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THE EFFECT OF ORAL TERBUTALINE IN ASTHMA

By

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Adrenergic stimulant drugs such as isoprenaline, orciprenaline and ephedrine are widely employed to reverse the bronchospasm which occurs in asthma and, to some extent, in chronic obstructive airways disease. In general, these sympathomimetics have a non-specific action producing bronchodilatation via the β_2 receptors and a chronotropic and inotropic effect on the myocardium via the β_1 receptors. It has been suggested that the excessive stimulation of myocardial receptors, possibly within the setting of a coexistent respiratory acidosis and arterial hypoxemia occurring during a severe asthmatic attack, may induce arrhythmias, and misuse of these agents has been considered an important cause of mortality in asthma (6).

Consequently, modifications in the side chains of the isoprenaline molecule have been introduced to obtain a preferential β_2 receptor action and avoid undesirable cardiovascular effects. In addition, the benzene rings of these compounds have been altered to render the drugs more resistant to metabolism by catechol-o-methyl transferase, which normally breaks down isoprenaline, and thereby increase the duration of action. One of these compounds, terbutaline, synthesized by Wetterlin and Svenson in 1966, was tested in

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a group of asthmatic patients to assess the effectiveness of bronchodilatation, the duration of action, and some aspects of the circulatory response.

PATIENTS AND METHODS

Thirteen asthmatic patients, (10 males and 3 females) selected from patients under the care of the Johannesburg Hospital Respiratory Unit were investigated. All had a history of airway obstruction and known reversibility to bronchodilators. No cigarette smokers were included, although some had smoked in the past. The ages ranged from 13 to 65 years (mean age 42 years). All bronchodilator drugs were omitted on the day of the study. Control measurements were performed on each patient until these were steady and were repeated 10 minutes after an oral dose of 5 mg terbutaline and again after 30 minutes, 1 hour and hourly thereafter for 7 hours. On each occasion, one second forced expiratory volume (FEV_1), forced vital capacity (FVC), heart rate (HR) and blood pressure (BP) were recorded. In all cases, the control value for ventilatory tests was less than 70 per cent of the subject's predicted value. Values were measured in litres BTPS.

RESULTS

Fig. 1 shows the mean FVC and FEV_1 values together with the standard error as a percent increase over the control figures. The FVC improvement was highly significant at 10 minutes ($p < .001$) and retained this significance throughout the test. The increase was also significant for FEV_1 , ($p < .01$) at 10 minutes and remained significant at 7 hours ($p < .05$). All the patients improved though, as is evident from Fig. 1, there was a wide range of response. The mean heart rate, systolic and diastolic blood pressures fell during the first thirty minutes; thereafter they remained stable. Mean heart rate decreased slightly during the procedure (Fig. 2).

DISCUSSION

These results demonstrate that oral terbutaline is a potent bronchodilator, having a rapid and prolonged action with a negligible effect on the cardiovascular system when given as a 5 mg dose to asthmatic subjects, suggesting selective β_2

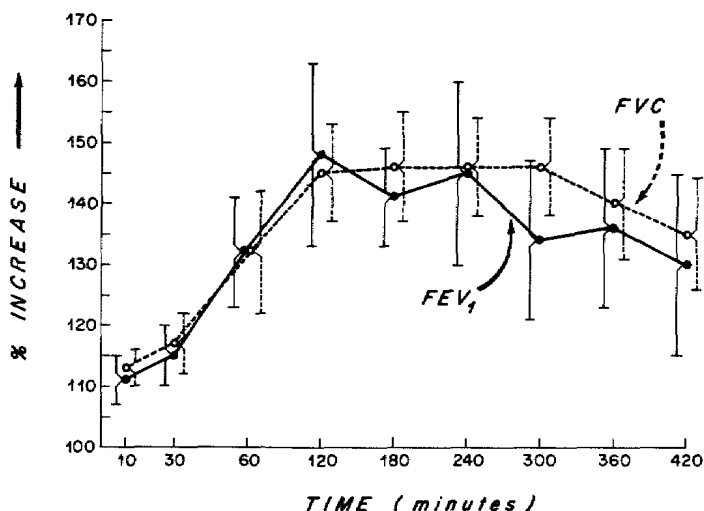


Fig. 1.

Mean forced vital capacity (FVC) and mean forced expiratory volume (FEV_1) after 5 mg terbutaline in 13 asthmatic patients.

receptor stimulation. The decrease in airway obstruction is in agreement with other studies (2, 3, 7), though some have shown a small rise in pulse rate (3, 7). Side effects were minimal and never severe enough to preclude the use of the drug. Previous studies have not attempted to demonstrate the rapidity of onset noted nor followed the patients for as long as 7 hours.

