EFFECTS OF PROLONGED ADMINISTRATION OF PIRBUTEROL BY MOUTH IN CHRONIC ASTHMA

Pirbuterol is a β_2 -adrenoceptor stimulant drug which has little effect on the myocardium (Van Arman, Miller & O'Malley, 1961). Willey, Grant & Pocock (1976) established dose-response curves for the bronchodilator activity of this drug administered orally in a study of ten patients with chronic asthma. They showed that single doses of 15 mg and 20 mg produced maximum bronchodilatation 2 h after administration and that 10 mg also produced a significant though less marked effect, which continued for 5 hours. The aim of the present study was to assess the value of regular oral administration of pirbuterol in the treatment of chronic asthma and to determine whether this could produce tachyphylaxis in respect of bronchodilator activity. As 15 mg or 20 mg of pirbuterol had, at the time of starting this study, not been approved by the Committee on the Safety of Medicines for regular administration, the maximum permitted dose (10 mg 4 times a day) was used.

Twenty-one patients (four female and seventeen male) with a mean age of 57.7 years (range 18–72 years) were included in this single blind study. All the patients were known to have chronic asthma and were regular users of bronchodilator inhalers. The patients were reviewed initially and then at 4-weekly intervals for 16 weeks. During the first 4-week period the patients were given two placebo capsules four times per day. Throughout the second, third and fourth periods they were given identical capsules containing pirbuterol 10 mg four times per day. For each 4-weekly review the patients were given a diary card on which they recorded daily (a) severity of asthma (scale 1–4, 1=fewest symptoms), (b) frequency of inhaler usage, (c) changes in therapy and (d) side effects of treatment. They were told not to take any bronchodilator treatment for a period of 12 h before each assessment.

At each visit the chest was examined, pulse rate and blood pressure were recorded, and the patients were tested for tremor. The forced expiratory volume in 1 s

(FEV₁) was then recorded with a Gaensler spirometer and this was repeated 2 h after pirbuterol (10 mg). Thereafter an aerosol of 0.5% salbutamol was administered for 3 min by intermittent positive-pressure ventilation (IPPV) and 15 min later a third FEV₁ was recorded. Samples of venous blood were taken at each visit for haemoglobin estimation, white cell count and differential count, platelet count and measurements of urea, electrolytes, glucose, bilirubin, alkaline phosphatase, SGOT, SGPT and creatinine phosphokinase. An ECG was recorded initially and then at the end of the second period.

Twenty-one patients completed the first and second 4-week periods. The mean daily symptom score ($\pm$ s.e. mean) fell from 2.28 (± 0.110) in the first (placebo) period to 2.041 (± 0.126) in the second (pirbuterol) period, and the mean daily inhaler usage from 5.661 (± 0.776) to 4.783 (± 0.748), but these differences were not statistically significant.

Five patients were withdrawn from the study after the end of the second period, three because of severe asthmatic symptoms considered to represent a failure of treatment, one because of intolerable tremor, and one because of the development of left ventricular failure. This fifth patient had an initial ECG showing left bundle branch block and there was no change after the onset of pulmonary oedema.

The 4-week average of the mean daily symptom scores and mean daily inhaler usage for the sixteen patients who completed 16 weeks of observation are shown in Table 1. Mean symptom scores were lower in the second, third and fourth periods than in the first (placebo) period, but the differences were not statistically significant. Mean daily inhaler usage was significantly less in the second period than in the first ($P < 0.05$) but in the third and fourth periods inhaler usage again increased. There was, however, no statistically significant difference in inhaler usage between the first, third and fourth periods.

Of the twenty-one patients four complained

Table 1 Mean daily symptom score ($\pm$ s.e. mean) and mean daily inhaler usage ($\pm$ s.e. mean) in sixteen patients observed for 16 weeks

	0–4 weeks	5–8 weeks	9–12 weeks	13–16 weeks
Treatment	Placebo	Pirbuterol	Pirbuterol	Pirbuterol
Mean daily symptom score	2.267 (± 0.141)	1.998 (± 0.141)	2.051 (± 0.155)	2.129 (± 0.141)
Mean daily inhaler usage	5.693 (± 0.984)	4.504 (± 0.910)	5.018 (± 1.050)	5.316 (± 0.869)

Table 2 Mean FEV₁ ($\pm$ s.e. mean) before and after pirbuterol (10 mg) and after salbutamol by IPPV at end of 4 week periods in sixteen patients observed for 16 weeks

	At 4 weeks	At 8 weeks	At 12 weeks	At 16 weeks
Treatment	Placebo	Pirbuterol	Pirbuterol	Pirbuterol
Mean initial FEV ₁ (l)	1.359 (± 0.138)	1.369 (± 0.148)	1.322 (± 0.141)	1.175 (± 0.140)
Mean FEV ₁ after pirbuterol (10 mg) (l)	1.528 (± 0.152)	1.503 (± 0.170)	1.388 (± 0.152)	1.413 (± 0.161)
Mean FEV ₁ after salbutamol by IPPV (l)	1.981 (± 0.152)	2.003 (± 0.170)	1.925 (± 0.152)	1.888 (± 0.141)

spontaneously of transient mild tremor, and fourteen were observed to have mild tremor after the administration of pirbuterol. There were no other side effects and no haematological abnormalities were demonstrated. All the biochemical investigations were normal apart from an elevation of the creatinine phosphokinase in four patients. No ECG changes were detected after 1 month's treatment.

The mean FEV₁ recordings for the sixteen patients studied for 16 weeks are shown in Table 2. The mean initial FEV₁ recorded at the end of each period did not change significantly, nor did the increase in FEV₁ recorded after pirbuterol at the end of the first, second and fourth period, although that recorded at the end of the third period was significantly lower ($P < 0.05$). There was a highly significant further increase in FEV₁ ($P < 0.01$) after the administration of salbutamol by IPPV over that recorded after pirbuterol at the end of every 4-week period. The response to salbutamol over the 16 weeks of observation did not alter significantly.

The results of this study do not suggest that oral pirbuterol is an effective form of treatment for chronic asthma. Although a small but statistically significant increase in FEV₁ was recorded 2 h after pirbuterol administration, the patients reported virtually no overall symptomatic improvement or reduction in inhaler usage during the treatment period. Pirbuterol administered in this dose produced slight or moderate tremor in the majority of patients. If a higher dose had been used in an attempt to achieve a greater bronchodilator effect, many patients might have found this

side effect intolerable. The poor clinical response is not surprising when one considers that the increase in FEV₁ produced by oral administration of pirbuterol was small and well below that observed after the administration of salbutamol by intermittent positive pressure ventilation (IPPV).

There was no indication that the bronchodilator response to oral pirbuterol diminished with continued administration of the drug, but the response was so unimpressive that it would have been difficult to identify any such evidence of tachyphylaxis.

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