

## Interaction of corticosteroids and catecholamines in the treatment of asthma

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**Shenfield, Gillian M., Hodson, Margaret E., Clarke, S. W., and Paterson, J. W. (1975).** *Thorax*, 30, 430–435. **Interaction of corticosteroids and catecholamines in the treatment of asthma.** Twelve patients with airways obstruction (due to asthma and/or chronic bronchitis) were given a trial of prednisone therapy to assess reversibility. Six asthmatic patients responded well but no predictive criteria were found. In three patients improvement in forced expiratory volume in 1 second (FEV<sub>1</sub>) was detectable at 6 hours but not at 3 hours. One patient took 36 hours to show any sign of improvement. None of the patients who improved reached their peak FEV<sub>1</sub> before six days treatment with prednisone, which suggests that a 'trial of steroids' should last for at least one week.

Potentialiation, as measured by either a greater peak rise or a more sustained increase in FEV<sub>1</sub> after isoprenaline, was observed in five of the six asthmatic patients responding to steroids.

It is concluded that potentialiation of catecholamines is one of the mechanisms by which corticosteroids may act in asthma.

Corticosteroids have been used to treat asthma since Carryer *et al.* (1950) showed that intramuscular cortisone was effective in three patients. Their mode of action is still not known. Several theories have been proposed and have been reviewed by Aviado and Carrillo (1970). Their actions at cellular level have been discussed by Baxter and Forsham (1972), and Feldman, Funder, and Edelman (1972). Schayer (1964) proposed a single action for all glucocorticoids but it is more probable that they produce their therapeutic effect by several different mechanisms. One of these may be the potentialiation of the actions of both endogenous and exogenous catecholamines. Kennedy (1961) published records of a series of asthmatic patients, three of whom showed a clear increase in their response to isoprenaline when they were on corticosteroids. Franklin *et al.* (1958) studied 58 patients with 'obstructive pulmonary emphysema' and found that, in general, the increase in vital capacity after inhaled isoprenaline was greater when the patients were on corticosteroids. However, not all their patients showed this pattern of response. Lukas (1951) also described one patient who showed such potentialiation

on ACTH. Bass (1972) claimed that responses to isoprenaline were greater without than with corticosteroids.

In view of this conflicting evidence we decided to record the response to isoprenaline in a group of patients receiving a trial of steroid therapy.

### METHODS

Fourteen patients were studied initially but two were withdrawn from the series, one because of deterioration necessitating treatment with intravenous hydrocortisone, and the other because of poor reproducibility of pulmonary function tests. Details of the 12 remaining patients are given in Table I. Patients were considered to have extrinsic asthma if they had positive skin tests to more than one common allergen. All were admitted with deteriorating airways obstruction for a trial of corticosteroid treatment. None was ill enough to need intravenous hydrocortisone. Before starting the study it was established that the patients knew how to use a pressurized aerosol and a dry spirometer (Vitalograph). All of them were on oral bronchodilator drugs, and these were taken at 6 am and after the lunchtime

TABLE I

Patient	Age and Sex	Diagnosis	Length of History (yr)	Previous Steroids	Other Treatment
AC	57 M	Intrinsic asthma	2	No	Oral salbutamol
MB	36 F	Extrinsic asthma	27	No	Oral orciprenaline
BB	47 F	Intrinsic asthma	24	On 5 mg bd 15 yr	Oral salbutamol
VM	52 F	Extrinsic asthma	12	No	Oral salbutamol
MaB	51 F	Intrinsic asthma	2	No	Oral Franol Oxytetracycline
MN	48 F	Intrinsic asthma	0.25	No	Oral salbutamol Oxytetracycline
DW	59 M	Intrinsic asthma	1.5	On 5 mg bd 1 yr	Oral salbutamol
JA	67 M	Bronchitis Emphysema	15	Short course 1 yr before	Amesec
CC	61 M	Bronchitis Emphysema	14	No	Oral salbutamol Frusemide Oxytetracycline
FD	70 M	Extrinsic asthma Bronchitis	65	No	Oral salbutamol Frusemide Oxytetracycline
BH	67 M	Bronchitis	15	No	Tolbutamide Oral salbutamol Frusemide
DB	66 F	Intrinsic asthma Bronchitis	12	No	Ampicillin Oral salbutamol

and evening measurements had been made. No aerosol bronchodilators were allowed at times other than the study sessions. When practical, baseline measurements were made throughout one day before starting prednisone but in some patients only one or two baseline sessions were possible. The dose of prednisone was started at 40 mg above the previous dose so that most patients received 40 mg, but patients BB and DW had 50 mg a day. This was given in four divided doses: at 6 am, after the lunchtime and evening measurements, and at 10 pm.

