Intravenous prednisolone in chronic bronchial asthma

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Ellul-Micallef, R. and Fenech, F. F. (1975). Thorax, 30, 312–315. Intravenous prednisolone in chronic bronchial asthma. A single injection of 40 mg prednisolone phosphate was given to 10 patients with chronic bronchial asthma. Changes in pulmonary function were followed over a 30-hour period. Statistically significant changes occurred in the tests employed one hour after the injection of prednisolone. The maximum change for the group as a whole was seen to occur after eight hours. This time course of response is very similar to that obtained in previous studies on similar groups of patients with oral prednisolone where the peak effect occurred nine hours after the drug had been given. Intravenous hydrocortisone produces a much earlier peak effect, at five hours, when it is administered to chronic asthmatic patients.

Although corticosteroids have been used in the treatment of bronchial asthma for over 20 years (Carrer et al., 1950), little is yet known with any certainty of the possible modes of action of corticosteroids or even of the precise site where they act in this condition. The time course of response to oral prednisolone and to intravenous hydrocortisone in chronic bronchial asthma has only recently been worked out (Ellul-Micallef, Borthwick, and McHardy, 1972; 1974). Various time intervals, mostly based on clinical impressions, ranging from two hours (Cope, 1972) to 48 hours (Herxheimer, 1966) had previously been suggested.

It has been found that a statistically significant improvement (P<0.001) in the peak expiratory flow rate (PEFR) occurred two hours after 40 mg of prednisolone acetate were given orally in a single dose in a group of patients with chronic bronchial asthma. The maximum change in pulmonary function variables measured occurred nine hours after the drug had been given, and these changes ceased to be statistically significant at 36 hours. When 200 mg of hydrocortisone sodium succinate were injected intravenously the mean change in PEFR was significantly increased (P<0.05) one hour after the injection, the peak effect being attained in five hours. The mean change in PEFR was no longer significant 12 hours after hydrocortisone had been administered; the maximum change in PEFR following oral prednisolone was 57%±8.5 and that due to intravenous hydrocortisone 51%±8.0 of the initial pre-treatment values (Ellul-Micallef et al., 1972; 1974).

This difference in the time course of the two corticosteroids was thought to be due mainly to two causes—to the different routes of administration used and to the fact that the two drugs are known to be metabolized at different rates. The purpose of the present work was to find out what happened when prednisolone was administered intravenously to patients with chronic bronchial asthma, in an attempt to discover which of these two causes contributed most to the different time course of response.

MATERIALS AND METHODS

Fifteen patients who were diagnosed clinically as suffering from chronic bronchial asthma, here defined as a condition in which widespread reversible airway obstruction is present for a prolonged period with or without brief spontaneous remissions, gave informed consent to their participation.

Ten of the fifteen managed to complete the clinical trial; two others improved spontaneously on hospital admission and the remaining three developed acute asthma. The relevant anthropomorphic and clinical information for the ten

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patients is summarized in the Table. Their airway obstruction had failed to respond to bronchodilator drugs, and they were finding it increasingly difficult to cope with their work but were reasonably comfortable in bed. They were admitted to hospital to determine whether their condition could be reversed by corticosteroid therapy. None of the patients had received corticosteroids before. No other drugs were given besides the test doses of corticosteroids, and as far as can be ascertained none had been receiving drugs capable of interfering with corticosteroid metabolism prior to their admission to hospital (Jubiz et al., 1970; Brooks et al., 1972).

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Height (m)</th>
<th>Duration of Disease (yr)</th>
<th>Initial FEV₁ (ml)</th>
<th>Predicted FEV₁ (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>38</td>
<td>F</td>
<td>1.53</td>
<td>12</td>
<td>1350</td>
<td>2700</td>
</tr>
<tr>
<td>2</td>
<td>53</td>
<td>M</td>
<td>1.52</td>
<td>6</td>
<td>950</td>
<td>2600</td>
</tr>
<tr>
<td>3</td>
<td>42</td>
<td>F</td>
<td>1.68</td>
<td>24</td>
<td>1900</td>
<td>2700</td>
</tr>
<tr>
<td>4</td>
<td>21</td>
<td>M</td>
<td>1.64</td>
<td>4</td>
<td>2450</td>
<td>3900</td>
</tr>
<tr>
<td>5</td>
<td>13</td>
<td>M</td>
<td>1.26</td>
<td>5</td>
<td>900</td>
<td>1600</td>
</tr>
<tr>
<td>6</td>
<td>26</td>
<td>M</td>
<td>1.63</td>
<td>15</td>
<td>2050</td>
<td>3700</td>
</tr>
<tr>
<td>7</td>
<td>55</td>
<td>F</td>
<td>1.42</td>
<td>7</td>
<td>1200</td>
<td>1700</td>
</tr>
<tr>
<td>8</td>
<td>12</td>
<td>M</td>
<td>1.30</td>
<td>6</td>
<td>1050</td>
<td>1700</td>
</tr>
<tr>
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<td>18</td>
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<td>1.54</td>
<td>8</td>
<td>1150</td>
<td>2700</td>
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<tr>
<td>10</td>
<td>15</td>
<td>F</td>
<td>1.28</td>
<td>10</td>
<td>1050</td>
<td>1600</td>
</tr>
</tbody>
</table>

The study was conducted over four days. Placebo injections of normal saline were given at 0900 hours on the first two days of the trial in order to obtain repeated pre-treatment baseline measurements and to make certain that the patients were in a stable clinical state. On the third day 40 mg of prednisolone phosphate was administered as a single intravenous injection. Measurements of ventilatory function were made at 0800 hours and hourly each day till 2100 hours, with a gap of three hours at lunchtime.

