TIARAMIDE—A NEW ORAL DRUG FOR THE TREATMENT OF ASTHMA

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- 1 Tiaramide, an anti-inflammatory drug, inhibits the action of mediators released from mast cells and has direct smooth muscle relaxant properties. It may therefore have a beneficial effect in asthma.
- 2 A double-blind crossover trial comparing the bronchodilator activity of tiaramide and placebo over 16 days was undertaken in 13 patients with asthma.
- 3 Peak expiratory flow rate (PEFR) was recorded on three separate occasions every day and frequency of salbutamol aerosol usage was noted on a diary card.
- 4 During treatment with tiaramide the mean mid-morning PEFR (362 l/min) was higher than mean PEFR on placebo (328) ($P < 0.001$) as was the evening PEFR (378) compared with placebo (388) ($P < 0.001$).
- 5 There was a significant reduction in daily use of the salbutamol inhaler whilst on tiaramide (1.8) compared with placebo (2.3) ($P < 0.05$).
- 6 Tiaramide may be a useful addition to existing prophylactic treatment for asthma.

Introduction

Oral drugs continue to have a role in the management of asthma, both in patients with moderately severe disease who require oral therapy in addition to inhaled drugs, and in patients who are unable to use an inhaler. The β -adrenergic receptor agonists and xanthine derivatives are commonly used but may cause side effects such as muscular tremor and gastrointestinal symptoms at therapeutic doses.

Tiaramide (Sotine, Fisons Ltd, Loughborough), a 5-chlorobenzo-thiazolinone derivative, is a new oral drug with bronchodilator activity, but its action is different from that of the drugs usually used in asthma. It is a direct smooth muscle relaxant (Takashima *et al.*, 1979; Folco *et al.*, 1979), and antagonises endogenous bronchoconstrictor substances with some selectivity for prostaglandin $F_{2\alpha}$ and slow reacting substance of anaphylaxis (SRS-A). It has a greater specificity for bronchial rather than vascular smooth muscle and should produce effective bronchodilatation without undesirable cardiovascular side-effects (Fisons unpublished observations). Tiaramide is not a β -adrenergic receptor agonist (Takashima *et al.*, 1979; Folco *et al.*, 1979) or a cyclic AMP phosphodiesterase inhibitor, and it has no effect on intracellular levels of cyclic AMP (Folco *et al.*, 1979) (or of cyclic GMP). It is neither a specific anti-histamine nor an atropine-like drug (Fisons unpublished observations).

Tiaramide has anti-anaphylactic properties in animals which appear to be associated with inhibition

of mast cell degranulation but which are different from those of sodium cromoglycate (Takashima *et al.*, 1979; Renoux *et al.*, 1978) and whose relevance to the clinical activity of the compound is uncertain.

Assessment of the action of a bronchodilator drug in asthma is difficult because these patients have variations in airflow obstruction during the day and from day to day irrespective of treatment. Regular measurements of peak expiratory flow rate (PEFR) daily during randomized treatment and placebo periods of four days each gives a satisfactory estimate of airflow obstruction (Heaf & Mattila, 1969; Wright & McKerrow, 1959) and forms the basis of this present study. PEFR's were recorded using a mini-Wright peak flow meter, which compares well with the Wright peak flow meter (Wright, 1978; Perks *et al.*, 1979).

Methods

Informed consent was given by 13 patients with chronic reversible airflow obstruction. This was defined as a forced expiratory volume in 1 second (FEV_1) of less than 70% predicted normal for age, sex and height, with at least 15% reversibility after inhalation of salbutamol, recorded not more than 1 month before entry to the study. The trial was approved by the hospital Ethical Committee.

Individual patient data are summarised in Table 1.

Table 1 Individual patient data

Patient number	Sex	Age (years)	Duration of asthma (years)	Drugs*	FEV ₁ (l)	% Predicted normal	Reversibility %
1	F	26	15	B,S,A	1.05	40	66
2	M	51	10	I,B,S	2.65	76	24
3	M	39	6	I,S	1.18	29	134
4	M	18	16	I,S	2.15	52	87
5	F	43	41	B,S	0.90	35	78
6	F	18	16	B,S,Ph	2.24	68	57
7	F	32	29	I,B,S	1.58	61	29
8	M	46	42	I,S	3.40	96	18
9	M	50	49	B,S,Pr	1.44	50	33
10	M	57	10	B,S	1.17	39	40
11	F	26	26	I,B,S	3.65	109	22
12	F	51	50	I,B,S	1.16	48	38
13	M	34	22	I,B,S	3.10	74	39

