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Lack of effect of 4 weeks of oral H_1 antagonist on bronchial responsiveness

R.E. Ruffin, K.M. Latimer

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ABSTRACT: Ten patients with stable chronic asthma completed a randomized double-blind placebo controlled crossover study examining the effect of 120mg terfenadine twice daily for 4 weeks on bronchial responsiveness. Bronchial responsiveness was measured by methacholine inhalation tests performed by the tidal breathing technique at 0, 2 and 4 weeks of active and placebo treatment periods separated by a one week washout period. There were no significant differences in mean baseline forced expired volume in 1 sec (FEV_1) for placebo and terfenadine treatments ($p>0.05$) and there were no differences between geometric mean provocative concentrations of methacholine to cause a 20% fall in FEV_1 ($PC_{20}M$) at 2 and 4 weeks of terfenadine (0.89 and 0.99 $mg \cdot ml^{-1}$) from placebo (0.94 and 0.84 $mg \cdot ml^{-1}$) ($p>0.05$). Examination of individual $PC_{20}M$ values during terfenadine treatment showed that 5 patients had $PC_{20}M$'s outside their 95% confidence interval; 2 increased both 2 and 4 week values, 1 increased one value and 2 decreased one value each. It is concluded that terfenadine does not produce clinically significant changes in stable asthmatics.

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Histamine is one of the preformed medications released from sensitised mast cells when interaction occurs between antigen and specific IgE, Fc, R1 receptors on the surface of the basophils [1]. RAFFERTY *et al.* [2] have used pharmacological techniques to show that a histamine (H_1) antagonist inhibits the allergen induced early asthmatic response by about 50% in the first ten minutes of the early response. Further, the same investigators [3] have shown that in stable asthmatics oral H_1 antagonists can produce bronchodilation which confirms previous work [4] and implies that at least in some asthmatic patients histamine is playing a role in maintaining constricted airways. The mechanism by which this comes about could be *via* leakage of mediators from asthmatic basophils which *in vitro* can occur faster than from non-asthmatic basophils [5].

Histamine may have many other effects aside from direct bronchoconstriction. Histamine may affect sensory receptors to increase reflex bronchoconstriction [6], it may increase intracellular cyclic GMP production [7], it increases pulmonary epithelial permeability [8], and antihistamines have been shown to inhibit mediator release from human blood basophils and eosinophils [9].

These other effects of histamine may affect airway responsiveness. Airway responsiveness can be related to the susceptibility of asthmatics to develop acute bronchoconstriction in response to a variety of stimuli, *e.g.* allergen [10] and exercise [11]. Therefore it is of interest to know whether chronic treatment with histamine antagonists will reduce airway responsiveness in an asthmatic population. The present study was designed to examine this possibility within individual asthmatics as well as an asthmatic group using one of the newer H_1 antagonists (terfenadine), which has few, if any, sedating effects [12]. The novel design feature was the capability of establishing 95% confidence limits for airway responsiveness for individual patients.

Methods and materials

Twelve stable asthmatics were recruited from the outpatient department at Flinders Medical Centre (table 1) to enable the study to be completed by the planned 10 patients. Each patient had previously had histamine or methacholine responsiveness tested in the laboratory and the study was approved by the Flinders Medical Centre Clinical Investigation Committee. The entry criteria for patients were a diagnosis of asthma, (on the basis of past history of variable wheeze, dyspnoea, and cough with previously documented reversible airflow obstruction and improvement with asthma treatment) a measurable endpoint ($<8 mg \cdot ml^{-1}$) to methacholine challenge test, no change to maintenance beclomethasone within the 6 months prior to study entry, no symptoms of a viral infection or exposure to relevant allergen except housedust within 6 weeks of the study.

Table 1. – Clinical features

Patient	Sex/Age	Atopy	Entry FEV_1 % predicted	Maintenance medication
1	F/50	+	105	B1000, S400
2	F/38	+	96	B2000, C8, S400
3	F/36	+	109	B800, C8, S400
5	M/47	+	95	B800, C8, S400
6	M/24	+	92	B1500, S400
7	F/38	+	105	S200
8	M/44	+	93	B800, S800
9	F/38	+	115	B200, S800
10	M/34	+	75	C8, S400
12	F/45	+	96	B4000, S400

B = beclomethasone diproprionate, dose in mcg per day; C = cromoglycate sodium, dose in mg per day; S = salbutamol, dose in mcg per day. Atopy = >3mm wheal to one or more skin prick tests of rye grass, house dust and cat dander.

