PREDNISOLONE COMPARED WITH CORTISONE IN TREATMENT OF CHILDREN WITH CHRONIC ASTHMA

BY

D. C. THURSBY-PELHAM, M.R.C.P., D.C.H.
Consultant Paediatrician, North Staffordshire Royal Infirmary, Stoke-on-Trent

AND

M. C. S. KENNEDY, M.R.C.S., L.R.C.P.
Medical Research Council Staff; Clinical Assistant in Respiratory Physiology, Stoke-on-Trent

In a previous investigation (Kennedy and Thursby-Pelham, 1956) we reported the effect of oral cortisone on the ventilatory function of children with chronic asthma. We have now completed a similar investigation using prednisolone, and the relative efficacy of the two drugs can be compared.

In the previous investigation 12 children who had asthma associated with poor ventilatory function were given a trial course of cortisone by mouth. The effects on the ventilatory function of each child were compared with those obtained with a similar course of placebo tablets. In the present investigation 12 children who had a trial course of cortisone six to nine months previously were given a similar course of prednisolone, using one-fifth of the dose of cortisone, and the results of the two treatment regimes are presented.

Present Investigation

Children Studied.—The 12 children selected from the asthma clinic for treatment with prednisolone had all had a controlled trial on cortisone. Six of these (Cases 37, 11, 26, 23, 44, and 62) were reported in our previous communication, and a further six had a similar trial at a later date. Only those children who could attend the clinic twice weekly and who would co-operate in the breathing tests were selected. There were 10 boys and 2 girls, whose ages ranged from 9 to 15 years. All had been under observation for not less than six months and had been found to have impaired ventilatory function between their acute attacks and when free from symptoms. Table I briefly summarizes the cases.

Method of Assessment.—As in the previous investigation, we have measured the expiratory flow rate over the first 0.75 second of expiration (E.F.R.[40]) as described by Kennedy (1953). This measure is an index of the maximum ventilatory capacity at the theoretical breathing rate of 40 breaths a minute. All the children attended the clinic twice weekly, and at each attendance the E.F.R.[40] was measured with a spirometer before and after a five-minute inhalation of adrenaline (1 in 1,000).

TABLE I.—*Summary of Children Studied (At the Beginning of the Investigation)*

Case No.	Sex and Age	Duration of Asthma (Years)	Approx. Frequency of Acute Attacks	History of Other Allergy	Predominant Type of Asthma	*
80	M 10	2	Weekly	None	Allergic + psychological	74%
5	M 14	13	3 a year	Infantile eczema	,, ,,	65%
78	M 13	13	4 ,, ,,	None	Allergic	44%
20	M 9	7	2–3 a year	Infantile eczema	Allergic + infective	51%
43	M 13	10	Monthly	Eczema, hay-fever	Allergic	49%
25	M 9	5	2–3 a month	Eczema	,,	72%
37	M 10	6	6 a year	None	,,	65%
23	M 12	11	6–9 a year	Eczema, hay-fever	Allergic + infective	59%
62	M 13	12	Monthly	None	,, ,,	42%
44	F 15	8	2–3 a month	Eczema	Allergic + psychological	27%
26	F 10	3	2–3 ,, ,,	Hay-fever	,, ,,	88%
31	M 13	3	Monthly	None	Allergic + infective	50%

* $\frac{\text{Mean E.F.R.}^{40}}{\text{Predicted normal E.F.R.}^{40}} \times 100$

Treatment Regime

Cortisone Trial.—Each course consisted of 100 tablets. The cortisone tablets were 25 mg. each, and the placebo tablets, which were indistinguishable from the cortisone, consisted of lactose with a trace of quinine. Dosage : five cases (Nos. 5, 78, 20, 43, and 25) received 75 mg. of cortisone daily for two weeks, followed by 62.5 mg. daily in divided doses for the rest of the course. Seven cases (Nos. 80, 31, 26, 23, 44, 62, and 37) received 75 mg. daily for two or three weeks and then 50 mg. daily in divided doses for the rest of the course.