The patients were studied three times a day: between 8.30 and 9.30 am, between 12.30 and 1.30 pm, and between 5 and 6 pm. In each test period, baseline measurements were made of pulse rate, forced expiratory volume in 1 second (FEV<sub>1</sub>), and forced vital capacity (FVC). The patients then took two puffs from an isoprenaline inhaler (Medihaler Iso containing 100 µg isoprenaline sulphate per puff). At intervals of 5, 15, and 30 minutes after the inhalation measurements of pulse rate, FEV<sub>1</sub> and FVC were repeated. On every occasion the patients blew into the spirometer three times, and the best of the three readings were taken, as recommended by Pemberton and Flanagan (1956) and Freedman and Prowse (1966). For each individual patient, the same Medihaler was used throughout the studies, and all observations were made by the same two observers (MEH and GMS). The measurements

were repeated on seven consecutive days after the start of prednisone treatment.

#### RESULTS

Response to prednisone was judged by the patient's subjective feeling and an improvement in both exercise tolerance and pulmonary function tests over the seven days (Table II). Using these criteria, the first six patients were judged to have improved on prednisone; the other six patients were considered as 'failures', and the prednisone was stopped. Results were analysed in terms of FEV<sub>1</sub>, since FVC proved to be more effort-dependent and less reproducible. This is shown in Fig. 1 (patient CC—a failure), which also illustrates the reproducibility of the FEV<sub>1</sub> response. On each occasion the baseline FEV<sub>1</sub> and FVC and the level reached 5 minutes after two puffs of isoprenaline are shown. It can be seen that, in terms of FEV<sub>1</sub>, there was no improvement on prednisone either before or after isoprenaline.

In Table II the baseline FEV<sub>1</sub> is the best of three obtained at the first study. The improvement in FEV<sub>1</sub> expressed as a percentage of the predicted FEV<sub>1</sub>, is striking in the first six patients (Table II). For these 'responding' patients the best FEV<sub>1</sub> was not reached for a minimum of six days. In the non-responding group three achieved their best FEV<sub>1</sub> on the first day, indicating if anything deterioration on steroids. The other three were at their best later in the study but the maximum

TABLE II

Patient	Predicted FEV <sub>1</sub> (litres)	Baseline FEV <sub>1</sub> (litres)	% Predicted	Best FEV <sub>1</sub> * (litres)	% Predicted	No. of Days on Steroids for Maximum FEV <sub>1</sub> Response
AC	3.1	1.2	39	1.85	60	7
MB	2.3	1.15	50	2.0	87	7
BB	2.1	0.8	38	2.2	105	7
VM	2.4	0.65	27	1.85	77	7
MaB	2.4	0.75	31	2.2	92	7
MN	1.9	1.1	58	2.85	150	6
DW	2.5	0.85	34	1.05	42	1
JA	2.8	0.6	21	0.7	25	7
CC	3.4	0.6	18	0.7	21	5
FD	2.1	0.4	19	0.55	26	2
BH	2.1	0.35	17	0.4	19	1
DB	1.9	0.5	26	0.7	37	1

\*Before isoprenaline.

