 1987) and LT D_4 (Gaddy *et al.*, 1990; Kips *et al.*, 1989) receptor antagonists have been shown to possess bronchodilator activity when administered to asthmatic subjects, suggesting that there is continuous basal secretion of both mediators in asthmatic airways that contributes to the control of baseline airway tone. While patients with asthma have elevated levels of PG D_2, PG $F_{2\alpha}$, and 9α,11β-PG F_2 in airway lavage fluid when compared with normal volunteers (Liu *et al.*, 1990), the lack of effect of BAY u 3405 on baseline FEV_1 during the 60 min after ingestion and prior to agonist challenge, even in those subjects with the lowest FEV_1 values, suggests that increased basal secretion of contractile prostanoids contributes little to baseline airway calibre, and confirms the observations with two other TP receptor antagonists, GR 32191 (Beasley *et al.*, 1989) and AA-2414 (Fujimura *et al.*, 1991).

BAY u 3405 is rapidly absorbed to reach peak plasma concentrations within 1 h of dosing. The fact that more than doubling the dose of oral drug had no additional effect in protecting the airways against PG D_2 may suggest that maximal effect was achieved with the 20 mg dose. Further dose-response studies will be necessary to investigate this aspect of drug performance.

In conclusion, this study has shown that a novel TP receptor antagonist BAY u 3405, specifically antagonised the constrictor actions of inhaled PG D_2 when administered orally to patients with asthma. The extent of protection afforded by this drug is at least as good as that reported for other TP_1 antagonists, and as such warrants further study in asthma as a potential therapeutic candidate.

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