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BRONCHIAL ASTHMA AND CHRONIC BRONCHITIS TREATED WITH HYDROCORTISONE ACETATE INHALATIONS

BY

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Foulds *et al.* (1955) reported good results in 12 out of 15 patients with asthma who were treated with inhalations of hydrocortisone acetate in fine-particle powder. Brockbank and Pengelly (1958) and Helm and Heyworth (1958) carried out short-term controlled trials which showed that a statistically significant number of patients responded well to these inhalations as compared with the number responding to inhalations of placebo powder.

The purpose of the present paper is to record the results of two years' experience with inhalations of hydrocortisone acetate powder in patients with asthma and wheezy bronchitis and to suggest some indications for this treatment. An attempt has also been made to estimate the quantity of "inhaled" powder which enters the stomach rather than the tracheo-bronchial tree.

Material

The patients selected had all suffered from asthma or wheezy bronchitis for at least one year, and their condition had been severe enough to necessitate periods off work, except in two patients whose asthma was almost entirely nocturnal. There were 25 men and 28 women treated. The ages varied between 15 and 61 years, the mean being 40 years.

Groups and Definitions.—Bronchial infection was judged to be present if the sputum contained macroscopic pus. Where necessary the pus was examined microscopically to differentiate pus due to eosinophils rather than true pus cells. For convenience of analysis the cases were divided into five groups: (1) recurrent acute asthma without significant bronchial infection; (2) chronic asthma without significant bronchial infection; (3) recurrent acute asthma with significant intermittent infection; (4) chronic asthma with significant intermittent infection but little persistent sputum; and (5) chronic wheezy bronchitis with significant persistent or intermittent infection and more than $\frac{1}{4}$ oz. (7 ml.) of sputum daily. The main difference between patients in groups 4 and 5 was in regard to the daily quantity of sputum, but infection tended to be a more prominent feature in group 5 than in group 4.

Method

All patients with significant bronchial infection when first seen were admitted to hospital for investigation and treat-

ment with antibiotics and routine antispasmodic drugs before receiving hydrocortisone inhalations, and patients whose signs and symptoms cleared completely concurrent with elimination of pus from the sputum were excluded. If the sputum rapidly became purulent again on stopping the antibiotic it was restarted and the patient remained on a small maintenance dose while starting hydrocortisone inhalations. All patients with infection were instructed to start antibiotics again should an exacerbation of infection occur while remaining on the inhalations after discharge from hospital. Patients with severe asthma (without infection) when first seen were admitted to hospital and were treated routinely with antispasmodic drugs for a few days before inhalations were given.

The patients inhaled fine hydrocortisone acetate powder from a "pabracort" inhaler, the powder being in capsules containing 15 mg. of hydrocortisone and 75 mg. of lactose powder, both being ground fine to a mean particle size of 5 microns. The initial dose varied between one capsule three times a day and one capsule daily given as half a capsule twice daily according to the severity of the wheezing at the beginning of treatment. The dose was reduced to the minimum maintenance necessary as soon as improvement occurred. Most patients were able to reduce the dose to half a capsule twice daily within the first week; this was the usual maintenance dose, although some needed to continue with two capsules daily, and some were able to reduce to half a capsule daily.

Treatment was stopped entirely in patients with recurrent acute asthma once the attack had been relieved for a week, and they were provided with capsules and instructed to restart at the onset of symptoms in a dose of between one and three capsules daily according to the severity of the attack. All patients were given any other routine treatment necessary, and this often included an antispasmodic drug before the hydrocortisone inhalation in order to facilitate deep inspiration. Those who responded well but later relapsed while continuing treatment were given prednisone by mouth in addition to the inhalations.

Patients who had failed to make any definite improvement during two weeks' treatment with inhalations were assessed as failures and the treatment was stopped.

Follow-up and Assessment of Results

The assessment of the results of treatment was made on both subjective and objective grounds. All patients had had prolonged routine treatment before starting the inhalations, and this provided a baseline from which the changes in signs and symptoms could be judged. All patients were seen by the same physician at monthly intervals or less while remaining on the treatment. Special attention was paid to the symptoms of dyspnoea and tightness of the chest, to exercise tolerance, and to the need for bronchodilator drugs. On physical examination the presence or absence of wheeze was noted and, if present, was assessed as slight, moderate, or severe on each visit.

Patients with significant bronchial infection (groups 3, 4, and 5) were instructed to bring a 24-hour specimen of sputum for inspection on each visit.