* Drug key

B = Inhaled steroid

I = Sodium cromoglycate

S = Salbutamol inhaler

A = Ipratropium bromide inhaler

Ph = Sustained-release aminophylline

Pr = Prednisolone

The trial was over 20 days divided into 5 periods of 4 days each. The first period was single-blind (placebo) to enable the patient to become familiar with the protocol and has not been included in the analysis. Thereafter the remaining 4 periods were randomised so that a placebo period alternated with a treatment period (tiaramide 100 mg four times daily or 200 mg four times daily) in a double-blind fashion. Patients continued their usual prophylactic treatment (i.e. sodium cromoglycate, oral or inhaled steroids) with no change in dose, but discontinued all bronchodilators with the exception of inhaled salbutamol which was used only as necessary. PEFRs were recorded three times daily; the first ('early morning') before taking any treatment, the second 2 h later ('mid-morning') and the third at night 1 h after taking the last test tablets ('evening'). On each occasion the best of three measurements in the standing position was recorded on a diary card, as was the frequency and timing of use of the salbutamol inhaler after each 24 h period, together with any side effects.

Results were analysed by obtaining the mean values for early morning PEFR for the 4 days of each of the 4 periods (2 placebo periods P1, P2 and 2 tiaramide periods T100 and T200). Results were similarly calculated for the mid-morning PEFR and evening PEFR. Using these mean values for the 3 PEFR recordings and the mean daily use of the salbutamol inhaler during each period, an analysis of variance was carried out, incorporating the following contrasts:

(a) between placebo periods (P1 v P2)

(b) between tiaramide periods (T100 v T200)

(c) placebo v tiaramide (P1, P2 v T100, T200)

The patient with the lowest percent of predicted normal FEV₁ (29%) was withdrawn from the trial because of an exacerbation of asthma requiring a change in treatment. Another patient repeatedly recorded unusually high PEFR values (greater than 800 l/min). The peak flow meter was found to be faulty and therefore the readings were excluded from the analysis.

Results

During treatment with tiaramide, the early morning PEFR (308 l/min, mean value) recorded prior to the first dose showed a small but significant ($P < 0.05$) improvement compared with PEFR on placebo (293) (Table 2). There were also small but significant differences ($P < 0.05$) between placebo periods.

The mid-morning PEFR (362) measured 2 h after the first dose of tiaramide showed a greater improvement and was higher than PEFR on placebo (328) ($P < 0.001$). There were no significant differences in PEFR between the 100 mg and 200 mg tiaramide periods. Again, small increases in PEFR occurred in successive placebo periods, but these changes were not statistically significant.

The evening PEFR (378) 1 h after the last dose also showed a significant ($P < 0.001$) improvement compared with PEFR on placebo (338). Additionally,

Table 2 Mean PEFR results (l/min) and daily aerosol use during the 4 periods

Treatment period	Early morning PEFR (l/min)	Mid-morning PEFR (l/min)	Evening PEFR (l/min)	Daily aerosol Usage
P1	282	319	327	2.5
P2	303	337	350	2.1
Mean P1, P2	293	328	338	2.3
T100	304	356	362	1.8
T200	312	367	394	1.8
Mean T100, T200	308	362	378	1.8
s.d.	24.03	30.76	31.05	2.86
	<i>n</i> = 11	<i>n</i> = 11	<i>n</i> = 11	<i>n</i> = 12
Significance of contrasts				
P1, P2 ν T100, T200	<i>P</i> < 0.05	<i>P</i> < 0.001	<i>P</i> < 0.001	<i>P</i> < 0.05
T100 ν T200	NS	NS	<i>P</i> < 0.05	NS
P1 ν P2	<i>P</i> < 0.05	NS	NS	NS

200 mg tiaramide was more effective (PEFR 394) than 100 mg (PEFR 362) ($P < 0.05$). There were no significant differences between placebo periods.

The salbutamol inhaler was used significantly less per day ($P < 0.05$) during the tiaramide periods (1.8) compared with placebo (2.3) (Table 2).

