STEROID THERAPY IN ASTHMA

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In the following article the indications for the use of steroids in asthma are considered. The risks attendant upon such treatment are discussed. A comparison is made between the effects of the naturally occurring preparations and some of the modern synthetic analogues. The following table shows roughly equivalent doses of the various oral steroid preparations, so that comparable doses can readily be determined:

Corticoids

<table>
<thead>
<tr>
<th>Steroid</th>
<th>Equivalent Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisone</td>
<td>100 mg. (25 mg. tablets)</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>80 mg. (20 mg. tablets)</td>
</tr>
<tr>
<td>Prednisone</td>
<td>20 mg. (5 mg. tablets)</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>20 mg. (5 mg. tablets)</td>
</tr>
<tr>
<td>Methyl-prednisolone</td>
<td>16 mg. (4 mg. tablets)</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>0.5-1 mg. (0.5 mg. tablets)</td>
</tr>
</tbody>
</table>

Cortisone acetate and prednisolone acetate may also be used intramuscularly.

Contra-indications of Steroid Treatment

There are certain circumstances in which the use of steroids is contra-indicated: these include pulmonary tuberculosis and peptic ulcer, which should be excluded before treatment is commenced. Steps can be taken to minimize the risks in these conditions if the use of steroids is considered necessary to save life as in severe status; in pulmonary tuberculosis by simultaneous treatment with appropriate antibiotics; in peptic ulcer with alkalis. If there is evidence of cor pulmonale, the use of corticotropin or salt-retaining corticoids may precipitate failure, but the newer steroid preparations with diminished salt-retaining properties may be given cautiously. Hypertension may be increased. In diabetes mellitus it may be necessary to adjust the dosage of insulin. Long-term treatment of asthma with corticoids is rarely justified if these conditions are present.

Hazards of Steroid Therapy

The conditions already referred to (peptic ulcer, diabetes, hypertension and pulmonary tuberculosis) may occur as complications during the course of treatment even in the absence of a previous history. Peptic ulcer is a serious hazard not only because of its high incidence, but also because the symptoms, including those of perforation, may be masked and hence readily overlooked. Anderson found evidence of peptic ulcer in 14.6 per cent. of 144 cases on long-term steroid therapy, and other workers have reported figures in the neighbourhood of 10 per cent.

Certain other risks occur with the use of all corticoids. These may be divided into those which may develop within a short time and those only seen after longer treatment.

Risks Associated with Short-term Treatment

Silent and hence easily overlooked infection may arise in the lung or blood stream, and this must be remembered if the patient's progress appears to be deteriorating. Example: Male, aged 55, with severe recurrent asthma. Treatment with corticotropin was commenced with favourable response, but later the patient deteriorated and died. At post mortem an unsuspected right upper lobe pneumonia was discovered.

Acute mental disturbance of a manic, depressive or schizophrenic kind may develop. The nature of these is probably related to the basic personality of the patient. Example: Male, aged 24, with severe chronic asthma was much improved with cortisone. He became acutely excited, however, and was unable to stop working. A bricklayer by trade, he stated that his union had reprimanded him for laying too many bricks. Small doses of phenobarbitone in this case restored his activities to normal.

A woman, aged 42, stopped treatment with prednisolone after two days because 'my brain was on fire; I was unable to sleep or rest.'

Blind reliance on steroids as a symptomatic remedy may be associated with (1) a lessening of effort directed to finding and dealing with the precipitating cause, (2) inadequate bronchodilator therapy in status which may only respond to steroids after 48-72 hours, or which indeed may fail to respond at all.

Additional Risks Associated with Long-term Treatment

Increase in weight, the development of hirsuties, moonface, striae, and osteoporosis are fre-
quenty seen and should be sufficient reason for avoiding the unnecessary use of those preparations. Their development, like other complications, is related to the dose of steroid used.

Suppression of the patient's suprarenal cortical activity will always take place if steroids are used for any length of time. Should conditions arise during treatment demanding an additional output of corticoids, e.g. injury, any form of anaesthesia or surgical treatment, sudden collapse and death may occur unless extra corticoids are given. Generally speaking, the equivalent of 200 mg. of cortisone should be prescribed on the day of the operation and the day following with gradual reduction to the basic level over the next week.

Sudden cessation of corticoid therapy may precipitate severe asthma which in the absence of appropriate treatment may lead to death. Though relapse of the condition may take place in other diseases treated with steroids under similar circumstances, asthma is the only one except Addison's disease where death may occur as a result. Example: Male, aged 42. Successful treatment with cortisone which had been maintained for six months was stopped suddenly. The patient went into severe status, corticoids were not prescribed and he died. Another patient with a precisely similar history recovered after resumption of cortisone in large doses.