At entry to the study a methacholine test (MT) was performed according to the tidal breathing technique described by COCKCROFT *et al.* [13]. Briefly the method consisted of the forced expired volume in 1 second (FEV_1) being measured until reproducible values (within 3%) were obtained and then sequential 2 min mouth tidal breathing periods from a face mask of an aerosol produced by a Wright nebuliser (output 0.15ml·min^{-1}) driven by an airflow of 9 l·min^{-1}. 0.9% saline was used as the control and FEV_1 was measured at 30sec, 90sec and at 1 min intervals after the end of inhalation until reproducible results were obtained (within 3%) and the FEV_1 had begun to increase. The lowest reproducible FEV_1 was used in calculations. Doubling concentrations of methacholine (range 0.03 to 8mg·ml^{-1}) were inhaled until a 20% or greater fall in FEV_1 was achieved. At this time the induced bronchoconstriction was reversed by inhaled salbutamol. The provocative concentration of methacholine to cause a 20% fall in FEV_1 ($PC_{20}M$) was interpolated from a log dose response curve. Medication abstention prior to MT consisted of no inhaled medications (salbutamol, cromoglycate and beclomethasone) for 6 h. For the MT conducted at 2 and 4 weeks of each treatment phase, the test medication was taken as usual. All MTs were performed at the same time of the afternoon and baseline FEV_1 values were required to be within ±15% for the data to be acceptable, or if this limit was exceeded the patient was replaced.

Patients were randomised in this double-blind study to receive four weeks of terfenadine 120mg bid or matching placebo bid and after a one week washout the treatment was crossed over within patients. During the study MT were performed at 0, 2 and 4 weeks of each treatment phase, and peak flow rate diurnal variation monitored at home daily with a mini-Wright peak flow meter. This was done by recording the best of 3 peak flow readings before medication in the morning and the best of 3 peak flow readings 10 minutes after medication in the evening and diurnal variation calculated by

$$\frac{\text{PFR (pm-am)}}{\text{PFR (pm)}} \times 100$$

Patients were asked "Did you notice anything different whilst taking the medication" at each review in order to detect unwanted side effects of the drug treatment.

Analysis of group data was performed by analysis of variance [14] of FEV_1, diurnal variation of peak flow rates, and logarithmically transformed $PC_{20}M$ within a treatment period, and by paired t-test between treatment periods [15]. Individual $PC_{20}M$ data were examined by establishing 95% confidence limits [16] for individual patients derived from the 3 placebo $PC_{20}M$ and the 0 week terfenadine $PC_{20}M$. The derivation of the individual 95% confidence limits was based on untransformed data.

Results

Two patients were withdrawn from the study: patient 4, a 35 yr old male because of a viral infection causing an exacerbation of asthma requiring treatment with oral prednisolone; and patient 11 a 61 year old male because of baseline FEV_1 measurements exceeding a ±15% range. The group data shows no significant differences ($p>0.05$) for FEV_1, PFR diurnal variation and $PC_{20}M$ either within a treatment period or between treatments.

However establishment of 95% confidence intervals for $PC_{20}M$ (fig. 1) shows two features: (a) that the reproducibility of the $PC_{20}M$ as reflected by the confidence intervals is variable between patients, and (b) that two patients had both active treatment $PC_{20}M$ values increased above the 95% confidence limits, and there was 1 patient with the 4 week active $PC_{20}M$ measured above, and 2 patients with the 4 week active $PC_{20}M$ decreased below the 95% placebo/baseline confidence interval. The use of a halving or doubling concentration range about the mean $PC_{20}M$ value to decide a significant change shows that only in patient 12 did the 4 week $PC_{20}M$ value fall outside the range. In patients 2, 7, 10 and 12 the 95% confidence limits fell outside the halving or doubling range, and in the remainder of the patients the 95% confidence limits were inside the halving or doubling range.