The results of the inhalation of hydrocortisone acetate powder in bronchial asthma and wheezy bronchitis are shown in the Table.

Of the 53 patients, 43 (81%) improved on hydrocortisone inhalations, whereas 10 (19%) were no better. Of the 43 patients who improved, 13 (30%) relapsed after periods of 1 to 11 months, whereas 30 (70%) maintained the improvement up to the time of writing for between two months and two years. The best results were obtained in group 1 patients with recurrent acute asthma without infection, whereas the results in group 5 patients with wheezy bronchitis were disappointing.

Complications.—There were no definite complications in the present series, but one man had mild dyspepsia for a few weeks which may have been due to the hydrocortisone.

Several patients put on weight, which was probably due partly to improved health and partly to the effects of hydrocortisone absorption.

Table of Results

Group	No.	Not Improved	Improved	Improved but later Relapsed	Maintained Improvement to Present	Duration of Improvement in Patients	
						Relapsing	Remaining Well
1	12	1	11	1	10	9 months	2 months to 2 years.
2	18	3	15	5	10	4-11 months.	Mean 1 year
3	7	0	7	2	4	Mean 7 mths.	3-18 months.
4	7	0	7	4	4	2-5 months.	Mean 8 months.
5	9	6	3	1	2	Mean 3½ mths.	2½-11 months.
						1-6 months.	Mean 5 months.
						Mean 3 mths.	3-18 months.
						2 months	Mean 11 mths.
Total	53	10	43	13	30		1-4 months.
							Mean 2½ mths.

Case Histories

Group 1.—A 20-year-old girl had had eczema, hay-fever, and intermittent asthma all her life. In March, 1955, she started a course of mixed inhalant desensitization, but after a short period of apparent improvement she became worse than ever in the autumn, and had three months of almost continuous wheezing which was little affected by routine measures. She was then started on hydrocortisone inhalations, and the symptoms rapidly resolved. She continued to use the inhalations on about two days out of three in a dose of one capsule daily for the next two years, and remained very much improved during this period, with only six weeks off work, compared with eight months off work in the previous two years.

Group 3.—A 37-year-old woman with no relevant family history had begun to get asthma at the age of 13. The attacks remained fairly mild and were precipitated mainly by emotion or exertion until the age of 18, when she had several years of freedom. At the age of 25 she again began to get attacks of asthma following colds and bronchitis. In November, 1956, she had a cold followed by persistent bronchitis with fever and purulent sputum: the infection finally cleared after several courses of antibiotics, but she continued to have attacks of wheezing, especially at night, and failed to respond to energetic routine measures, including antispasmodic and antihistamine drugs. After two weeks of continued night attacks with little sleep, she started hydrocortisone powder inhalations: she took one capsule in the afternoon and another in the evening. She slept well for the first time that night and had no further wheezing while carrying on with the inhalations for the next two weeks. After stopping the inhalations she remained free of asthma until a further attack following a cold one year later. This attack was again relieved by a few days of hydrocortisone inhalations.

Group 4.—A 61-year-old woman with no relevant family history had begun to have a slight cough and sputum at the age of 18. At 38 she first began to have severe wheezing attacks with no known precipitating factors: the attacks were intermittent for many years, but at the age of 58 the wheezing became almost continuous, with intermittent severe attacks necessitating weeks in bed. Finally she was confined to bed for three months with chronic status asthmaticus, and was admitted to hospital. On admission she was acutely short of breath and had a marked expiratory wheeze: she had 2 to 3 oz. (60-85 ml.) of mucopurulent sputum daily, a culture from which yielded pneumococci. She was treated with antibiotic and routine antispasmodic drugs, and, concurrent with the clearing of the pus from the sputum, she greatly improved. Two days later, however, in spite of continued penicillin and the fact that her sputum remained mucoid, she relapsed severely, with a return of severe wheezing. She started hydrocortisone inhalations in a dose of one capsule three times a day and

made steady improvement, becoming almost symptom-free at the end of a week. She continued on daily inhalations, the dose varying between one and two capsules daily, and remained greatly improved for 18 months up to the time of writing, although with considerable day-to-day variation. She continued to need antispasmodic drugs, but no further antibiotic treatment has been necessary.

Assessment of Proportions of "Inhaled" Powder

Entering the Stomach and Tracheo-bronchial Tree

It seemed certain that some of the "inhaled" powder would be swallowed whatever method of inhalation was used, since some would become arrested in the mouth, pharynx, and glottis.