The longer the patient has received corticoids and the greater the dose, the longer will be the period of gradual withdrawal required. Corticotropin is sometimes recommended as a stimulant of cortical activity after withdrawal of oral corticoids, but this procedure is not entirely free from risk, since it may precipitate an Addisonian type of crisis by exhausting the atrophic suprarenal glands. After one year's treatment with corticoids a minimal period of three months will be required for withdrawal.

Risks Attendant Upon the Use of Corticotropin Only

Long continued or intermittent treatment with corticotropin may be associated with acute ana phylactic episodes (Serafini, West), sometimes leading to death as in the following case: Female, aged 55, with chronic asthma, was treated with an intravenous drip containing corticotropin. This had previously been used successfully. Within two minutes of the drip being set up she complained of tingling in the hands, became cyanosed and died. Other cases have been recorded (Hill and Swinburn, Bloom and Wolff, Burrage and Irwin, Quarles van Ufford).

Many patients on long-term corticotropin acquire resistance to its effects presumably also as a result of antibody formation, so that it ceases to be useful (West).

Treatment

Corticoids are used in asthma in short courses for controlling status asthmaticus, or for milder attacks that do not respond to the usual symptomatic remedies employed by the patient; long-term treatment may be given to those who have repeated attacks of status asthmaticus which threaten life, or when disability prevents them from earning their living or in other ways makes life intolerable.

Status Asthmaticus

There are many reports of the value of these drugs in this condition (Lockey and Paul, Baldwin et al., Ball, Pearson). The Medical Research Council carried out a double blind controlled trial with cortisone: only those cases who had failed to respond to routine methods of treatment for the first 24 hours after admission were included in the trial. It is noteworthy that in ten hospitals in the course of approximately one year only 32 cases fulfilled these conditions; a remarkable tribute to the older methods of treatment with broncho-dilator preparations. Alternate patients were treated with cortisone or placebo tablets according to a prearranged dosage scheme. Statistical analysis showed that those treated with cortisone began to recover more quickly and were restored to normal sooner than the controls. Since corticoids may not exert their effect for 12 hours to four days, it is imperative that standard treatment with oxygen and broncho dilators (subcutaneous adrenalin and intravenous aminophyllin) should be continued at intervals until relief occurs. In most series a certain number of failures are recorded and this is a further reason for continuing with broncho dilator drugs. Status is usually associated with bronchial infection, and if this is present appropriate antibiotics must also be given simultaneously. Failure of treatment may be due to the following causes:

1. Inadequate dosage or the use of inactive material.
2. Uncontrolled infection of the respiratory tract or para-nasal sinuses.
3. Organic lung damage such as pulmonary fibrosis, structural emphysema or bronchiectasis.
4. Harmful side-effects, particularly severe hypertension or right-sided heart failure, or with corticotropin, allergic reactions.

In the first instance hydrocortisone hemi succinate may be given intravenously (100 mg. in 2 ml.), and in very severe cases may be repeated
preferably in a glucose saline drip so that 200-400 mg. are administered in the first 24 hours. This is preferably followed by oral prednisolone, 40-60 mg. in 24 hours. Other preparations can be given in comparable doses, but cortisone or hydrocortisone are now seldom employed because of their salt-retaining properties. The dosage of prednisolone is reduced as soon as improvement is noted by 5-10 mg. every few days until the patient has been weaned after two to three weeks. At any sign of relapse the dosage must be increased.

The most potent effect is probably obtained by corticotropin which may be given as a continuous intravenous saline drip so that 40 units are administered in the first 24 hours.

**Interruption Treatment of Less Severe Attacks**

Many patients are able to control attacks and possibly prevent the development of status by the timely use of oral corticoids. If results are to be attained with reasonably small doses, the treatment must be commenced early, and to achieve this the patient must be entrusted with an adequate supply of tablets. He should be told to commence the course only if he is unable to control attacks by the use of broncho-dilator tablets, aerosol spray or any other form of remedy, which he habitually employs. Since considerable judgment on the part of the patient is required, this treatment is not suitable for those who are unstable or unintelligent.

A dosage scheme in which 20 5-mg. tablets of prednisolone are given over eight days, commencing with 20 mg. in divided doses for the first two days, and reducing the dose by 5 mg. each two days, has been found to be effective in a high proportion of cases. In others a larger initial daily dose of 30 mg. may be necessary. If the asthma persists for more than two days, or gets worse in spite of this treatment, the patient should, of course, consult his doctor if he has not already done so, in order that larger doses may be given or alternative treatment provided.