Prednisolone Trial.—Prednisolone was prescribed as 5-mg. tablets. All the above cases had a course lasting six weeks. For the first three weeks the dose was 15 mg. of prednisolone daily (5 mg. t.d.s.), and for the remaining three weeks the dose was reduced to 10 mg. daily (5 mg. b.d.). 75 mg. of cortisone daily or 15 mg. of prednisolone daily are hereafter referred to as *full dosage*, as no higher doses were used in these trials. 62.5 mg. and 50 mg. of cortisone and 10 mg. of prednisolone are referred to as *reduced dosage*.

The courses of cortisone were preceded or followed by a course of placebo in a blind trial. The results showed variable amounts of improvement on cortisone, and it was noteworthy that none showed a better response to placebo. As the effects of suggestion were ruled out by this means, the course of placebo was not repeated in the prednisolone trial, which was compared with the readings obtained during the preceding two months, when the patients received no treatment except the adrenaline inhalations associated with the routine tests.

Symptomatic Results

The general effects produced by prednisolone therapy were similar to those produced by cortisone. During both trials all the children except two had a marked increase in appetite and weight. These two cases failed to gain weight while taking either prednisolone or cortisone. The rest showed weight increases of 2 to 10 lb. (0.9 to 4.5 kg.) on cortisone and 2 to 12 lb. (0.9 to 5.4 kg.) on prednisolone. The mean weight gain in both trials was 4 lb. (1.8 kg.). Both steroids produced a general increase in well-being and energy in all the cases.

Salt was not restricted during the prednisolone trial. The knowledge that sodium retention was unlikely to be produced by prednisolone encouraged us to continue the higher dose level for a longer period than with cortisone, though in fact neither oedema nor hypertension was observed during either treatment regime. Most of the 12 children studied were free from asthmatic symptoms, such as wheezing and coughing, while on full doses, though about half had symptoms while on reduced doses. On prednisolone, 15 mg. daily, only one child had asthmatic symptoms, whereas three had some symptoms recorded while on the equivalent dose of cortisone, 75 mg. daily. The number of children who were free of asthmatic symptoms during treatment with cortisone and with prednisolone are shown in Table II.

TABLE II

	No. in Trial	No. of Children Free of Asthmatic Symptoms	
		On Full Dosage	On Reduced Dosage
Cortisone trial	12	9	7
Prednisolone trial ..	12	11	6

N.B. Same 12 children in both cortisone and prednisolone trials.

Ventilatory Function Before and After Treatment

Overall Response of Individuals

The mean E.F.R.[40] values of the individual children recorded during the administration of placebo tablets and the mean values recorded during treatment with cortisone are compared in Table III. Similarly, in Table IV, the mean values obtained during treatment with prednisolone are compared with those obtained during a control period. The difference between the control or placebo E.F.R.[40] value and the mean E.F.R.[40] during treatment has been expressed as a percentage of the control value to provide a measure of the response to the drug under trial. Tables III and IV show the response of individual children to adrenaline and cortisone or prednisolone, and also the combined effect of adrenaline and the steroid under trial. On comparing the results of cortisone and prednisolone, we found that two of the 12 children (Cases 5 and 25) responded better (by 10% or more) to cortisone, whereas 7 (Cases 80, 20, 43, 37, 62, 44, and 46) responded better to prednisolone. The adrenaline response is much the same in the two trials, whether given alone or in addition to either cortisone or prednisolone.

Overall Response of Group

The mean overall response of the 12 children to cortisone and prednisolone, as judged by the E.F.R.[40] results, has been extracted from Tables III and IV and is given in Table V.

The duration of the equivalent dose levels of cortisone and prednisolone varied slightly—namely, the cortisone dose was usually reduced after two weeks, whereas prednisolone was reduced after three weeks. This might account for the greater overall response to prednisolone. A more valid comparison was made when their effects were compared at definite time intervals.