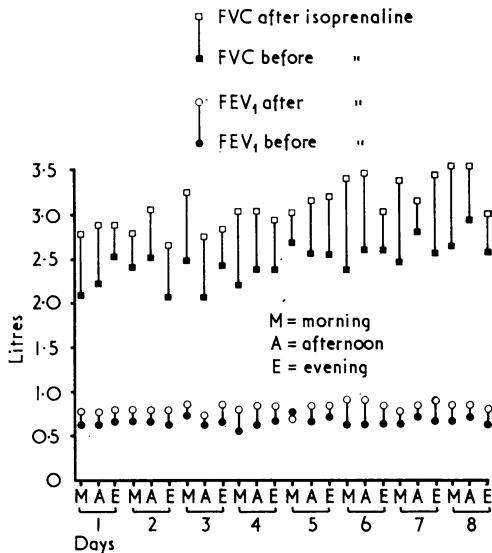


FIG. 1. Patient CC. Effect of prednisone treatment, as measured by forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV<sub>1</sub>) and the response to isoprenaline.

improvement in FEV<sub>1</sub> whilst on steroids was only 0.15 litres (19–26% predicted normal).

The remaining analysis of results was done with the first six patients who responded to prednisone, and the FEV<sub>1</sub> 5 minutes after isoprenaline was studied.

Figure 2 shows the FEV<sub>1</sub> response in these six patients divided into three daily periods to eliminate the effects of diurnal variation. When plotted in this way all the patients showed some potentiation. This was very consistent with AC and BB. With MN and MB the response varied, and with MaB potentiation was best seen in the evenings in the second half of the study, whereas

with VM the best potentiation was seen in the mornings.

For all these results only the best of the 5-minute readings have been used. It seemed possible that potentiation might also be expressed in a maintenance of improvement over 30 minutes or in a maintenance of the three 'blows'. There are two main patterns of serial FEV<sub>1</sub> in patients with airways obstruction: either their best blow is the first and the effort causes bronchospasm with deterioration following the next two blows, or the efforts clear secretions and the final blow is the best. Each of the patients seemed to have his own pattern but corticosteroids in no way changed it. Thus in this respect there was no evidence of potentiation.

To obtain a numerical expression of the maintenance of improvement over the 30 minutes, results were expressed as:

$$\left[ \frac{\text{FEV}_1 \text{ at 5 min} - \text{FEV}_1 \text{ at 30 min}}{\text{FEV}_1 \text{ at 5 min} - \text{FEV}_1 \text{ at 0 min}} \times 100 \right] - 100$$

Thus 0% would indicate that at 30 minutes the measurements had fallen back to baseline values after the improvement at 5 minutes, and a high value indicates maintained improvement. Table III gives the mean results of the three percentages thus obtained for each day for all six patients. BB and VM clearly showed better maintenance of improvement after the baseline day. AC and MB kept much the same pattern throughout but maintained some of their improvement at 30 minutes even on their baseline day. MaB and MN did not improve at all overall on the baseline day, and the results are erratic, so that there is only definite evidence of potentiation in this respect in two patients, one of whom (VM) did not show potentiation as judged by an increased FEV<sub>1</sub> response.

