

A Trial of Tiaramide in Asthma

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Tiaramide hydrochloride is a new non-steroidal anti-inflammatory agent previously shown to inhibit allergic responses both *in vitro* and *in vivo*. Clinical studies in asthmatic adults and children have also shown benefit. We report a double blind cross-over study in 35 adult asthmatic patients comparing oral tiaramide 200 mg four times daily with oral salbutamol 4 mg four times daily and placebo. Symptoms and bronchodilator inhaler usage were recorded in diary cards and morning and evening peak expiratory flow rates were also monitored. Both tiaramide and salbutamol had a significant therapeutic effect compared with placebo. More patients preferred tiaramide than salbutamol and there were fewer side effects during treatment with tiaramide. Tiaramide may be a useful oral therapy in asthma particularly for those patients intolerant of oral beta-adrenergic agonists.

Key words: anti-inflammatory agent; asthma; autacoids; tiaramide.

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Tiaramide hydrochloride is a new compound (a chlorbenzothiazalinone) developed in Japan with some unique pharmacological properties. Although not a beta-adrenergic agonist, it is a bronchodilator which also selectively inhibits the activity of prostaglandin F₂ alpha, histamine and bradykinin though it does not inhibit prostaglandin synthesis. It was first used in Japan in 1975 as a non-steroidal anti-inflammatory agent having a prominent inhibitory action especially on acute inflammation in animals (5). Later pharmacological studies demonstrated an inhibitory effect on allergic reactions in animal experimental models and direct antagonism of certain autacoids (histamine, bradykinins, prostaglandins, etc.).

Tiaramide hydrochloride was also found to reduce the bronchoconstrictor response to both inhaled antigens and inhaled histamine in children (2).

Clinical studies in adults and children with asthma suggested possible benefits more striking in some patients than others (3, 4). We undertook a double blind cross-over study to compare the efficacy and patient tolerance of

tiaramide, salbutamol and placebo in patients with chronic obstructive airways disease.

MATERIAL AND METHODS

The trial was designed to compare the effects of tiaramide hydrochloride 200 mg, salbutamol 4 mg and placebo tablets, each administered four times daily. The design of the trial was approved by the local ethical committee and all patients gave informed consent. Adult patients who had not received treatment with an oral beta-adrenergic bronchodilator within 2 weeks and who had evidence of airways obstruction reversible by at least 15% after a bronchodilator inhalation were invited to take part. Each patient was asked to keep a diary card of all medication, all untoward symptoms, and records of peak expiratory flow rate (PEFR) night and morning, using a mini-Wright peak flow meter. They also kept a symptom score of wheeze, cough, sputum, limitation of activity, and sleep disturbance.

For each patient the trial consisted of four periods. During the first 2 weeks (baseline

period) all oral bronchodilators were withdrawn and each patient received two placebo tablets (containing lactose and excipient flavoured with quinine) four times daily. The dose of inhaled sodium cromoglycate, inhaled or oral corticosteroids and other incidental medication was standardised during this period and continued unchanged throughout the trial. The patients were allowed to use a bronchodilator aerosol as required, and recorded each dose. If PEFr measurements were recorded within 4 h of aerosol usage, they were not used in the analysis.

During three further 2-week periods (treatment period) the patients received either two 100 mg tablets of tiaramide, or two 2 mg tablets of salbutamol (Salbuvent brand – which closely resembled both tiaramide and placebo tablets), or two placebo tablets identical to tiaramide, all taken four times daily. The tablets were issued in opaque containers directly from pharmacy to the patients and the order of the treatment was randomised, and unknown either to the patient or the clinician. Our patients have not previously experienced treatment with either tiaramide or Salbuvent. At the end of each period the patients were asked to express an opinion as to the effectiveness of the treatment (very effective, moderately effective, slightly effective, no effect, made condition worse), and the clinician also recorded an opinion based on the clinical findings and discussion with the patient. At the end of the trial both patient and clinician ranked the treatment in the double blind phase of the trial in order of preference.

Patients were withdrawn from the trial if their condition deteriorated, if they required new medication, or if unacceptable side effects were experienced.

PATIENTS

During this trial 35 patients were studied, 19 males and 16 females, with mean age 45.3 years (range 20–68 years). Five patients had severe symptoms, 25 moderate and five mild. Three patients had mild or controlled hypertension, but routine haematological and biochemical investigations were normal in all cases. The mean duration of symptoms was 20.9 years (range

0.6 to 55 years). All patients had been shown to have reversible airways obstruction, the forced expiratory volume in one second (FEV_1) improving by at least 15% after an inhalation of a bronchodilator. At the start of the study period of the trial the mean reversibility of FEV_1 was 30.4% (range 8.3% to 76.9%).

Prior to the study, all but two patients regularly used a beta-agonist aerosol and of these, eight were also taking inhaled, five oral and one both inhaled and oral corticosteroids in fixed doses during the trial. One patient used inhaled ipratropium bromide and four were using inhaled cromoglycate, 11 were also taking other drugs – cimetidine, xipamide, bendrofluazide-K and diazepam. No patient had been treated with oral salbutamol.