TABLE V.—*Percentage Change in the Mean E.F.R.[40] Values of 12 Children*

Cortisone Trial			Prednisolone Trial		
Adrenaline	Cortisone	Cortisone and Adrenaline	Adrenaline	Prednisolone	Prednisolone and Adrenaline
+14% (Nil–29%)	+21% (Nil–67%)	+38% (13–75%)	+16% (4–29%)	+31% (11–64%)	+52% (33–82%)

Group Response Related to Time and Dose

Fig. 1 shows the mean E.F.R.[40] values of nine children who had comparative data at weekly intervals, first during treatment with cortisone and later with prednisolone. The baseline values for the two trials have been taken from the average reading during the respective control periods. They are not the same in the two trials because the prednisolone trial was carried out six to nine months after the cortisone trial, when the children were older and larger. For the same reason the predicted normal E.F.R.[40] value differs in the two trials. The predicted normal E.F.R.[40] values are calculated from the height and age, using the following formula (Kennedy, Thursby-Pelham, and Oldham, 1957):

$$\text{The predicted E.F.R.}^{40}\ (\text{l./min.}) = 3.23 \times X_1 + 2.41 \times X_2 - 135$$

where X_1 = height in inches

X_2 = age in years.

The absolute values of the E.F.R.[40] given in Fig. 1 shows that the group achieves its highest response to full doses of cortisone and prednisolone during the second and third weeks of treatment (cortisone was not administered to the whole group during the third week). When the dose is reduced the response wanes, and two weeks after the cessation of cortisone and prednisolone treatment the absolute

TABLE III.—*Twelve Children with Ventilatory Insufficiency. E.F.R.[40] Values, Before and After Adrenaline Inhalations and During Treatment with Placebo and with Cortisone*

Case No.	Oral Placebo			Oral Cortisone			Response to Adrenaline $\frac{b-a}{a}\times 100$	Response to Cortisone $\frac{c-a}{a}\times 100$	Response to Cortisone + Adrenaline $\frac{d-a}{a}\times 100$
	No. of Readings	E.F.R.[40] l. min.		No. of Readings	E.F.R.[40] l./min.				
		Before Adrenaline a	After Adrenaline b		Before Adrenaline c	After Adrenaline d			
80*	10	42 (33–48)	44 (34–53)	10	54 (51–58)	54 (44–59)	+7%	+26%	+26%
5*	11	51 (32–68)	62 (33–72)	11	64 (56–76)	76 (67–80)	+22%	+25%	+49%
78*	13	36 (28–48)	41 (33–48)	11	60 (44–79)	63 (46–77)	+14%	+67%	+75%
20	7	29 (20–33)	31 (23–37)	15	29 (20–40)	36 (23–44)	+7%	Nil	+24%
43*	14	35 (23–60)	40 (27–55)	11	35 (24–50)	42 (30–60)	+14%	"	+20%
25*	11	44 (22–62)	56 (30–64)	10	55 (40–66)	69 (53–77)	+14%	+25%	+57%
37*	10	45 (34–50)	46 (37–57)	14	47 (34–68)	51 (44–66)	+2%	+4%	+13%
23*	16	64 (53–80)	77 (61–103)	12	79 (66–96)	89 (81–96)	+20%	+23%	+39%
62	10	44 (32–59)	44 (29–57)	12	57 (37–79)	67 (39–79)	Nil	+30%	+52%
44	10	26 (18–37)	31 (22–44)	6	28 (19–35)	35 (30–46)	+19%	+8%	+35%
26*	5	46 (40–52)	55 (50–62)	9	53 (50–57)	59 (52–66)	+20%	+15%	+28%
31	8	42 (30–59)	53 (33–68)	14	61 (27–82)	68 (48–92)	+29%	+30%	+45%
						Mean	+14%	+21%	+38%

* Patients in whom placebo followed cortisone.

TABLE IV.—*Twelve Children with Ventilatory Insufficiency. E.F.R.[40] Values, Before and After Adrenaline Inhalations, During Treatment with Prednisolone, and During a Comparable Control Period*

