A Comparative Assessment of Carbuterol, Fenoterol and Hexoprenaline in Allergic Asthma

A. VAN AS, I. McDONALD, T. GEBHARDT, R. DOWDESWELL

SUMMARY

Carbuterol tablets (20 mg) were compared with the tablets of fenoterol (2.5 mg) and hexoprenaline (1 mg). The three drugs were shown to be equally effective for a period of 4 hours, but carbuterol and fenoterol exerted a statistically significant bronchodilating action for 7 and 8 hours respectively, while the action of hexoprenaline lasted for 4 hours in the majority of patients. The aerosols of carbuterol (200 mg) and fenoterol (400 mg) appeared to be similar in inhibiting exercise-induced asthma, whereas hexoprenaline (200 mg) did not appear to be as effective.


It is generally accepted that among other actions sympathomimetic substances exhibit a varying degree of selectivity on β-adrenoceptors and produce either cardiac responses (inotropic and chronotropic responses) or smooth muscle relaxation (bronchodilatation and vasodilatation). For the treatment of bronchospasm it is desirable to utilize a β-adrenoceptor agonist with a selective action on the bronchi and without unwanted cardiac responses in adequate therapeutic doses. A variety of sympathomimetic drugs which satisfy these criteria of selectivity have been developed over the past 10 years. Carbuterol (Bronsecur; SKF) which has become available recently, fits into the category of a selective β2-adrenoceptor agonist with a predominant bronchodilator action. The purpose of this article is to report a comparison of the action of carbuterol with that of fenoterol (Berotec; Boehringer Ingelheim) and hexoprenaline (Ipradol; Continental Ethicals) in both the tablet and the aerosol form.

PATIENTS AND METHODS

Tablet Administration

Eight patients, 1 man and 7 women, mean age 40.75 years (range 21 - 60 years) were asked to participate in the study. All the patients had demonstrable type 1 skin prick reactions to a variety of allergens, an elevated total IgE level in the serum, and sputum or blood eosinophilia at some stage of their illness, as well as a known bronchodilator response of at least 20% to a β-adrenoceptor stimulant (either hexoprenaline or salbutamol). Seven patients used hexoprenaline aerosols, 5 took hexoprenaline tablets, 1 used salbutamol aerosol, 2 took choline theophyllinate orally, 5 used beclomethasone dipropionate inhalation, 3 inhaled disodium cromoglycate, and 1 had a weekly tetracosactide depot (1 mg) injection. The patients were asked to report to the pulmonary function laboratory at 08h00, having taken no medication for the previous 12 hours. They were allowed to sit for at least 20 minutes to reach a basal state before the investigation was commenced. The pulse rate and blood pressure (physthmomanometer) were recorded in turn, and a sample of handwriting was also recorded and the outstretched hand observed as an index of tremor. After this, three forced vital capacity manoeuvres were performed on a dry-seal spirometer (Cardiopulmonary Instruments) and the best of the three efforts was recorded. The forced expiratory flow volume curve was recorded during these manoeuvres. The bronchodilator tablet (carbuterol 2 mg, or fenoterol 2.5 mg, or hexoprenaline 1 mg) was then administered by a single-blind method in a randomized order. The measurements described above were repeated, in the same order, after 30 minutes, 45 minutes, 1 hour and hourly thereafter for a further 7 hours. The investigation was continued either for the full 8-hour period or until the timed vital capacity had returned to within 15% of the baseline value. The three different agents were assessed at a minimum of weekly intervals and each patient was started at approximately the same level of predicted timed vital capacity in order to provide a meaningful comparison of responses.

Aerosol Administration

Four patients fulfilling the same criteria for allergic asthma as described above and with previously objectively documented responses to exercise were studied. The group consisted of 3 men and 1 woman, mean age 20.3 years (17 - 40 years). A technique similar to that described by Fitch and Godfrey to induce bronchospasm after exercise was utilized. This response was then used as a model to test the efficacy of aerosol-administered bronchodilators to inhibit or modify bronchospasm induced by exercise. The patients were all exercised at the same time of the day and a test was undertaken only if the initial peak expiratory flow (PEF) was greater than 80% of the predicted value for that patient. After the patient had reached the basal state a flow volume curve was measured, and on the control day exercise on a treadmill was continued for 6 minutes at a 10% gradient and a previously determined speed to produce a cardiac frequency of 160/min. During the exercise, PEF (Pneumotachograph; Erich Jaeger) was measured at 1-minute intervals, and
after cessation of exercise at 1-minute intervals for 4 minutes and then again at 10 minutes. During the test days an aerosol of carbuterol (2 puffs = 200 μg), hexoprenaline (2 puffs = 200 μg) and fenoterol (2 puffs = 400 μg) was administered sequentially at weekly intervals to all 4 patients after a control volume curve had been recorded. Fifteen minutes after this, another flow volume curve was recorded. Exercise as described above was then commenced. Most attention was paid to the PEF because this measurement has been shown to parallel derivatives of the vital capacity or airway resistance. On the control day the measurements of PEF were expressed as a percentage of the initial value. On the test days, after it had been ascertained that the subjects had a PEF of greater than 80% of the predicted value, the bronchodilator was administered and the measurement repeated 15 minutes later. All subsequent measurements of PEF were expressed as a percentage of this latter measurement.