An attempt was made to estimate, roughly, the relative proportions of powder entering the stomach and the tracheo-bronchial tree in two normal subjects who "inhaled" fine powder, propylidone ("dionosil"), in exactly the same manner as used for the hydrocortisone. It was hoped that a partial bronchogram might be obtained in this way, but, in spite of the fact that 4 to 5 g. of the powder was "inhaled," subsequent chest x-ray pictures showed only a few small opacities in the bronchial tree, probably due to clumping of the powder. It could be seen, however, that there was a considerable quantity of the opaque medium in the stomach of both subjects. This experiment was therefore repeated at a later date. Ryle tubes were passed and the stomach's contents aspirated, and the quantity of propylidone present was estimated. It was found that about half the "inhaled" powder was present in the stomach in each case.

Although this powder was finely ground, the experiment was hardly comparable to the hydrocortisone lactose inhalations because the propylidone was far more irritating, and necessitated considerable local anaesthetization of the throat and larynx before it could be "inhaled" at all. In addition there was a greater tendency for the powder to form "clumps." In view of these facts, three normal subjects each "inhaled" 1 g. of finely powdered lactose, having already swallowed a Ryle tube, and after drinking 4 oz. (114 ml.) of water the stomach contents were aspirated as thoroughly as possible. It was found that about 20% of the total powder "inhaled" had entered the stomach of each subject. This lower proportion was expected in view of the comparative ease of inhalation of the lactose powder as compared with propylidone.

Discussion of Results

The early results of treatment were remarkably good and many patients obtained rapid relief of wheezing, often within a few hours and after days of unsuccessful preliminary routine treatment. Once relief had been achieved, it was unusual for further acute attacks to occur for a time, provided the inhalations were continued. In the groups with chronic asthma, however (groups 2 and 4) and the group with recurrent acute asthma and intermittent infection (group 3), relapses began to occur after the first month, and became more frequent the longer the follow-up continued. These relapses were not necessarily complete, however, and some of the patients classified as having relapsed were confident that they remained better than before starting the inhalations. On the other hand, some of the patients regarded as having maintained their improvement up to the time of writing were certainly not so well at the time of assessment as they had been earlier in their treatment.

It is clear that in these groups of patients there is a tendency to relapse if treatment is maintained in the same way as was shown to occur in the Medical Research Council's (1956) trial in chronic asthma, where the advantage of patients receiving cortisone by mouth over those receiving placebo tablets rapidly diminished after the first two months until at the end of six months there was no significant difference between the two groups. In the group with recurrent acute asthma without infection, however, the

improvement has been maintained in all but one patient over a mean period of 10 months. All these patients have been able to stop the inhalations as soon as relief of the bouts of wheezing has been obtained and to restart at the onset of the next attack, whereas the patients with chronic asthma usually found it impossible to stop the inhalations without rapid return of wheezing, although they were able to vary the daily dose according to their symptoms.

The results were very disappointing in the patients with wheezy bronchitis (group 5), and only three out of nine improved, and the disability in these three was relatively mild. This result is not surprising, since we have found, in agreement with Moyes and Kershaw (1957), that little or no benefit is obtained in patients with chronic wheezy bronchitis and infection by the addition of oral corticosteroid drugs to long-term antibiotic therapy. It would also seem that the presence of considerable secretion in the bronchial tree is against successful local action of hydrocortisone. We have, however, treated a few very early cases, in which cough, sputum, and wheezing have been present for only a few weeks or months, with combined antibiotics and hydrocortisone inhalations with encouraging results, and it seems possible that at this stage local hydrocortisone may help in the resolution of the hypersensitive and irritable state of the bronchial mucous membrane during and after infection.

Reason for Relapse.—The reason for relapse in some of our patients who did well for a time is uncertain. It is possible that local tolerance to the hydrocortisone in the bronchial mucous membrane develops, but it would certainly not appear to be due to the development of a general tolerance to the corticosteroid group of drugs, as nine of these patients, after relapse, responded very well to the addition of a relatively small dose of oral prednisone (5 to 10 mg. daily) while continuing with hydrocortisone inhalations. One of these patients developed a gastric ulcer while taking prednisone, and, after a period of hydrocortisone inhalations only, oral cortisone (25 mg. daily) was added with maintained benefit and absence of gastric upset.