Case No.	Control Period			Oral Prednisolone			Response to Adrenaline $\frac{x-w}{w}\times 100$	Response to Prednisolone $\frac{y-w}{w}\times 100$	Response to Prednisolone + Adrenaline $\frac{z-w}{w}\times 100$
	No. of Readings	E.F.R.[40] l./min.		No. of Readings	E.F.R.[40] l. min.				
		Before Adrenaline w	After Adrenaline x		Before Adrenaline y	After Adrenaline z			
80	7	43 (41–48)	49 (46–57)	12	63 (46–70)	69 (48–75)	+14%	+46%	+60%
5	10	61 (50–70)	70 (56–77)	11	68 (56–81)	81 (70–86)	+15%	+11%	+33%
78	10	50 (40–68)	56 (44–78)	11	82 (58–101)	85 (57–106)	+12%	+64%	+70%
20	12	35 (18–45)	39 (23–55)	11	47 (32–35)	54 (40–60)	+11%	+34%	+54%
43	10	45 (35–55)	47 (36–55)	8	55 (50–61)	63 (53–74)	+4%	+22%	+40%
25	10	47 (37–58)	54 (44–62)	11	54 (28–68)	69 (36–79)	+15%	+15%	+41%
37	10	44 (40–51)	52 (46–57)	10	51 (44–62)	61 (55–72)	+18%	+16%	+39%
23	11	71 (55–86)	82 (68–92)	11	83 (55–110)	96 (77–105)	+15%	+17%	+35%
62	7	45 (31–46)	55 (42–73)	7	64 (52–84)	76 (57–92)	+22%	+42%	+69%
44	10	28 (22–37)	36 (31–43)	10	39 (24–51)	51 (26–64)	+29%	+39%	+82%
26	11	65 (42–70)	69 (58–77)	11	68 (61–72)	81 (77–88)	+23%	+21%	+45%
31	10	52 (39–70)	58 (40–79)	9	76 (50–88)	82 (56–92)	+12%	+46%	+58%
						Mean	+16%	+31%	+52%

E.F.R.[40] values for the group were almost back to their pretreatment or baseline level. Although the group as a whole does not reach the predicted normal value during treatment, it is shown below that a number of individuals achieved their predicted normal values at the height of their response.

The group response to aerosol adrenaline was interesting—the highest response in *both* trials occurred during the one to two weeks post-treatment period, whereas the adrenaline response was reduced to less than the pretreatment level during the first week on prednisolone and the first two weeks on cortisone. During the remaining weekly periods on treatment the adrenaline response was enhanced.

In Fig. 2 the response of the same nine children to the two drugs is compared by expressing the results as a percentage increase in the E.F.R.[40] over a baseline value. On the whole, the results are remarkably similar. It appears that prednisolone is more effective during the first week, whereas cortisone is more effective during the second week. Prednisolone showed a further response in the third week on full dosage, but there were no comparable data for cortisone.