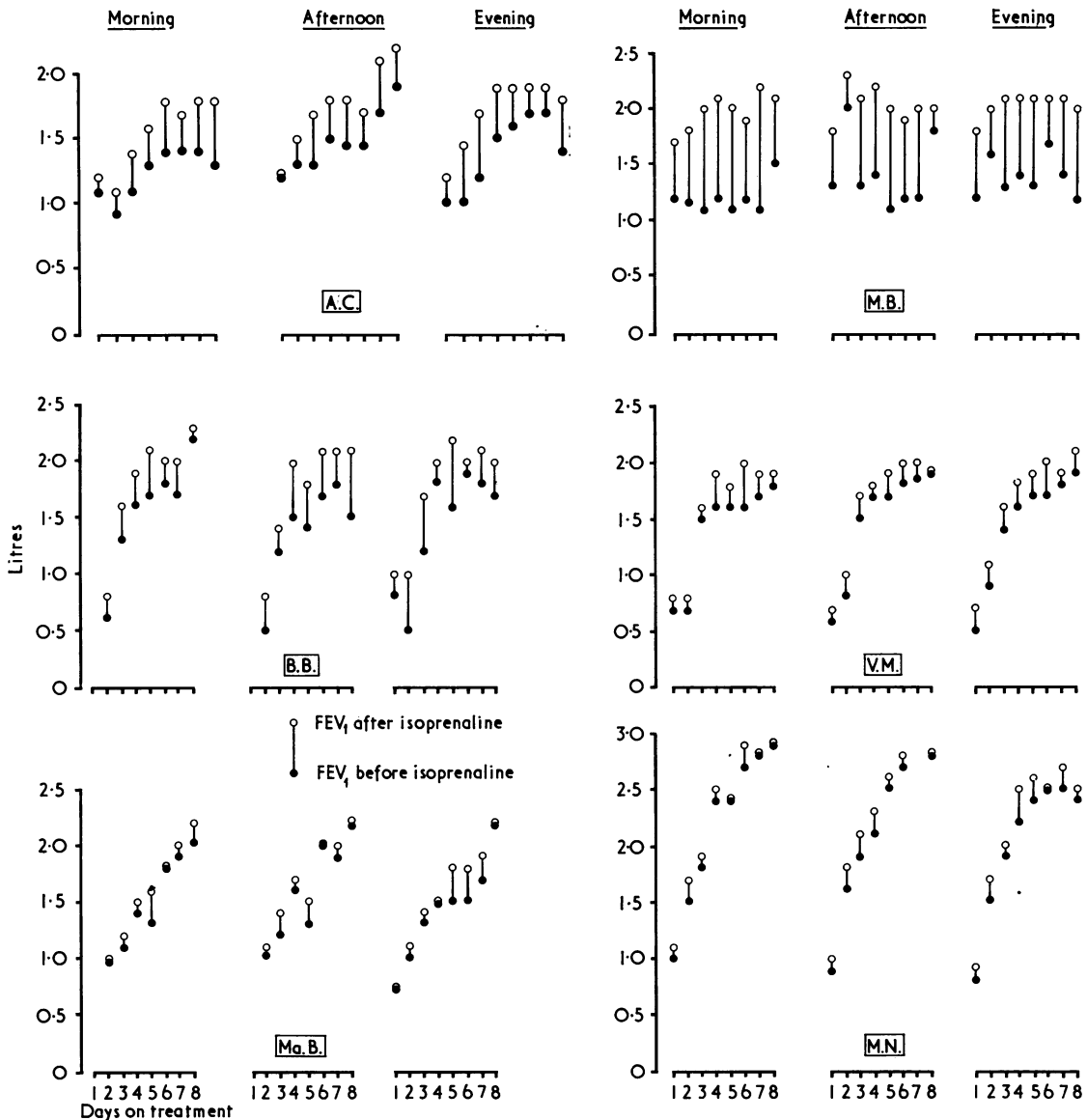


FIG. 2. Effect of prednisone treatment, as measured by forced expiratory volume in 1 second (FEV<sub>1</sub>) and the response to isoprenaline in six patients 'responding' to steroids.

These studies were not designed to find the time of onset of action of prednisone but some information was available. AC, MB, and VM all had a full day of baseline measurements and started their prednisone at 6 am the next morning. None had improved at 9 am but all showed a raised baseline FEV<sub>1</sub> at lunchtime (6 hours from the onset). MN started her prednisone at 4 pm on day 1 and MaB at 9 pm on day 1. Both had an

improved baseline by the 9 am measurements the next day (17 and 12 hours respectively). BB started her prednisone at 6 pm on the 'baseline' day but showed no improvement until 9 am, 36 hours later.

DISCUSSION

Of the nine patients with a clinical diagnosis of asthma, six showed a response to steroids. The

TABLE III

Patient	Baseline	Day						
		1	2	3	4	5	6	7
AC	83	90	90	95	70	86	69	100
MB	64	60	80	67	71	64	82	28
BB	0	28	5	93	76	81	59	31
VM	0	58	95	84	97	98	64	100
MaB	100	66	0	-33	13	83	-56	-33
MN	100	-51	83	47	-50	55	75	58

$$\left[ \frac{\text{FEV}_1 \text{ at 5 min} - \text{FEV}_1 \text{ at 30 min}}{\text{FEV}_1 \text{ at 5 min} - \text{FEV}_1 \text{ at 0 min}} \times 100 \right] - 100$$

patients who did not respond to steroids were older (mean 65; range 59 to 70 years) than those who did (mean 48; range 36 to 57 years), and five had chronic bronchitis.