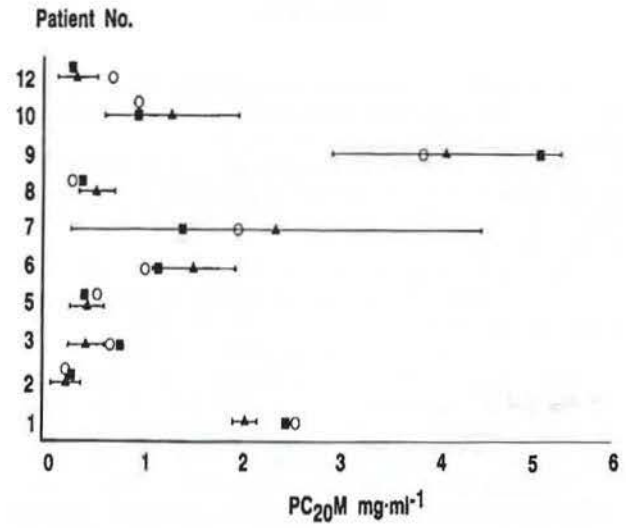

Fig. 1. – 95% confidence intervals around mean of baseline/placebo individual $PC_{20}M$ values ($mg \cdot ml^{-1}$). ■: $PC_{20}M$ after 2 weeks on 120mg bid terfenadine. O = $PC_{20}M$ after 4 weeks on 120mg bid terfenadine. ▲: mean $PC_{20}M$ of placebo and prior to start of terfenadine (baseline). ⊢⊣ : 95% confidence interval of placebo/baseline $PC_{20}M$.

No significant correlation was observed between peak flow diurnal variation and log $PC_{20}M$ (r=0.08) which is of interest as both measures have been used in the assessment of asthma severity or control. The baseline FEV_1 of patient 8 declined in the active treatment phase, but this did not seem to have an effect on $PC_{20}M$.

No patient complained of drowsiness or sleepiness on active or placebo treatment in response to the general question for unusual effects.

Discussion

This study has shown no group change in airway responsiveness during a 4 week treatment period with terfenadine 120mg bid. Small changes in $PC_{20}M$ were seen with treatment in five patients using the technique of 95% confidence limits, but these small changes were not all in the one direction and indicate perhaps that confidence limits need to be based on more than 4 measurements.

Previous workers [2] have shown that terfenadine 120mg is a very effective H_1 antagonist and is capable of moving a histamine dose response curves to the right by 20-fold. Further, terfenadine has been shown not to directly alter methacholine tests [2]. Therefore any changes occurring in methacholine responsiveness can be inferred to be due to an indirect effect of the treatment.

It may be argued that the dose of terfenadine used in this study could be increased and potentially show a larger effect. However, the reasons for selecting this dose were because it is the largest dose recommended for use and because it had been shown to be an effective histamine antagonist in the airway at this dose.

No bronchodilator effect of terfenadine was seen in this group of patients, but the study design did not allow for the testing of acute bronchodilator response. Nonetheless it may have been possible to detect a change in baseline FEV_1 at week 2 or 4 on terfenadine compared with the 0 week measurement. The observation of no bronchodilator effect reflects the study design and the patient population having a mean baseline FEV_1 of 98% of predicted.

The extent of increase in $PC_{20}M$ that is clinically relevant is arguable. It appears that the change observed in this population is unlikely to be clinically significant although this result cannot be extended to all asthmatics. In the 2 of 10 patients having small reductions in airway responsiveness on terfenadine treatment there were no apparent predicting factors for their response. All patients were atopic and there is a range of airway responsiveness in the group of patients. It could be argued that the longstanding use of beclomethasone and cromoglycate may mask subsequent changes in responsiveness, but it is of note that the two patients showing small changes in airway responsiveness were on moderate doses of beclomethasone (both) and cromoglycate (one). Patient 7 had no change in airway responsiveness and was on salbutamol alone. Therefore, although the use of protective medications could minimise changes in airway responsiveness by terfenadine, they do not eliminate the possibility, and there was room for improvement in airway responsiveness in this group.

How do these results fit with current understanding of asthma pathophysiology? Asthma is regarded as an inflammatory disease and histamine has been shown to be one of the mediators of an early asthmatic response to allergen. Histamine causes vasodilation and oedema as well as bronchoconstriction. Terfenadine may block the histaminic vascular and bronchospastic effect both of which could increase airway responsiveness. Further, it has been shown that terfenadine inhibits the release of histamine from mast cells *in vivo* in man and also the levels of kinins (17). The observation of no clinical change in airway responsiveness with terfenadine therefore suggests that in stable patients (with 9 of 10 on steroids and/or cromoglycate) there is no further reduction in airway responsiveness possible, by using antihistamines in addition to anti-inflammatory drugs. That is histamine effects in stable chronic asthma or in stable asthmatics on inhaled steroids or cromoglycate are minimal and other mediators or inflammatory cells are important. The place to examine the effects of terfenadine modifying airway responsiveness is in the acute allergen challenge situation or in the setting of other acute insults to the airways.