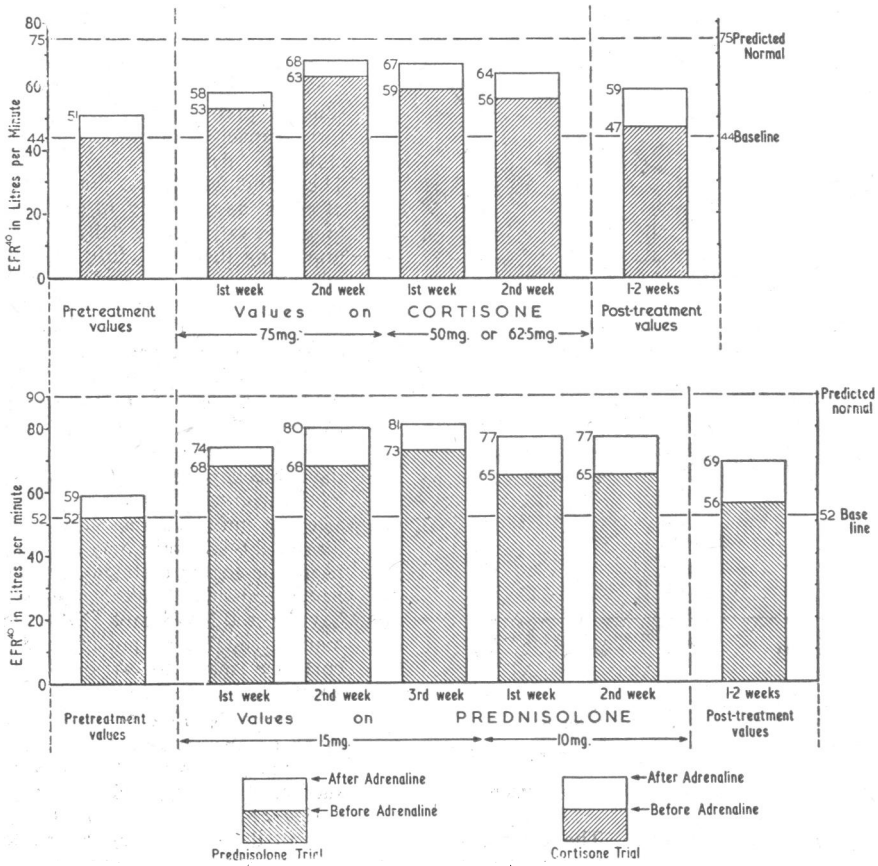

FIG. 1.—Mean E.F.R.[40] values before, during, and after treatment with cortisone and later with prednisolone (nine children).

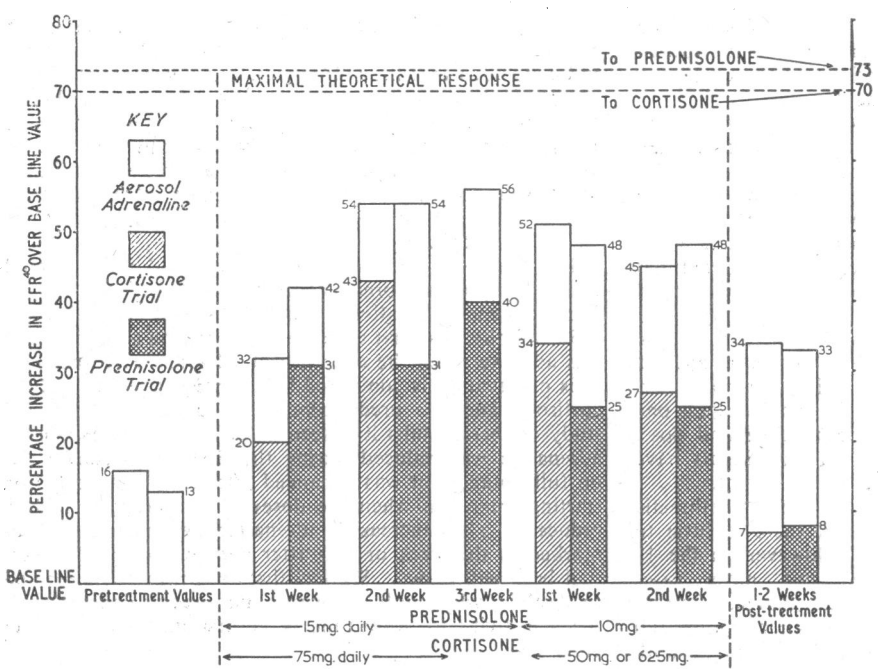

FIG. 2.—Response to cortisone and prednisolone before and after adrenaline inhalations.

Individual Response Related to Time and Dose

Fig. 3 shows the E.F.R.[40] values recorded over the period of two years in Case 78. The vertical line above each reading plotted on the graph represents the increase in E.F.R.[40] after adrenaline inhalations. The response of oral cortisone and oral prednisolone is demonstrated. A course of long-acting corticotrophin Z, 40 units intramuscularly three times weekly, is shown for comparison.

It will be seen that the E.F.R.[40] in Fig. 3 approaches the predicted normal for a boy of the same height and age only when he is on cortisone, prednisolone, or corticotrophin. The first course of cortisone (October, 1955) produced a good response, and his E.F.R.[40] rose almost to his predicted normal value. The second course of cortisone (January and February, 1956), which was started as a lower dose, was not so effective. It is interesting to see that the response to long-acting corticotrophin is very similar in time and magnitude to prednisolone.

From a study of the individual graphs of the 12 children it was seen that with the doses used the E.F.R.[40] rose to a peak after two to three weeks of treatment. The rise was quicker with prednisolone than with cortisone. The peak response of half the children (Cases 86, 5, 78, 25, 23, and 26) rose to within 5% of their predicted normal E.F.R.[40] values at some time during treatment in one or both trials.