Among the patients who did respond the time of first measurable improvement is interesting. Three patients had improved at 6 hours but not at 3 hours, and two between 0 and 17 hours or 0 and 12 hours. This differs from the findings of Ellul-Micallef, Borthwick, and McHardy (1972), who showed improvement one hour after administration of prednisone. Our finding of earliest response between 3 and 6 hours corresponds with that of Collins (personal communication) who found improvement at about 6 hours after giving intravenous hydrocortisone. One of our patients showed no response until 36 hours; thus any 'trial' of steroids should continue for a minimum of 36 to 48 hours. None of the responsive patients reached their best FEV<sub>1</sub> until they had been on prednisone for six days, which would support the principle of a week's trial.

All of our steroid-responsive patients, while on prednisone, showed some potentiation of their response to isoprenaline, as defined by an increased increment in FEV<sub>1</sub> and/or a maintenance of the improvement for 30 minutes. Interestingly, the patient who showed the latter phenomenon most convincingly had the least evidence of potentiation, as judged by an increased FEV<sub>1</sub> response. We have shown that potentiation occurs but is not invariable. This is in keeping with the findings of Franklin *et al.* (1958). Kennedy (1961), Gregg (1969), and Lukas (1951) similarly showed potentiation in some patients although they did not discuss this particular finding. Bass (1972) claimed to find the opposite: less response to isoprenaline in patients on corticosteroids. Unfortunately his patients were on dexamethasone during their 'control' period, and neither the dose of dexamethasone nor of the subsequent ACTH or other steroid was stated.

Since potentiation can occur with isoprenaline it presumably can also occur with endogenous catecholamines, and this may be one of the ways in which corticosteroids work in asthma. There is considerable evidence of the potentiating effect of corticosteroids. Mendelowitz, Gitlow, and Naftchi (1958) studied four patients with Cushing's syndrome and 13 patients on therapeutic corticosteroids and showed that their noradrenaline sensitivity was increased. Animal experiments have shown potentiation of catecholamines by glucocorticoids in the isolated heart (Nasmyth, 1957), and in blood vessels (Fouler and Chou, 1961; Altura, 1966). Kalsner (1969) showed that only sympathomimetic amines with the catechol nucleus were potentiated.

Kalsner (1969) also suggested that hydrocortisone exerted its action by inhibiting catechol-O-methyl transferase, and it is known that inhibitors of this enzyme also inhibit the uptake of catecholamines into smooth muscle (Gillespie, 1973).

Exogenous catecholamines such as isoprenaline are partially inactivated by uptake into smooth muscle, and so inhibition of this process could well potentiate catecholamine action.

Patients with asthma may, of course, respond well to corticosteroids without showing potentiation (that is, an increased peak or duration of response to isoprenaline). Aviado and Carrillo (1970) have reviewed the other possible mechanisms of corticosteroid action. These include direct smooth muscle relaxation on bronchoconstricted rats and rabbits (Carrillo and Aviado, 1968; Aviado and Carrillo, 1969). Lefcoe (1956) also suggested that hydrocortisone had a direct action on the tracheal smooth muscle of guinea-pigs and cats, but Geddes and Lefcoe (1973) thought that the action was probably due to preservatives in the solutions used. Fouler and Chou (1961) and Altura (1966) found no direct action of corticosteroids in their preparations.

Other possible mechanisms are alteration of vascular permeability, anti-inflammatory, inhibition of antibody formation, and inhibition of histamine synthesis or storage: all have been reviewed by Aviado and Carrillo (1970). Modern views of corticosteroid action include induction of protein synthesis (Feldman *et al.*, 1972) which would perhaps explain immunological effects. Baxter and Forsham (1972) suggest that glucocorticoids bind to the cell nucleus, influencing RNA synthesis. Such subcellular mechanisms remain to be clarified, as do the interactions between catecholamines, corticosteroids, and

cyclic AMP (Anderson, Bergh, and Svedmyr, 1972; Breckenridge, 1970).

In summary, we have shown that potentiation occurs between prednisone and isoprenaline in asthmatic patients. However, it is unlikely to be the sole mechanism of corticosteroid action.

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