The wide variation in response in the study could be explained partly by the variation in the control values of the patients. Thus, it has been shown (4, 5) that the response to a bronchodilator depends on the pretreatment status so that subjects with a lesser degree of obstruction are more sensitive to bronchodilators. The pretreatment values in this study varied from 25 per cent to 65 per cent of the predicted values. The maximum response of individual patients also varies so that, for example, an improvement of 20 per cent

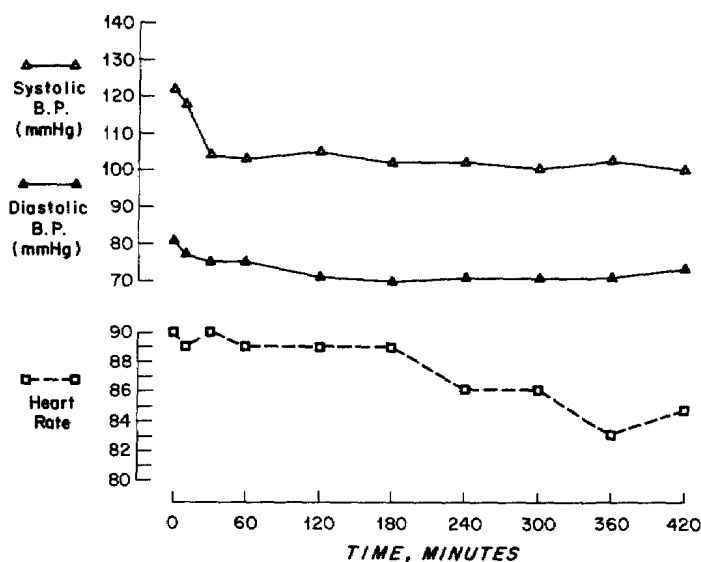


Fig. 2.

Effect of 5 mg terbutaline on blood pressure and heart rate. Mean values of 13 asthmatic patients.

may reflect the best value obtainable in a patient while another may be capable of doubling his pretreatment value. All the patients studied had been using bronchodilators, (isoprenaline, orciprenaline or salbutamol) over a prolonged period prior to the test. It has recently been argued (1) that prolonged β -receptor stimulation may induce resistance to bronchodilators; presumably the degree of resistance would be variable, depending on a number of factors, thus contributing to the wide range of response in this trial. Possibly it is the group with increased resistance to endogenous or exogenous β -stimulation who succumb because of excessive self-administration in an unavailing attempt to break an asthmatic attack. These patients would also, due to the severity of the attack, develop more severe hypoxaemia and respiratory acidosis

and be more susceptible to arrhythmias during a severe episode.

The prolonged relief of bronchial obstruction may be particularly useful in treating patients who suffer nocturnal episodes. The effects noted should provide satisfactory long-term maintenance therapy while also being sufficiently rapid to afford relief in mild to moderate exacerbations of bronchospasm.

SUMMARY

The bronchodilator, terbutaline, was tested in 13 asthmatic patients to assess its effects on airway obstruction and the cardiovascular system. A satisfactory separation of effects was noted with a rapid onset and prolonged duration of bronchodilatation and minimal circulatory effects.

REFERENCES

1. *Connolly, M. E., Davies, D. S., Dollery, C. T. & George, C. F.*: Resistance to β -adrenoceptor stimulants (a possible explanation for rise in asthma deaths). *Brit. J. Pharm.* 43, 389-411, 1971.
2. *Formgren, H.*: A clinical comparison of the effect of oral terbutaline and orciprenaline. *Scand. J. Resp. Dis.* 51, 195-202, 1970.
3. *Freedman, B. J.*: Trial of new bronchodilator, Terbutaline, in asthma. *Brit. Med. J.* 1, 633-636, 1971.
4. *Hume, K. M. & Gandevia, B.*: Forced expiratory volume before and after isoprenaline. *Thorax* 12, 276-278, 1957.
5. *Hume, K. M. & Rhys Jones, E.*: The response to bronchodilators in intrinsic asthma. *Quart. J. Med.* 30, 189-199, 1961.
6. *Inman, W. H. W. & Adelstein, A. M.*: Rise and fall of asthma mortality in England and Wales in relation to use of pressurized aerosols. *Lancet* 2, 279-285, 1969.
7. *Leggs, J. S., Gaddie, J. & Palmer, K. N. V.*: Comparison of two oral selective β_2 -adrenergic stimulant drugs in bronchial asthma. *Brit. Med. J.* 1, 637-639, 1971.

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