Table I shows their assessment without treatment, where the mean E.F.R.[40] values have been expressed as a percentage of the predicted normal to provide an index of abnormality. All these children with chronic asthma had an impaired ventilatory capacity.

Discussion

We have found that the E.F.R.[40] provides a valuable method of following the progress of patients with

poor ventilatory function due to chronic asthma. In this investigation we have found it useful for assessing the value of different doses of cortisone and prednisolone.

In evaluating the results of this investigation, certain unavoidable difficulties and variables should be kept in mind. Although each child has a reduced ventilatory capacity, even when free from symptoms, many control readings are required to form an adequate baseline in a chronic disease which varies in severity from day to day. An assessment of the severity of the complaint in each child can only be made quantitatively by relating the baseline value with the predicted normal value for the individual. From these two values one can also estimate theoretically the maximal possible response to treatment.

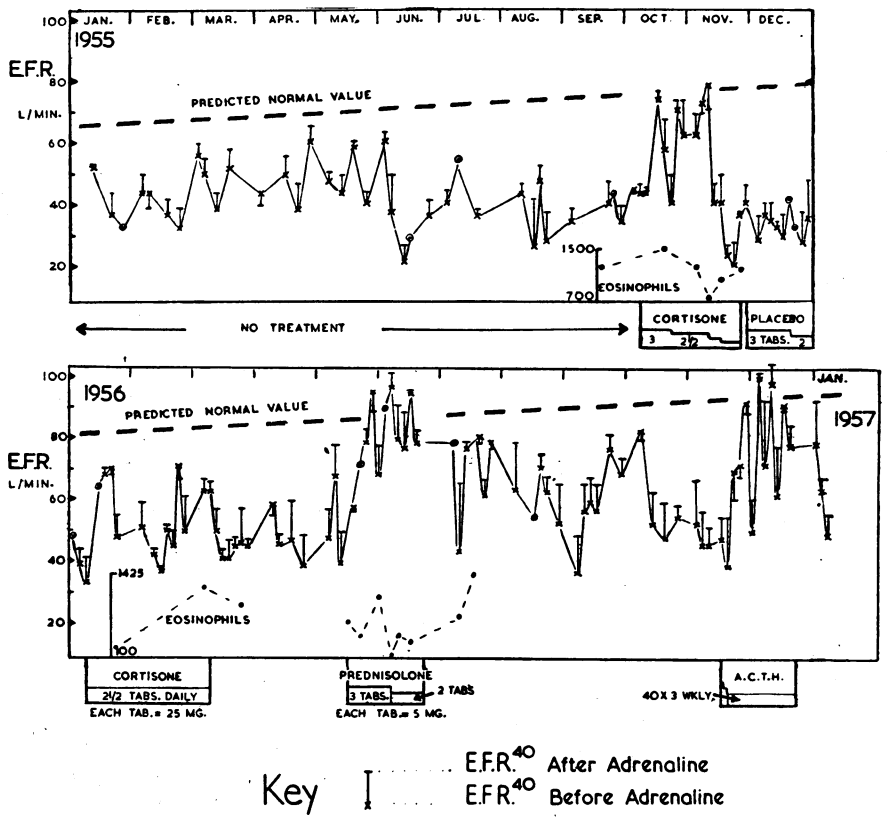

FIG. 3.—Case 78. Graph of E.F.R.[40] readings during 1955, 1956, and the beginning of 1957.

In this paper the therapeutic effects of cortisone and prednisolone are compared. The cortisone trial was carried out 9 to 24 weeks before the prednisolone. To make a valid comparison, therefore, the response to cortisone and to prednisolone had to be assessed using baselines and predicted normal values referable to each course of treatment.

In assessing the results it should also be remembered that prednisolone was given in full doses for a longer time than cortisone.

The data are open to various methods of analysis. One can measure the overall response of the group and of individuals to courses of treatment with cortisone and prednisolone, but this rather crude form of analysis tells one nothing about the response in relation to time and dose. Thus, further analysis of the group and individuals have been made which take these variables into account.