Local or General Action

Cotes *et al.* (1956) showed that there was a rise in urinary excretion of 17-hydroxycorticosteroids after the inhalation of fine particle hydrocortisone powder. This demonstrated that some general absorption had taken place, but the site of the absorption was uncertain. From our observations there would seem to be little doubt that a considerable proportion of the inhaled powder enters the stomach and is absorbed. This proportion probably varies greatly according to the condition of the patient and the technique followed by him, but is probably in the region of 20–50%. Most of the remainder must enter the tracheo-bronchial tree, and the depth of penetration probably also depends on the preceding factors. It would seem a fair assumption that some of this powder will be absorbed from the bronchial mucous membrane, and highly probable that some will be expelled by cough and cilia action and finally swallowed and absorbed from the stomach. If the dosage is large, therefore, there must be some general action from absorption of the hydrocortisone, and doubt may arise about whether or not any local action occurs.

Assuming that about 75% of the “inhaled” powder is absorbed, we can perhaps compare the results of the inhalations of hydrocortisone with those likely to be obtained by the same dose of oral cortisone, since oral hydrocortisone is recognized to be somewhat more powerful than cortisone: the starting dosages in the M.R.C. trials in chronic asthma and status asthmaticus were 300 and 350 mg. of cortisone daily respectively, and on the seventh day patients in the chronic asthma group were still receiving 100 mg. of cortisone daily, the dosage after this being left to the physician in charge of the patient. Foulds *et al.* (1955) gave 15 mg. of hydrocortisone acetate powder by inhalation daily and had good results in 12 out of 15 patients. Our starting dosage scheme was varied according to the patient's condition and the technique followed by him, but the maximum was

45 mg. daily for the first week, and the maximum maintenance dose was 30 mg. daily, the usual maintenance dose being 15 mg. daily.

The early results in our series were good in most patients, and often remarkably rapid, with relief of previously intractable wheezing within a few hours in some. We doubt whether similar results would have been obtained with a starting dose of 15 to 45 mg. of oral cortisone daily. We therefore believe that in successfully treated patients a considerable local action takes place. Further strong confirmation of this was obtained by Brockbank and Pengelly (1958), who report good results in a controlled trial using a much lower dosage of hydrocortisone powder than in the present investigation.

Indications for Hydrocortisone Inhalations

It would appear that hydrocortisone powder inhalations have most chance of maintained beneficial effect in patients with recurrent acute asthma with symptom-free intervals. In these cases the treatment can be used to break the individual attack and then be stopped, thereby reducing the chance of loss of the local effect of the powder. The results in chronic asthma are clearly not so good, for, although most of these patients improved with the inhalations for a time, relapse was more frequent, and in advanced cases the improvement did not appear to be as great as may occur with oral prednisone. However, the treatment is relatively cheap and certainly far less likely to produce severe complications; it would therefore seem well worth while trying as a first measure, since relapse does not seem in any way to jeopardize the chances of success with oral prednisone.

In patients with intermittent infective bouts followed by acute asthma, very good results can often be obtained by hydrocortisone inhalations in combination with antibiotic treatment.

Nine of our patients were seriously ill and could be classed as being in status asthmaticus at the onset of treatment, and only two failed to respond; but we feel that the ability to inhale the powder is so restricted while the extreme wheezing continues that it is probably preferable and safer to use intravenous hydrocortisone and aminophylline, or oral cortisone, or prednisone in such severely ill patients, at least until some partial relief has been obtained, when treatment could be continued with hydrocortisone inhalations with or without combined oral treatment. The two patients who failed to respond were obese middle-aged women with marked wheezing and extremely poor respiratory movements.

This treatment is unlikely to be effective in patients with advanced wheezy bronchitis, but is probably worthy of trial in combination with antibiotics in patients with symptoms of mild bronchitis which have been present for only a few weeks or months.

Summary

53 patients with asthma or bronchitis were treated for periods of two months to two years with inhalations of fine-particle hydrocortisone acetate powder.

These inhalations were found to be an effective form of treatment in many patients with bronchial asthma. There is a strong tendency to relapse if the treatment has to be maintained, but prolonged benefit may continue if the inhalations can be used intermittently for recurrent attacks of asthma.

Although this treatment may be successful in status asthmaticus, it is probably less effective in this condition than intravenous or oral corticosteroid drugs, and its use is not recommended if the patient is dangerously ill.

A considerable proportion of the “inhaled” hydrocortisone is probably absorbed, but the dosage is low compared with that used in oral corticosteroid therapy,

and the chance of toxic effect is therefore much less. The optimum dosage is uncertain, but it probably varies from patient to patient.

Little or no benefit is likely to be obtained from this form of treatment in patients with established chronic bronchitis.