Statistical analysis of the results in Table II was carried out by the paired t test analysis. All three drugs were compared with each other at the times tested as well as each test value compared with the control value. A χ² test was applied to the data in Table I. The aim of this analysis was to assess any significant differences in the proportion of patients in whom the drugs were still effective after 6 and 7 hours.

RESULTS

Tablet Administration

Two derivatives from the flow volume curve, namely the forced expiratory volume in 1 second (FEV₁) (Fig. 1) and maximal expiratory flow at 50% of forced vital capacity (MEF₅₀) (Fig. 2), illustrate the responses produced by the three orally administered bronchodilators. All three drugs have a sustained bronchodilator action which is significant. However, two points emerge and are illustrated in Tables I and II.

Table 1 shows that a greater number of the patients who had taken carbuterol remained in the study after a period of 4 hours compared with those who had taken either fenoterol or hexoprenaline. The χ² test shows that at 6 hours there is a significantly greater proportion of patients in the carbuterol group than in either of the other two groups (P<0.05). At 7 hours there is no significant difference, but a similar trend is apparent, on inspection of the data, at 7 and 8 hours. Table II shows that carbuterol and fenoterol produced a statistically significant degree of bronchodilatation for 7-8 hours, whereas hexoprenaline results in a statistically significant response for 4 hours when judged on the criterion of FEV₁ change. The response of the MEF₅₀ was similar in carbuterol and fenoterol, both of which exhibited a statistically significant longer period of action than did hexoprenaline. The discrepancy in the duration of activity when the MEF₅₀ and FEV₁ are compared may be due to the fact that the former is a measure of small airway function and is more sensitive to minor fluctuations, whereas the FEV₁ is physiologically a less sensitive measurement and reflects an overall index of air flow obstruction.

The effects of the three drugs on cardiac frequency and systolic and diastolic blood pressure are shown in Figs 3-5. In the doses administered none of the three agents exerted a significant effect on the cardiovascular system. The small fluctuations are not statistically significant. The drop in cardiac frequency associated with hexoprenaline

<table>
<thead>
<tr>
<th>TABLE I. NUMBER OF PATIENTS REMAINING AT EACH TEST PERIOD*</th>
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<tr>
<td></td>
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<tr>
<td>Hexoprenaline</td>
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<tr>
<td>Fenoterol</td>
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<tr>
<td>Carbuterol</td>
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* The test was discontinued when the FEV₁ fell to within 15% of the baseline value.
TABLE II. PERCENTAGE PREDICTED FEV\textsubscript{10} AND MEF\textsubscript{50} FOR EACH TEST PERIOD (MEAN AND STANDARD DEVIATION)