Both cortisone and prednisolone suppress asthmatic symptoms effectively in most cases, and there is little to choose between them in this respect. However, in the 12 cases studied prednisolone rendered two more cases symptom-free than did cortisone on full dosage. Prednisolone has the advantage of not causing salt retention and oedema. Ventilatory capacity is greatly improved by both cortisone and prednisolone. Individuals who responded usually showed a peak response by the second or third week. The response was rather quicker with prednisolone.

Each group had routine E.F.R.[40] readings recorded twice weekly, and the results for each individual were plotted on separate graphs. Analysis of these 12 graphs showed that the full-dosage response was maintained in seven cases on prednisolone and in four cases on cortisone when the dose was reduced. In the remainder, the effect waned as soon as the dose was reduced. Within a week of withdrawing either cortisone or prednisolone, the ventilatory capacity of most of the children deteriorated abruptly. These findings suggest that 75 mg. of cortisone or 15 mg. of prednisolone is a satisfactory daily dose in improving the ventilatory capacity of children with chronic asthma. In many cases these are the minimum doses which will maintain the ventilatory capacity at a near normal level.

In the recent Medical Research Council (1956) trial of the effect of cortisone acetate in chronic asthma the subjects were for the most part adults who received variable doses after an initial loading dose. The disappointing results may well have been due to the maintenance dose being too low. We agree with Savidge and Brockbank (1954) that many cases that do not respond to cortisone may do so on bigger doses.

Favourable reports have been made on the treatment of asthma with prednisolone and prednisone, such as Arbesman and Ehrenreich (1955) and Barach *et al.* (1955). The latter measured the effect of these steroids on the ventilatory capacity; we were also interested to note that they found that prednisone gave a quicker response than cortisone, because we observed that this was also true with prednisolone. The *British Medical Journal* (1957) reviewed the evidence on the activity of prednisone and prednisolone, and concluded that the anti-inflammatory and antirheumatic effect of these new steroids is about equal to that of cortisone, but that weight for weight these new compounds are four to five times more active. From the findings reported here it would appear that the same generalization holds good for the anti-asthmatic effect of these drugs, and that weight for weight prednisolone is at least five times more active than cortisone.

The effect of the adrenaline inhalations during the trials with cortisone and prednisolone was interesting. In our previous communication (Kennedy and Thursby-Pelham, 1956) we observed that the effect of cortisone and adrenaline was additive when the overall group figures were examined. This observation is confirmed in the present report both for cortisone and for prednisolone. From a more detailed study of these results it is seen (Fig. 2) that the response to adrenaline was reduced during the first and second weeks on full dosage, but was enhanced after the third week from starting treatment when the doses of both drugs had been reduced. This increased adrenaline response was most marked in the week or two after cortisone or prednisolone had been withdrawn. We feel that further study is required to explain why, with cortisone and prednisolone therapy, the sensitivity to adrenaline is at first inhibited and later enhanced.

Summary

Twelve children with chronic asthma were given a trial course of cortisone and later a trial course of prednisolone, and the results are compared.

The expiratory flow rate (E.F.R.^{40}) was used to assess the cases and to measure the response to treatment.

The general effects and relief of symptoms produced by the two drugs were similar, rather more children being rendered symptom-free by prednisolone than by cortisone, on a given dosage.

Seven cases responded better to prednisolone, and two cases responded better to cortisone. The results show that 15 mg. of prednisolone and 75 mg. of cortisone produced a similar satisfactory effect, and on this dosage a peak response was generally observed after two to three weeks. When the dose was reduced, the response usually waned.

The response to adrenaline is at first inhibited and later enhanced during either cortisone or prednisolone therapy.

We acknowledge with thanks the work of Mr. J. Booth, S.R.N., and Mr. L. Drury in the asthma clinic and for technical assistance. We are also grateful to Dr. A. J. McCall, of the North Staffordshire Royal Infirmary, for laboratory assistance, and to Mr. N K. Harrison, of the photographic department, St. Bartholomew's Hospital, for Figs. 2 and 3.

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USE OF PRESSOR AGENTS IN SHOCK IN MYOCARDIAL INFARCTION

BY

OLIVER GARAI, M.R.C.P.