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INHALATION OF HYDROCORTISONE ACETATE FOR BRONCHIAL ASTHMA

A SHORT-TERM CONTROLLED TRIAL

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The beneficial effects of oral cortisone in some asthmatic patients have been clearly demonstrated by the Medical Research Council (1956). Hydrocortisone, when given locally as a surface application on the skin or by injection into the joints and tendon sheaths, is of value in many allergic and inflammatory conditions, and when inhaled into the nose as a powder may considerably improve allergic conditions of the nasal mucous membrane, including hay-fever (Foulds *et al.*, 1955); Herxheimer and McAllen, 1956). It would therefore seem reasonable to expect a favourable response in allergic bronchial asthma if, by inhalation, sufficient hydrocortisone could be brought into contact with the surface of the bronchial mucous membrane.

Foulds *et al.* (1955) used hydrocortisone acetate in fine-particle powder for 15 patients with bronchial asthma, with encouraging results in 12. Brockbank *et al.* (1956) found no evidence of benefit in patients treated with inhalations of hydrocortisone succinate solution in a "blind" controlled trial; but in a similar trial, using hydrocortisone acetate powder inhalations, Brockbank and Pengelly (1958) report improvement in a statistically significant number of patients on the hydrocortisone as compared with a placebo powder.

The assessment of benefit from any form of "new" treatment in bronchial asthma is notoriously difficult, since so many factors, including emotion, may be important in precipitating attacks and prolonged natural remissions may occur. It is therefore desirable to submit any method of treatment to a controlled trial before a fair assessment of its value can be made.

The purpose of the present investigation is to test by a controlled trial the short-term effect of the inhalation of hydrocortisone acetate in fine-particle powder in cases of bronchial asthma.

Material and Method

The patients selected for the trial had been subject to bronchial asthma for at least one year, and with one exception the condition had been severe enough to necessitate periods off work. The exception was a patient whose attacks were almost entirely nocturnal. In no instance was the history or the state of the sputum indicative of the presence of considerable recurrent or chronic bronchial infection. Patients who had more than $\frac{1}{4}$ oz. (7 ml.) of mucoid sputum daily or who had had any previous treatment with corticosteroid preparations or corticotrophin were excluded.

The "double blind" method of trial was used and patients regarded as suitable were placed by random selection by the hospital group pharmacist into either the hydrocortisone or the placebo group. Both groups were treated by the inhalation of powder from capsules with the aid of a "pabracort" inhaler. The capsules contained either 15 mg. of hydrocortisone acetate (ground to a main particle size of 5 microns), together with 75 mg. of lactose or, in the case of the placebo, 100 mg. of lactose, also in fine particle powder. It was not felt necessary to adopt a rigid dosage scheme, since previous experience with this treatment had suggested that the number of capsules used each day probably bore no close relationship to the quantity of powder reaching the bronchial mucous membrane, and that this depended to a considerable extent on the intelligence of the patients and their ability to inspire deeply.

It was noted in this respect that no settled regime of dosage of oral cortisone was adopted in the Medical Research Council (1956) trial in chronic asthma after the first week of treatment.

The starting dose therefore varied between three capsules a day in severe cases that began the trial during an exacerbation, and one capsule a day taken as half a capsule twice daily in those beginning during a relatively mild phase. The maintenance dose was adjusted according to response, the maximum being two capsules daily and the minimum half a capsule daily. Most patients were maintained on one capsule daily. Patients were given any other routine treatment thought necessary, and where severe wheezing was present bronchial dilator drugs were used directly before the inhalation of the trial powder to facilitate deep inspiration.

In patients who remained severely ill and who had failed to improve on general treatment together with trial inhalations after several days, a "blind" change of treatment was made to the other half of the trial, the patient being unaware that any change had been made. In less severely ill patients who were progressing satisfactorily, but in whom the response was not very clear-cut, a "blind" change of trial treatment was made after one to two months.

Results

The assessment of the results of treatment was made both on subjective and on objective grounds. All patients had had prolonged routine treatment before starting the trial inhalation, and this provided a baseline from which the changes in signs and symptoms could be judged. All patients were seen by the same physician at monthly intervals or less while remaining on the trial. Special attention was paid to the symptoms of dyspnoea and tightness of the chest, to exercise tolerance, and to the need for bronchodilator drugs. On physical examination the presence or absence of wheeze was noted and, if present, was assessed as slight, moderate, or severe, on each visit. In patients with recurrent acute asthma, considerable reliance often had to be placed on the history concerning the frequency, length, and severity of the attacks before and during treatment, and a relatively longer period of observation was usually neces-