<table>
<thead>
<tr>
<th>Test Period</th>
<th>Baseline</th>
<th>30 min</th>
<th>1 h</th>
<th>2 h</th>
<th>3 h</th>
<th>4 h</th>
<th>5 h</th>
<th>6 h</th>
<th>7 h</th>
<th>8 h</th>
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<tbody>
<tr>
<td>Hexoprenaline</td>
<td>47.6 (15.5)</td>
<td>63.1 (25.3)</td>
<td>66.7 (27.5)</td>
<td>73.2 (28.5)</td>
<td>73.0 (26.5)</td>
<td>73.1 (24.7)</td>
<td>73.2 (24.7)</td>
<td>73.4 (24.7)</td>
<td>73.4 (24.7)</td>
<td>73.4 (24.7)</td>
</tr>
<tr>
<td>MEF\textsubscript{50}</td>
<td>20.4 (10.2)</td>
<td>40.4 (28.9)</td>
<td>51.4 (49.3)</td>
<td>59.0 (48.4)</td>
<td>58.1 (47.1)</td>
<td>55.4 (41.4)</td>
<td>54.5 (41.4)</td>
<td>54.4 (41.4)</td>
<td>54.4 (41.4)</td>
<td>54.4 (41.4)</td>
</tr>
<tr>
<td>Fenoterol</td>
<td>55.5 (8.9)</td>
<td>62.4 (15.1)</td>
<td>68.3 (17.8)</td>
<td>71.4 (20.7)</td>
<td>73.3 (18.4)</td>
<td>77.3 (16.4)</td>
<td>75.3 (16.4)</td>
<td>74.6 (12.7)</td>
<td>76.1 (12.7)</td>
<td>76.8 (12.7)</td>
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<tr>
<td>MEF\textsubscript{50}</td>
<td>27.5 (9.7)</td>
<td>38.3 (18.9)</td>
<td>42.6 (27.7)</td>
<td>48.0 (26.6)</td>
<td>51.5 (29.0)</td>
<td>54.5 (28.6)</td>
<td>47.3 (28.6)</td>
<td>43.6 (23.8)</td>
<td>43.6 (23.8)</td>
<td>43.6 (23.8)</td>
</tr>
<tr>
<td>Carbuterol</td>
<td>53.1 (14.6)</td>
<td>57.3 (16.8)</td>
<td>62.0 (12.5)</td>
<td>65.0 (10.1)</td>
<td>79.9 (12.2)</td>
<td>81.0 (15.8)</td>
<td>76.0 (17.2)</td>
<td>58.6 (34.0)</td>
<td>49.3 (44.5)</td>
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<tr>
<td>MEF\textsubscript{50}</td>
<td>28.4 (11.9)</td>
<td>33.0 (16.7)</td>
<td>37.1 (16.4)</td>
<td>40.4 (13.7)</td>
<td>62.5 (28.6)</td>
<td>62.5 (28.6)</td>
<td>62.5 (28.6)</td>
<td>43.6 (23.8)</td>
<td>43.6 (23.8)</td>
<td>43.6 (23.8)</td>
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* Statistically significant (P<0.05) improvement when value is compared with baseline value.

Fig. 3. The mean absolute change in cardiac frequency.

Fig. 4. The mean absolute change in systolic blood pressure.

Fig. 5. The mean absolute change in diastolic blood pressure.

represents data on only 2 patients. Tremor was not observed after any of the three agents.

Aerosol Administration

The changes produced in the PEF by exercise in 4 subjects are illustrated in Fig. 6. On the control day, PEF rose during the period of exercise and then decreased rapidly in the first few minutes of the recovery period, as has been previously described. The responses on the test days show that both carbuterol and fenoterol give
approximately the same degree of protection against exercise-induced bronchospasm, whereas the response to hexoprenaline is not much different from that on the control day. No statistical analysis was applied to these results because of the small number of subjects involved. However, inspection shows that at the end of 10 minutes carbuterol and fenoterol aerosol prevented the PEF from falling below 78% and 89% of the resting value respectively, whereas the value after the hexoprenaline inhaler was 63% compared with 64% on the control day.

Fig. 6. The mean PEF response of 4 asthmatic patients to exercise with and without prophylactic bronchodilator aerosol inhalation.

**DISCUSSION**

A direct comparison of the newer β₂-adrenoceptor stimulant bronchodilators reported in the literature is difficult, for very few authors compare a wide spectrum of agents during an investigation. However, in a study of adult asthmatics, carbuterol aerosol has been shown to be more effective than isoproterenol aerosol over a period of 10 days as well as over a period of 6 months. In children tested over a 5-day period there was a less striking difference between the two drugs. By the oral route, carbuterol was shown to be more potent than orciprenaline, salbutamol and terbutaline. This study also illustrated that carbuterol was in some respects superior to fenoterol. A double-blind single-dose cross-over trial at dosage levels of 2 and 4 mg for both carbuterol and salbutamol showed the former to be slightly more active than the latter. This investigation indicated that the side-effects of tachycardia and tremor were slightly more pronounced with 4 mg carbuterol than with salbutamol. Finally, as regards side-effects, carbuterol did not produce any unwanted alterations in blood gases at the 4-mg dosage level. Several of the abovementioned investigations have indicated that orally administered carbuterol has a bronchodilating action which lasts more than 4 hours.

The main purpose of this article is to report the efficacy and duration of action of carbuterol and to compare these properties with two accepted and established selective β₂-adrenoceptor agonists, fenoterol and hexoprenaline. The results of the investigation indicated that both carbuterol and fenoterol produced a statistically significant bronchodilatation for longer periods of time than did hexoprenaline (Table II). However, 2 patients showed a prolonged response to hexoprenaline, although this was not statistically significant. These data are similar to those reported in another study, which showed that oral hexoprenaline acted for no longer than 4 hours, but that fenoterol acted for at least 6 hours. In our study there was very little difference between carbuterol and fenoterol, which lowered airway resistance significantly for 7 and 8 hours respectively. Carbuterol, however, was active in a greater number of patients over a longer period than either fenoterol or hexoprenaline (Table I).