AND

K. SHIRLEY SMITH, M.D., F.R.C.P.

From the Cardiac Department, Charing Cross Hospital, London

The mortality from cardiac infarction, substantially reduced in recent years by the widespread use of anticoagulants, may be capable of still further reduction. There are many patients who develop, at the onset of the attack, a state of shock with low blood pressure. This may be so brief that it has almost passed by the time medical attention is obtained, but when persistent or worsening it has long been recognized as of serious significance. The onset of shock may be delayed for some days, but it is nevertheless of ill omen. When this condition complicates cardiac infarction the mortality rises to about 80% (Selzer, 1952; Gootnick and Knox, 1953; Fink, d'Angio, and Biloon, 1953; Griffith *et al.*, 1954).

Attempts to relieve shock and raise the blood pressure have commonly been unsuccessful, and the wisdom of such attempts has been questioned. Thus plasma and blood transfusions have been ineffective owing to overloading of the circulation and they are now rarely used. The place of digitalis is undecided, although good results have been reported by Gorlin and Robin (1955). Vasopressor drugs used by many investigators have usually been such substances as sympathomimetic amines or their derivatives, including adrenaline, ephedrine, and "paredrine"; all of them produce undesirable effects on the heart itself, such as tachycardia and an increase in the cardiac output and the work of the heart.

The use of pressor agents depends on the assumption that the peripheral vasoconstriction that occurs in the state of shock does not produce a sufficient increase in peripheral resistance. It has been thought that if this peripheral resistance could be further increased a rise of blood pressure would follow and bring about improved circulation to the heart and brain. However, an increase in peripheral resistance alone is not enough to raise the blood pressure; the force of the cardiac contraction itself must be increased in response to the increase in peripheral resistance. It has been found that certain newer amines may possess just such a beneficial direct action on the myocardium. In this paper the results of the use of certain pressor agents in 25 consecutive patients with shock in myocardial infarction are described.

Pressor Agents

Two compounds have been used in the treatment of these patients. They are L-noradrenaline ("levophed") and mephentermine sulphate ("mephine"). The properties and pharmacological and therapeutic effects of these preparations may be outlined as follows.

L-*Noradrenaline*, the most powerful pressor and general vasoconstrictor agent known, differs from adrenaline in its effects upon the cardiovascular system in some important respects. Unlike adrenaline, L-noradrenaline does not increase the rate or output of the heart. Whereas the total oxygen consumption is raised by 20–30% by adrenaline, it is virtually unaltered by L-noradrenaline. Adrenaline, by its direct effect on the heart, causes a rise in systolic pressure, while the diastolic pressure may fall as a result of the vasodilatation in the large vascular bed of the muscles. L-Noradrenaline, on the other hand, being an overall vasoconstrictor, increases both the systolic and the diastolic pressure. In experiments on dogs Sayen *et al.* (1952) demonstrated that the rise in oxygen tension in the ischaemic zone produced by L-noradrenaline infusion was greater than that caused by inhalation of pure oxygen. Both L-noradrenaline and adrenaline dilate coronary vessels (Burn and Hutcheson, 1949). The pharmacology of L-noradrenaline has been fully reported by von Euler (1955). In fully trained dogs Gazes *et al.* (1953) found that L-noradrenaline increased the contractile force of the heart whereas phenylephrine produced largely pressor effects. They also found that L-noradrenaline gave better results than phenylephrine hydrochloride ("neosynephine") when used to combat shock in patients after myocardial infarction.

Mephentermine sulphate has little or no direct action on the heart muscle and causes no alteration in the heart rate or changes in the electrocardiogram. Although the blood pressure rises owing to an increase in peripheral resistance, cardiac output is not significantly altered. In animal experiments (Hellerstein *et al.*, 1952) in which rotameters within the lumen of the vessels were used it was shown that coronary flow increased as the blood pressure rose; the work of the heart increased very slightly, but the cardiac output remained unchanged. If injections were made at too short intervals the response decreased. Mephentermine is metabolized rapidly and there is no danger of cumulative action. The intravenous dosage varies from 10 to 30 mg., and intramuscularly up to 70 mg., while 15 to 30 mg. can be given at half-hour intervals if necessary.

Method of Use of Pressor Agents

The indication for the use of either of these preparations was simply the existence of shock. While the usual well-