The advantage of such treatment is that severe attacks which might require hospitalization may be prevented, and provided the courses are not too close together, the risk of suprarenal suppression is small, compared with the effect of long-term treatment. The patient should acquire a fresh supply of tablets as soon as he has completed the course, in case a further attack develops.

**Long-term Treatment**

This implies treatment for three months or more. It is suitable for the small proportion of asthmatics who require repeated admission to hospital because of severe status with its attendant risk to life, or who lose long periods from work because of their asthma. Children will rarely be found to need such treatment which should be retained chiefly for patients over 40. A preliminary trial period in hospital or comparison between the effects of a placebo and the preparation to be used is advisable before committing the patient to what may well be a lifelong period of dependence on these substances with their attendant hazards.

Corticotropin or suprarenal corticoids may be employed. The former is given in slow-acting preparations in the form of a gel (A.C.T.H.A.R.) or zinc suspension: disadvantages are that it must be given by intramuscular injection, that resistance to it develops in a considerable proportion of cases (West) and that anaphylactoid reactions may occur. Other objections have already been considered. Nevertheless, many authorities have found it useful (Gay, Davies and Williams) in doses of 20-40 units daily.

Corticoids are more often used and may be prescribed as prednisolone 10-15 mg. daily or corresponding doses of other preparations. It is considered inadvisable to give doses greater than 20 mg. daily, except for a few days at the beginning of treatment or to tide a patient over an attack developing during treatment, because of the increased prevalence of side-effects with larger doses. Whether corticotropin or corticoids are employed, the dose should be reduced to the lowest capable of keeping the patient reasonably free from asthma; he should be impressed with the importance of weaning himself from the preparation if there is any evidence of a remission, and it may be found possible to convert him to the intermittent form of treatment previously described.

In a controlled trial carried out by the M.R.C. in which alternate cases of chronic asthma were treated with cortisone or a placebo for six months, there was no difference between the two groups at the end of this period, although those on cortisone were better than the controls after three months. While this does not imply that no case will benefit from this form of treatment for a period longer than three months, it does draw attention to the importance of careful selection of cases, and of relying on measurements such as vital capacity, periods of incapacity, quantity of symptomatic remedies employed rather than patients' statements in assessing the value of treatment. In a small series of ten cases (Pearson) treated for six months with cortisone and six months on dummy tablets, only two showed unequivocal improvement on cortisone; two others claimed to have improved but figures relating to
the number of attacks and the average vital capacity over the two periods showed that in fact they had done equally well or in one case better on the placebo. No case was rendered entirely free from symptoms. Steroids often have a stimulating effect which gives rise to a feeling of euphoria which may be mistaken for genuine improvement in the asthma. Savage and Brockbank, in a similar type of trial, found that of 13 cases six had good or excellent and four fair results, three were failures including two deaths Arnoldsson found that in a series of 144 patients 37.5 per cent. were symptom-free, but 20.1 per cent. of cases continued to have moderate to severe asthma and there were two deaths. In 37.5 per cent. hospital admission was required at least once during treatment. Steroid treatment is therefore in no sense curative, if reserved as it should be, for severe cases. In my own experience the best results are obtained in intelligent patients who increase the dose of steroid temporarily from time to time on their own initiative, when the condition appears to be deteriorating. In such cases the basal dose required does not usually need to be increased even when treatment is maintained for several years. Reasons for failure are mainly those already quoted in discussing the treatment of status. Brown suggests that the presence of eosinophils in the sputum is a useful indication that a satisfactory response will be obtained.

**Comparison of Individual Steroid Preparations**

Cortisone and hydrocortisone have been modified by a variety of comparatively simple chemical changes to produce first prednisone and prednisolone and later three analogues of prednisolone, namely, methyl-prednisolone, triamcinolone and dexamethasone.

Prednisone and prednisolone, which are identical with cortisone and hydrocortisone except for a double bond in the 1-2 position, are weight for weight five times as potent as the parent substances therapeutically and have appreciably less tendency to retain salt and water and to expel potassium. Other side-effects (gluco-corticoid, ulcer formation, etc.) occur in much the same proportion of cases. Their use is justified because of their reduced effect on electrolyte metabolism and water retention.

Triamcinolone and methyl-prednisolone are 20 per cent. more potent therapeutically and have even less effect on electrolyte metabolism than prednisolone. There is no associated reduction in other side-effects, however (Kuppermann, Humstadt, Kendall and Hart), and triamcinolone may cause an insidious muscular weakness and wasting (Duboris, Williams, Maclean and Schurr). This alone makes its substitution for prednisolone unwise except in special circumstances. It is too early to be categorical as regards the value of dexamethasone, which is seven times more active therapeutically than prednisolone.