Analysis of individual patient data (Figure 1) showed that 8 of 11 had higher mean mid-morning

and evening PEFR values when on tiaramide (both periods) compared with placebo (both periods). Of these, four also showed a reduction in amount of inhaled salbutamol used, two showed no change or minimal reduction and two required no salbutamol throughout the trial. Of the three patients (Nos 5, 7 and 11) who showed no improvement in PEFR on tiaramide, one (No. 7) required less inhaled salbutamol. Only two patients (Nos 5 and 11) did not show an improvement in PEFR or a reduction in inhaled salbutamol used. Patient no. 11 had probably reached optimal lung function already (initial FEV₁ 109% predicted normal) and patient no. 5 had the lowest percentage predicted FEV₁ (0.9 l, 35% predicted) on admission to the trial apart from patient no. 3 (FEV₁ 1.18 l, 29% predicted) who was withdrawn because of an exacerbation of asthma. The numbers of patients in each of the above groups were too small to determine whether the age of the patient, severity and reversibility of airflow obstruction and concurrent medication would predict response to tiaramide.

Headache was the only side effect that could be consistently attributed to tiaramide, occurring in six patients on 200 mg, one patient on 100 mg, and two during each of the two placebo periods. The headache responded to simple analgesia and did not result in the withdrawal of any patient from the study.

Discussion

Tiaramide increases PEFR and reduces the amount of inhaled salbutamol required in patients with asthma. The main improvement was noted in the mid-morning and evening PEFR results. Tiaramide has a short half-life of approximately 1.5 h, and would not be expected to have any effect on early morning PEFR, recorded prior to the first dose and approximately 8 h after the preceding night-time

Figure 1 Comparison of mean mid-morning and evening PEFR results and daily salbutamol use on placebo and tiaramide for individual patients.

dose. Although there was a slight improvement reaching statistical significance in the early morning PEFR when on tiaramide, there was also a difference of similar magnitude between the placebo periods, again reaching significance. This tendency for PEFR to improve during each successive placebo period was also seen in the mid-morning and evening results although the changes were not statistically significant. It emphasises the importance of randomisation of the placebo and treatment periods in the double-blind fashion. The 200 mg dose of tiaramide was shown to have a greater effect than 100 mg on the evening PEFR only but the reason for this is not clear.

Tiaramide has been shown to be effective in asthma. The majority of the patients studied were already taking prophylactic treatment in the form of sodium

cromoglycate and inhaled steroids in addition to a bronchodilator inhaler, yet tiaramide produced a further improvement in PEFR, and reduced the amount of inhaled salbutamol required. Oral drugs are indicated for patients with severe disease who still have symptoms despite the use of inhaled prophylactic drugs and for patients unable to use an inhaler. Tiaramide may therefore be a useful addition to existing prophylactic treatment.

We thank Dr J. Abel, Mr D.E. Hodder and Mr M.T. Stevens of Fisons Limited for general and statistical advice.

Tiaramide was supplied by Fisons Limited, Pharmaceutical Division, Loughborough, England and Fujisawa Pharmaceutical Company Limited, Osaka, Japan.

References

- FOLCO, G.C., VIGANO, T., SAUTEBIN, L., MALANDRINO, S., OMINI, C. & BERTI, F. (1979). The mode of action of tiaramide hydrochloride: a new anti-asthmatic drug. *Pharmac. Res. Comm.*, **11**, 703–718.
- HEAF, P.J.D. & MATTILA, M.J. (1969). Assessment of bronchodilator drugs on asthmatic outpatients by daily measurements of the peak expiratory flow rate. *Arzneim. Forsch.*, **19**, 1927–1929.
- PERKS, W.H., TAMS, I.P., THOMPSON, D.A. & PROWSE, K. (1979). An evaluation of the mini-Wright peak flow meter. *Thorax*, **34**, 79–81.
- RENOUX, M.L., WEILL, B.J., WALLACH, D. & CHWETZOFF, E. (1978). The anti-anaphylactic action of tiaramide hydrochloride. *Allergy*, **33**, 76–81.
- TAKASHIMA, T., ONO, T., OHTSUKA, M., MORI, J. & KUMADA, S. (1979). The mode of action of anti-anaphylactic effect of tiaramide hydrochloride. *Arzneim. Forsch.*, **29**, 903–910.
- WRIGHT, B.M. (1978). A miniature Wright peak flow meter. *Br. med. J.*, **2**, 1627–1628.
- WRIGHT, B.M. & MCKERROW, C.B. (1959). Maximum forced expiratory flow rate as a measure of ventilatory capacity. *Br. med. J.*, **2**, 1041–1047.

(Received May 5, 1982,
accepted June 6, 1982)