If the above points are taken into consideration, carbuterol exhibits a bronchodilating action which is equipotent with that of fenoterol. At one point, viz. 3 hours, carbuterol was statistically superior (P<0.05) to both fenoterol and hexoprenaline. This difference was not apparent at other times. As fenoterol has been described as the 'bronchodilator of choice in the world', the comparable performance by carbuterol in the present study attests to its efficacy when it is given orally. An additional point to mention is the activity of the drugs tested on the small airways, as indicated by the improvement in the MEF₆₅ (Fig. 2).

Exercise-induced asthma is troublesome in many asthmatic patients. For this reason, we chose this model to test the efficacy of the aerosols of carbuterol, fenoterol and hexoprenaline. On inspection, Fig. 6 shows that carbuterol and fenoterol are approximately equipotent in preventing exercise-induced asthma. No statistical analysis was done because of the small number of patients involved.

Side-effects were closely monitored and Figs 3-5 show that neither cardiac frequency nor blood pressure changed significantly during the 8-hour test period.

**CONCLUSION**

The direct comparison of different bronchodilators is difficult because of the lack of information on comparable dosage schemes, as well as the day-to-day variation in the responses of asthmatic patients. In addition, the fate of the drug in the body, viz. its absorption, metabolism and excretion, may vary from compound to compound. Furthermore, the slightly different dosage levels used in the current investigation may have led to the differences in response. As far as possible, recommended dosage schedules were followed. The exception to this was the dose of hexoprenaline; personal experience indicated that the oral dose of 0.5 mg was insufficient and thus 1 mg was used. In the case of the inhalers, the dose of fenoterol was double that of either carbuterol or hexoprenaline and this may have led to differences in response. However, despite these difficulties this investigation has indicated that carbuterol possesses a bronchodilating efficacy which is equivalent to that of fenoterol in respect of potency and duration of response. In comparison with hexoprenaline the efficacy of carbuterol is once again equivalent, but the latter possesses a more prolonged period of activity.
Side-effects were not a troublesome feature. In conclusion it can thus be said that carbuterol in tablet form is an effective, long-acting bronchodilator which is free of side-effects in the dosages administered. The aerosol of carbuterol has been demonstrated to be as effective as fenoterol in preventing exercise-induced bronchospasm.

We thank Mrs E. Anderson and Mrs M. Moore for technical assistance, and Miss D. Dawidowitz for her assistance in preparing the manuscript. We are indebted to the Director of Hospital Services of the Transvaal Provincial Administration, Dr H. A. Grove, for permission to perform this study. We also thank Dr F. Lombard of the Department of Statistics, Rand Afrikaans University, for performing the statistical analyses.

REFERENCES


The High Rugby Tackle – an Avoidable Cause of Cervical Spinal Injury?

A. T. SCHER

SUMMARY

The type and circumstances of injury to 14 rugby players with cervical spinal cord damage sustained during a tackle have been analysed. Two specific mechanisms of injury were evident. Four players were injured when their heads collided with fixed objects while they were attempting to tackle an opponent. Ten players were injured while being tackled and 5 of them were tackled around the neck. The risk of trauma to the cervical spine caused by the force applied to the neck in a high tackle is discussed. The susceptibility of the ligaments of the cervical spine to the rotational force exerted during a high tackle is stressed. An amendment to the rules of rugby, which would reduce cervical trauma, is suggested.


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Date received: 30 January 1978.

Most rugby injuries to the cervical spinal cord are sustained during either a scrum or a tackle. A previous analysis has shown that a specific mechanism of injury causes scrum injuries to the cervical spine. This mechanism is a combination of flexion and rotational forces which occurs when the scrum collapses, the front row players being exposed to the greatest risk (Fig. 1).

No single mechanism of injury has been shown to be responsible for injuries to the cervical spinal cord sustained during a tackle. Patients recently admitted to the Spinal Injuries Unit have provided us with additional clinical material. Correlation of the orthopaedic injuries sustained and the player's description of how these injuries were caused indicates that specific mechanisms of injury are responsible for some tackle injuries to the cervical spine. These mechanisms will be considered in further detail.

PATIENTS

Twenty-six players with cervical spinal cord injuries sustained during rugby matches have been admitted to the Unit since 1964. Nine of these players were injured in