West has suggested that ulcer formation is mainly the result of local action of steroid on gastric and duodenal mucosa. The reduced incidence of ulcer formation in corticotropin therapy supports this view. If such is the case the use of enterico-coated prednisolone or even long-acting intramuscular preparations may be valuable.

**Conclusion**

The value of corticotropin and corticoids in the short-term treatment of asthma is accepted. Their use does not replace standard treatment with broncho-dilators nor should it prevent a careful search for underlying aetiological factors. Long-term treatment is sometimes of value, especially for older patients: it should only be employed in those whose asthma cannot be controlled by other means, and objective methods of assessing results should also be employed. The risk of side-effects and the degree of suprarenal suppression is related to the dose of corticoid employed and the length of time that treatment is continued. The introduction of new modifications in the structure of the corticosteroid molecule has led to reduction in electrolyte disturbances together with increased therapeutic potency, but has not reduced incidence of side-effects other than those dependent on water and salt retention or potassium excretion. Muscle wasting is a new side-effect complicating triamcinolone therapy.

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nasal trouble left no doubt about the diagnosis of rhinitis medicamentosa due to adrenergic drugs and in main to naphazoline.

Unfortunately, it is still possible for the patients to obtain these drugs over the counter. Education of the patient is therefore needed, and their co-operation obtained to restrict the use to the worst episodes.

Steroid Hormones

The second large group of anti-allergic drugs which can exert their action at the site of their deposition on the mucous membrane are steroid hormones. Of the known active adrenocortical compounds, hydrocortisone and prednisolone (delta-tahydrocortisone) can act locally, whereas cortisone and prednisone cannot. Hydrocortisone is soluble in water, only 1 : 4,000, and hydrocortisone acetate is insoluble in water. Both drugs can be given as nasal snuff.

Herxheimer and McAllen (1956) saw good results in hay fever, using 15 mg. hydrocortisone locally daily. Good results in nasal allergy with prednisolone locally were reported by Anderson and Ogden (1956). The writer took part in two small controlled trials where patients with hay fever were treated by inhalation of either prednisolone snuff (1 mg. twice daily) or by an inert snuff containing lactose (Godfrey, Maunsell, and Pearson, 1957). The results in 1956 suggested that the daily inhalation of 2 mg. prednisolone snuff is of considerable value in the control of symptoms due to hay fever. The 1956 season was, however, unusually mild, and a further study during the pollen season of 1957, when pollen counts were much higher, showed that prednisolone snuff alone in dosages of 2-4 mg. did not sufficiently control severe cases. It is, however, considered as a most valuable help in treatment of hay fever and can be given in conjunction with antihistamines and hyposensitization. No side effects were observed; in particular the absence of the rebound phenomenon was noted. Prednisolone as prednisolone sulphate (Predsol) can be used in watery solution. The drops are instilled three to four times daily and this treatment is of valuable help in controlling seasonal and perennial rhinitis. Polypi sometimes considerably with hydrocortisone snuff as well as with prednisolone. An increase of infected episodes has not been noted.

An important use of prednisolone and hydrocortisone was mentioned previously, i.e. the counteraction of the rebound effect.

Since we have to learn more about the applications and results of the local steroid therapy it seems unfortunate that the pharmaceutical industry set out to combine vasoconstrictors and steroid hormones. For example, Cortibiotic nasal drops contain prednisolone, ofloxacin and the vasoconstricting phenylephrine; Hydrospray contains hydrocortisone, neomycin and the vasoconstricting propadine; Efocort nasal spray contains hydrocortisone, thiomersal and naphazoline nitrate, and in Delta-Fenox prednisolone is combined with two vasoconstrictors, phenylephrine and naphazoline. Other similar preparations are also on the market.

Since a certain amount of the locally applied hormones will be swallowed after travelling up the nasal passages via the naso-pharynx, one has to watch carefully for toxic general effects. In our cases neither gastro-intestinal trouble nor signs of Cushing's syndrome have been noted. Yet one should be careful and refrain from giving local steroids to patients with gastric ulcers, congestive heart failure, diabetes and tuberculosis. One should not be too enthusiastic about the improvement of the rhinitis and polypi but realize and let the patients realize that these drugs do not cure the disease but only suppress the clinical manifestations.

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Steroid Therapy in Asthma

R. S. Bruce Pearson

Postgrad Med J 1959 35: 463-469
doi: 10.1136/pgmj.35.406.463

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