The study design of establishing 95% confidence limits for individuals has merit and may alter the interpretation of other medications and their effect on bronchial responsiveness, *e.g.* beclomethasone and cromoglycate. There is the possibility of using individual's responsiveness testing to try to delineate patterns of response in a patient population. The only disadvantage is that it makes clinical studies more complex, and to obtain tight 95% confidence limits means establishing larger

numbers of placebo or control measurements. Using less than 4 measurements to establish 95% confidence limits allows the chance finding of a result outside the limit during repeated measures to occur more frequently. Blinding of treatment is necessary in these studies because of potential influence of the investigator on the results of the inhalation test. There should be some consideration given towards selecting patients on the basis of the reproducibility of their inhalation tests. A group of patients with highly reproducible airway responsiveness tests would increase the power of testing, but would not provide results that could confidently be extrapolated to the general asthmatic population. The $PC_{20}M$ values for the 3 placebo and the 0 week terfenadine measures for each patient were within a doubling concentration as has been reported in a study with technicians blinded to previous results [18], but the 95% confidence limits of the means were outside the doubling concentration in 4 of 10 patients. The 95% confidence limit derived for individuals is more relevant than applying an arbitrary doubling limit when examining short term interventions.

Airway responsiveness testing remains an important measure to indicate the level of risk of acute asthma under certain provoking situations. It is associated with the chance of developing an early asthmatic response from relevant allergen exposure [9] and with the risk of developing exercise induced asthma [10]. As such, reduction in airway responsiveness is likely to reduce asthma morbidity and should be one of the general treatment aims for asthma. On the other hand, airway responsiveness is not the absolute measure for asthma severity and diagnosis. It is interesting to note the diurnal peak flow variations in this study in the week before each $PC_{20}M$ measure is not related to $PC_{20}M$. The failure of this relationship could mean that inhaled steroids are able to modify diurnal variation before reducing airway responsiveness but this seems unlikely given the observation that inhaled steroids alter airway responsiveness within 4 weeks [19]. The more likely explanation is that steroids are not capable of returning airway responsiveness to near normal levels in all patients and that airway responsiveness is a more sensitive measure than peak flow diurnal variation in assessing asthma control. JOSEPHS *et al* [20] have presented data arguing against this interpretation. They found that in 14 of 20 asthmatics that individual PD_{20} measurements were not consistently related to diurnal peak flow variation nor to asthma symptoms.

It is possible that new medications with pharmacological activities beyond H_1 antagonists may hold more promise in the therapy for difficult to control asthmatics, but on the basis of this present study there are a few patients whose asthma control and asthma morbidity may benefit from the addition of a selective H_1 antagonist to other preventive medications.

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Effet de l'administration d'un antagoniste H_1 par voie orale pendant 4 semaines sur la réactivité bronchique. R.E. Ruffin, K.M. Latimer.

RÉSUMÉ: Dix patients atteints d'asthme chronique en état stable ont terminé une étude randomisée en double aveugle avec contrôle par placebo et permutation croisée, pour étudier l'effet de 120 mg de terfenadine deux fois par jour pendant 4 semaines sur la réactivité bronchique. Cette dernière a été mesurée par inhalation de methacholine au moyen de la technique de respiration 'a volume courant à 0, 2 et 4 semaines de traitement actif ou placebo, les périodes de traitement étant séparées par une semaine de washout. Il n'y a pas de différence significative dans le VEMS de base (FEV_1), pour le placebo et pour les traitements à la terfenadine ($p>0.05$), et il n'y a pas de différence entre les concentrations géométriques moyennes de methacholine qui déterminent une chute de 20% du VEMS ($PC_{20}M$) entre les semaines 2 et 4 de terfenadine (0.89 et 0.99 $mg \cdot ml^{-1}$) et le placebo (0.94 et 0.84 $mg \cdot ml^{-1}$) ($p>0.05$). L'examen des valeurs individuelles de $PC_{20}M$ pendant le traitement à la terfenadine a montré que 5 patients avaient des $PC_{20}M$ situés en dehors de l'intervalle de confiance de 95%, 2 patients ayant des valeurs augmentées à la fois à la 2e et à la 4e semaine, 1 ayant une valeur augmentée, et 2 une valeur diminuée. L'on conclut que la terfenadine ne provoque pas de modification cliniquement significative chez les asthmatiques en état stable.

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