Measurements of the forced expiratory volume in one second (FEV₁) and the forced vital capacity (FVC) were recorded by means of a dry wedge spirometer (Vitalograph Ltd.), while peak expiratory flow rate was measured with a Wright’s peak flow meter (Wright and McKerrow, 1959). The forced expiratory time was measured by placing a stethoscope on the posterior chest wall well above the diaphragm while the patient performed a forced expiration from a position of maximum inspiration and timing the procedure with a stopwatch from the first expiratory sound to the last (Rosenblatt and Stein, 1962). The best of three successive, technically acceptable attempts was chosen (Freedman and Prowse, 1966). Statistical significance was tested in all instances by means of Student’s t test (Snedecor and Cochran, 1971).

RESULTS

All the patients were screened for respiratory tract infection, all having three sputum specimens negative on culture for ordinary pathogens and sputum which was macroscopically mucoid. The radiographic examination of the chest showed some evidence of hyperinflation but was otherwise normal, as was the electrocardiogram. There was no clinical nor biochemical evidence of hepatic or renal dysfunction. Six patients (Nos. 3, 4, 5, 8, 9 and 10) were extrinsic asthmatics, having blood and sputum eosinophilia and showing positive skin reactions to a wide variety of allergens.

No significant day to day or diurnal variation was observed nor could any response to the placebo injections be demonstrated within either individuals or the group as a whole, although minor fluctuations in the different variables measured could be observed during the placebo days. These fluctuations were not however significantly different from the immediate pre-treatment values. The results obtained following the injection of prednisolone have therefore been compared with those measurements obtained immediately before drug administration. In order to reduce the effect of individual variation all measurements were expressed as a percentage of the pre-treatment value.

The injection of prednisolone produced consistent changes in each patient in FEV₁, FVC, PEFR, and FET at the time of their first measurement, one hour after drug administration. This increase was statistically significant for the group as a whole (P<0.001; P<0.05; P<0.001; P<0.025). The peak effect occurred at eight hours (Figures 1–4) and the changes were still significant after 30 hours. The pre-treatment range of FET was 6.0–11.5 sec, with a mean of 8.2 sec±1.6 sec. Forced expiratory time correlated well with FEV₁ (r=0.87), FVC (r=0.82), and PEFR (r=0.86).

DISCUSSION

The time course of intravenous prednisolone appears to be very similar to that of oral prednisolone in the chronic asthmatic patients studied. The different time course of response of oral prednisolone and intravenous hydrocortisone
In normal subjects prednisolone has a plasma halflife of about 240 minutes, while hydrocortisone has one of between 80 and 100 minutes (Peterson, 1959). Collins et al. (1970) failed to find any statistically significant difference in the handling of intravenous hydrocortisone between normal subjects and asthmatic patients. It would appear that oral prednisolone is very rapidly absorbed in patients with chronic bronchial asthma just as it is in normal subjects. It appears that the response to corticosteroids varies with the severity of the asthmatic condition (unpublished data). The time course of response to corticosteroids reported in this study was obtained in chronic bronchial asthmatics with a stable degree of airway obstruction and may not apply to the acute state.

FIG. 1. Effect of a single intravenous injection of 40 mg prednisolone phosphate on forced expiratory volume in 1 second in 10 asthmatic patients. Group mean values ±SEM are plotted against time after prednisolone administration and are expressed as percentages of the immediate pre-treatment values.

FIG. 2. Effect of a single intravenous injection of 40 mg prednisolone phosphate on forced vital capacity. Group mean values ±SEM are shown for 10 patients.

originally reported seems not to be due mainly to the different routes of administration used but very probably to the different ways in which the two drugs were handled metabolically, in particular to the different rates of their metabolic breakdown. It is known that the absorption of corticosteroids and their biological activity are not necessarily directly related (Schedl, 1965). Thus triamcinolone, which is a very poorly absorbed compound, seems to be well enough absorbed from the small intestine to be active in the clinical situation. It appears likely that in these patients it is the longer persistence in the plasma of free unconjugated prednisolone which accounts for its longer activity.

FIG. 3. Effect of a single intravenous injection of 40 mg prednisolone phosphate on peak flow rate. Group mean values ±SEM are shown for 10 patients.

FIG. 4. Effect of a single intravenous injection of 40 mg prednisolone phosphate on forced expiratory time. Group mean values ±SEM are shown for 10 patients.
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There is no definite answer at present as to which is the best pulmonary function test to perform in order to detect and be able to evaluate changes occurring in response to therapy in bronchial asthma. In general one must consider factors of motivation, training, and fatigue in assessing results of individual patients. It has been shown that simple tests of pulmonary function, if properly carried out, are equally as useful in monitoring changes in chronic asthmatic patients following corticosteroid therapy as more sophisticated tests, such as body plethysmography (Ellul-Micallef, 1972). In this study objective evidence of improvement in bronchial asthma has been obtained on the ward using a simple stethoscope and a stopwatch, measuring FET. The unavailability of sophisticated equipment should not therefore deter one from carrying out proper objective assessment in bronchial asthma.

We thank Professor W. H. Bannister for valued help in the preparation of this paper.

REFERENCES


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