Six patients withdrew from the trial. Two developed an attack of asthma during the period of preliminary observation and one failed to keep appointments. Three patients were withdrawn from the double blind part of the study, two during the salbutamol period with exacerbations of asthma, and one during the tiaramide period because of headache.

RESULTS

Diary cards

Scores for sleep disturbances, limitation of activity, cough, wheeze, sputum and aerosol bronchodilator usage were compared using the Friedman two-way analysis of variance by ranks, supplemented by individual period comparisons using the binomial test when significant differences were found. The only feature with a significant difference ($P < 0.025$) between the baseline and three treatment periods was wheeze. Binomial tests between pairs of treatments showed that only tiaramide gave significantly lower wheeze scores than placebo. There were no significant differences in aerosol bronchodilator usage either overnight or during 24 h.

Peak expiratory flow rate

The analysis of mean PEFr readings (Table 1) was performed by repeated measures analysis of

variance to compare the three test treatments. No significant difference was found in morning PEFR, but evening PEFR showed significant treatment variation ($P < 0.05$). The variation in sample size between the morning and evening peak flow figures reflects the exclusion of some data for analysis because patients had used an inhaled bronchodilator within the 4 h prior to recording their PEFR. Duncan's multiple range test was used to identify the source of the difference and showed that tiaramide and salbutamol mean PEFR was significantly higher than

during the placebo treatment although there was no significant difference between tiaramide and salbutamol.

Comparison of tiaramide and placebo (Table 2)

In order to examine the efficacy of tiaramide against that of placebo alone, comparisons of scores for these two periods at clinical assessments and on diary cards were performed. Table 2 summarizes the results and shows that tiaramide gave better results ($P < 0.05$) for both sets of effectiveness scores, patient's and investigator's overall preferences, diary card wheeze mean scores and mean 24-h aerosol bronchodilator usage. The sample size varies in the comparison because cases for which salbutamol data was incomplete were also included.

Side effects

One patient stopped taking tiaramide because of headache and nausea. Five others complained of headache when taking tiaramide, but three of these also had headache during either the baseline or the placebo period. Ten patients complained of shakiness with salbutamol, one also with tiaramide and one with placebo. One patient changed treatment periods early because of severe tremor with salbutamol

Table 1
Analysis of diary card peak expiratory flow rates

Treatment	Morning PEFR (l/sec)	Evening PEFR (l/sec)
Baseline	4.45	4.64
Tiaramide	4.47	4.96*
Salbutamol	4.60	4.97*
Placebo	4.39	4.65
Sample size	20	25
Significance of difference from placebo	NS	* = $P < 0.05$

Table 2
Tiaramide/placebo comparisons

Parameter	Number of patients with scores in favour of			<i>P</i> value
	Tiaramide	Neither	Placebo	
<i>Clinical assessment</i>				
Severity of symptoms	7	17	4	0.55
Patient effectiveness	10	16	2	0.04
Clinician effectiveness	15	8	4	0.02
Patient preference	18	6	5	0.01
Clinician preference	17	9	2	0.001
<i>Diary cards</i>				
Sleep disturbance	10	8	10	1.00
Sputum	9	8	8	1.00
Wheeze	20	3	4	0.002
Activity limitation	13	8	6	0.17
Cough	14	4	8	0.29
Night aerosol usage	13	9	6	0.17
24-h aerosol usage	18	5	5	0.01

DISCUSSION

This study confirms that tiaramide has a therapeutic effect in patients with asthma. The daily dose of tiaramide of 800 mg was selected as the most appropriate adult dose as a result of earlier studies which examined a protective effect of differing doses of tiaramide against acute antigen challenge in both animals (5) and children (2). Both patients and clinicians judged tiaramide to be more effective than placebo. The use of bronchodilator aerosols was reduced during treatment with both tiaramide and salbutamol. More patients preferred tiaramide to salbutamol (16 vs. 8) and there were fewer side effects during tiaramide treatment. About one third of the patients complained of tremor or palpitations during salbutamol treat-

ment as expected from previous experience (1).

Neither tiaramide nor salbutamol had any effect in improving morning peak flow rates, though neither preparation would be expected to have significant pharmacological activity 8 h or more after the previous dose since the half lives of oral tiaramide and salbutamol are 3 h and 2–7 h, respectively. Analysis of individual patients did not suggest that concurrent treatment with cromoglycate, or inhaled or systemic corticosteroids affected the likelihood of a response to tiaramide.

Non-steroidal anti-inflammatory drugs such as aspirin, which have an effect on prostaglandin synthesis, may cause severe asthmatic attacks. One patient in this trial was severely intolerant to aspirin, but did well on tiaramide and has continued treatment with it. Another patient, however, who has previously found aspirin acted as a bronchodilator also did well and has continued on tiaramide.

This preliminary study indicates that drugs active against autacoids such as prostaglandins may be useful therapeutic agents in the treatment of asthma, particularly in those patients who are intolerant of oral bronchodilators.

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