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Anti-allergic properties of pirquinozol (SQ 13,847) an orally effective agent. Evaluation in an anti-IgE-induced pulmonary function model in rats

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It has been reported previously that pirquinozol (SQ 13,847) is an orally effective anti-allergic agent as demonstrated in animal model systems (Free et al 1979; Casey et al 1980). Further, pirquinozol is a prodrug which requires conversion to the oxidative metabolite, SQ 12,903, for maximum expression of activity both in-vivo and in-vitro. In-vitro, SQ 12,903 inhibits histamine release from rat mast cells in a manner similar to that observed for disodium cromoglycate (DSCG) and doxantrazole (Free & Hall 1980). Prophylactically administered pirquinozol inhibits immunologically-induced bronchospasm in rats passively sensitized with whole rat serum containing IgE anti-egg albumin, as measured by changes in both airway conductance and dynamic compliance (Casey et al 1980).

We have reported the development of a model of reversed active lung anaphylaxis induced in rats by intravenous challenge with an anti-serum prepared against rat IgE myeloma protein (Casey & Abboa-Offei 1979). The technical advantages of this system include the lack of a necessary presensitization of the test animals and the ease of anaphylactic challenge; these changes resulted in increased consistency of responsiveness of the subject animals. Pharmacologically, the major advantage was the ability to observe duration of drug action, similar to that reported in the clinic for disodium cromoglycate (Kolotkin et al 1974; Orr 1974).

The results reported here confirm and extend the originally reported inhibition of bronchoconstriction by pirquinozol in an alternative rat model. Furthermore, the duration of action and time to peak efficacy have been determined at various doses.

Materials and methods

Anti-IgE-induced bronchoconstriction. The procedure for the reversed active lung anaphylaxis in rats has been prevously described (Casey & Abboa-Offei 1979). Briefly, antiserum against the purified rat IgE myeloma protein was prepared by immunization of rabbits and was quantitated by its ability to inhibit the induction of a passive cutaneous anaphylactic (PCA) reaction in rat skin. The highest dilution of rabbit anti-rat IgE antiserum capable of completely inhibiting the PCA reaction was considered the end point. The anti-rat IgE antiserum used in this investigation completely inhibited the rat PCA reaction at a dilution of 1/800 and is, therefore, defined as containing 800 PCA inhibition units ml^{-1}. In the studies reported here, rats were challenged with 40 units of anti-IgE antiserum. When normal rabbit serum was substituted for anti-IgE antiserum, there was no effect on pulmonary function.

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Table 1. Inhibition of PEFR decrease in anti-IgE-induced bronchoconstriction in rate by pirquinozol and disodium cromoglycate (DSCG).

Dose* mg kg^{-1}	% Inhibition ± s.e.m. Pirquinozol† oral	Pirquinozol† i.p.	DSCG‡ i.p.
1	21 ± 8	ND§	ND
2	45 ± 8	33 ± 12	ND
4	58 ± 15	84 ± 10	ND
8	57 ± 16	72 ± 14	36 ± 11
16	37 ± 16	79 ± 9	48 ± 12
32	ND	ND	77 ± 10

* Animals dosed 10 min before challenge.
† n = 8, ‡ n = 5, § not done.

For assessment of pulmonary function changes, the input data of airway volume, air flow and thoracic cavity pressure were transmitted to an on-line digital computer for calculation of peak expiratory flow rate. At selected time intervals, five sequential breaths were analysed, and averaged. Animals were observed for a total of 30 min following challenge. In the results reported here, anti-IgE challenge effects and pharmacological modification were based upon peak expiratory flow rate (PEFR) changes. Basal PEFR was in the range of 7·25–12·06 cc s^{-1}.

Compounds and drugs. Pirquinozol was provided by Dr B. R. Vogt of the Squibb Institute for Medical Research, DSCG was kindly provided by Fisons, Ltd, Leicestershire, England. For oral administration, compounds were prepared in a 1% carboxymethyl cellulose medium, while for intraperitoneal administration, a saline solution buffered with 0·02 phosphate at pH 7·2 was used.

Results

In order to make a comparison between the activity of pirquinozol and DSCG, rats were dosed intraperitoneally 10 min before challenge with rabbit anti-IgE serum (Table 1). Premedication with either compound resulted in a similar level of efficacy; however, maximum effectiveness was observed at 4 mg kg^{-1} with pirquinozol while 32 mg kg^{-1} was necessary to achieve maximum effect with DSCG. The calculated ID50 for pirquinozol was 2·5 mg kg^{-1} while the ID50 for DSCG was approximately 17·0 mg kg^{-1}.

Oral administration of pirquinozol 10 min before challenge also resulted in a peak effect at a minimum dose of 4 mg kg^{-1} (Table 1) and the ID50 was estimated to be 2·3 mg kg^{-1}. However, the level of efficacy was somewhat lower than had been observed when animals were dosed intraperitoneally. Although not statistically significant, there was obviously less of a biological effect at 16 mg kg^{-1}, reflecting either insufficient predose time or auto-inhibition.

Since one of the advantages of this model is the ability to observe duration of action, time studies were performed at three dose levels of pirquinozol. Animals were orally dosed once with either 4, 16 or 64 mg kg^{-1} at various times before challenge, and pulmonary response was monitored. As can be seen in Fig. 1, there was a temporal relationship between dose and efficacy. There is a significantly greater duration of action at 16 mg kg^{-1} than at 4 mg kg^{-1}, with no further increase in duration at the 64 mg kg^{-1} dose. In contrast to the lowest dose examined, the peak efficacy of the two higher doses occurs following a 30 min rather than a 10 min premedication period. Further, the peak efficacy is similar to the maximum efficacy seen in the i.p. administration studies.

We also determined if either a longer duration of action or increased efficacy could be achieved by multiple dosing of the test animals. For these studies, three groups of five rats were dosed twice with

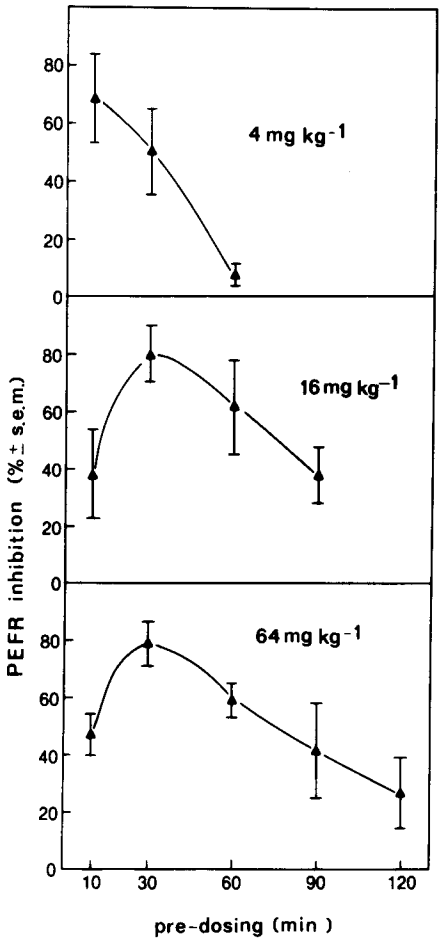

FIG. 1. Time duration study of orally administered pirquinozol at three different single doses of anti-IgE-induced bronchoconstriction in rats. Inhibition in reduction of PEFR. n = 5.

pirquinozol, 16 mg kg^{-1} orally 30 min apart and challenged 10, 30, or 60 min following the second dose. As can be seen in Fig. 2, the pattern of response was similar to that of the previous experiments (Fig. 1) in which rats received only a single dose of 16 mg kg^{-1}. The level of efficacy was somewhat less and there was no increase in duration of action.

Discussion

The model system of reversed active lung anaphylaxis in rats challenged with antibody against rat IgE (Casey & Abboa-Offei 1979) has been used to further profile the prophylactic activity of the new orally effective anti-allergic drug pirquinozol (SQ 13,847). In these studies, peak expiratory flow rate has been recorded as the singular, reproducible and sensitive pulmonary function parameter as opposed to airway conductance and dynamic compliance. In comparison with DSCG administered intraperitoneally, i.p. pirquinozol is more potent, yet of similar efficacy. Direct comparisons of activity by the oral route were not possible due to the well established lack of oral activity of DSCG in pulmonary function studies (Cox et al 1970).

Pirquinozol demonstrated remarkably similar potency following oral or intraperitoneal administration when animals were medicated 10 min before challenge; however the efficacy by the oral route was observed to be slightly less. The latter observation may be a function of the premedication timing. When higher doses were used, the optimum peak efficacy was found to be associated with the 30 min rather than the 10 min predosing (Fig. 1). Thus, what was initially considered to be possible autoinhibition was subsequently determined to be a reflection of a longer premedication time to peak activity at higher doses of pirquinozol.

The use of this model system has suggested that the duration of activity for pirquinozol is longer than would have been anticipated from the previous studies, particularly in the rat PCA reaction (Casey et al 1980). In fact, the extended duration of action appears to be similar to that previously reported for DSCG in the model (Casey & Abboa-Offei 1979) and reported for DSCG in clinical trials (Kolotkin et al 1974; Orr 1974).

The observation that multiple dosing did not increase the efficacy of the drug or extend the duration of prophylactic effect may reflect certain limitations of the model, primarily in terms of the maximum possible effect being no greater than that noted here for either pirquinozol or DSCG. That multiple dosing did not extend the duration of activity for pirquinozol may in part be an in-vivo correlate of the tachyphylaxis demonstrated for the compound in-vitro (Free & Hall 1980). Indeed, the level of efficacy after challenge 30 min following the second dose was less than that observed 30 min after a single premedication with 16 mg kg^{-1}. However, only one dose level and one time interval were examined and there is no available correlative data on the plasma concentrations of the active metabolite SQ 12,903. Therefore, with the addition of the latter information, it may be possible that a sustained duration of drug action is attainable with the proper dosing regimen.

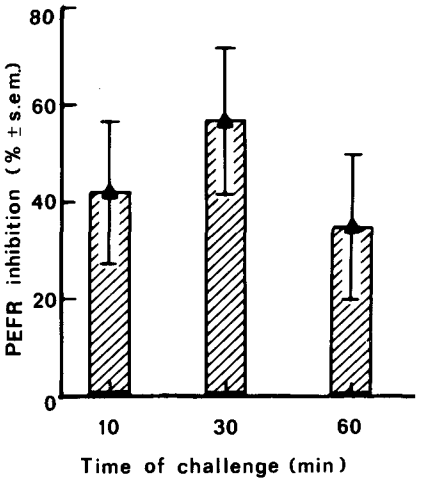

FIG. 2. Inhibition of reduction in PEFR in animals dosed orally twice, 30 min apart with pirquinozol (16 mg kg^{-1} oral) and challenged with anti-IgE after the second dose at the time intervals indicated. n = 5.

Thus pirquinozol is a potentially effective oral anti-allergic compound of similar pharmacological activity to DSCG and several other inhibitors of mediator release (Devlin 1980).

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