

The Treatment of Status Asthmaticus

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Asthma has proved difficult to define (42, 103, 116) and physicians do not always agree about when a patient should be called asthmatic. Status asthmaticus cannot be easier to define, but it seems much more seldom that physicians disagree about a diagnosis of status asthmaticus. The term will be used here to denote a sustained attack of severe asthma that has not responded to the treatment administered by the patient and his doctor. It is a serious and potentially lethal phase of the disease and if hospital admission is possible it will usually be required.

Status asthmaticus is an acute aggravation which may afflict the allergic as well as the non-allergic asthmatic. It may occur at any age, but the risk seems to be greatest in the middle-aged patient with asthma of late onset. It also seems to afflict women more often than men. In seven recent papers (7, 25, 58, 61, 70, 118, 119) out of a total of 1,540 patients, 1,136 were females and 404 males, i.e. a ratio of about 3:1.

We have now fairly good knowledge of the liberation of mediator substances from the mast cell in the reaction with specific allergens and about their possible significance in acute, asthmatic attacks. Yet we do not understand what happens when the patient lapses into status asthmaticus despite the use of the medication which in other situations has successfully brought him relief.

Objective assessment

The treatment of severe asthma must reasonably begin with an assessment of severity. Death

in asthma often comes suddenly and unexpectedly, and even experienced physicians may have difficulty in judging the severity of an attack. The patient may be a better judge in this respect (122), but many asthmatics are not very sensitive to changes in airway obstruction. Rubinfeld & Pain (111) found that 15% were unable to sense a reduction in FEV₁ below 50% of predicted value. An objective assessment ought usually to be the first step taken when dealing with a patient in status asthmaticus. It can be carried out in a few minutes, and it provides both a baseline from which the progress of the patient can be assessed and a grading of the severity of the attack.

The physical signs of wheezing, the use of accessory respiratory muscles and the presence of pulsus paradoxus have not been found to be reliable indicators of the severity of asthma (71, 121).

Counting the heart rate is the simplest of objective measurements and will provide some indication of the severity of the attack. An electrocardiogram and a chest radiograph should also be available. Tachycardia is always a feature of severe asthma and is related to the degree of hypoxaemia (107). The average heart rate is about 120-130. Scoggin (118) found an average rate of 126; Westerman (137) 139 with a range from 110 to 180; Rees (107) 118, range 96-160. Cooke et al. (25) found a heart rate above 90 in 87% of their patients and that 75% of the complications occurred in patients with a heart rate above 130.

Two important objective measurements that any emergency ward should be able to provide,

are estimations of one or more of the parameters of the forced expiration, and of the arterial blood gas tensions. The blood gas tensions may be estimated from capillary blood, but a puncture of the radial or brachial artery is usually easily performed and is to be preferred. The forced expiration may be recorded with a simple spirometer (Vitalograph, Vicatest, Monaghan and others) or with a peak flow meter.

A few patients may be too ill to cooperate in performing a measurement of peak flow or forced expiratory volume, but these are very simple manoeuvres to perform and it is usually possible to get a few acceptable measurements.

Most patients with severe asthma have a peak flow (PEF) below 100 l/min or a forced expiratory volume (FEV₁) below 1 litre. Recorded measurements from emergency ward admissions are PEF 60–120 l/min and FEV₁ 535–1520 ml (56), PEF 30–200 l/min (58), FEV₁ 325–2600 ml (61), FEV₁ 0–1250 ml (106), FEV₁ 200–800 ml (107).

The vital capacity (VC) is also considerably decreased during a severe attack of asthma, and the ratio FEV/VC under these circumstances is not useful as an index of airway obstruction (96).

The arterial oxygen tension in the severely ill asthmatic patient will always be reduced. The carbon dioxide tension is usually low, around 4 kPa (30 mmHg), but may be normal or increased in the most severely ill (25, 27, 58, 61, 68, 70, 106, 107, 113, 118, 123, 130, 134, 137). Thus there is an obvious tendency to hypoventilation in asthma, a pattern distinct from chronic bronchitis in which a decreased oxygen tension usually accompanies an increased carbon dioxide tension.

The arterial gas tensions bear some relation to the degree of airway obstruction. Decreased P_aO₂ is rarely found before FEV₁ is below 2 l or below 50% of predicted normal value. The fall in FEV or PEF and the decrease in P_aO₂ are roughly proportional (61, 70, 90, 92, 106, 107). An increase in P_aCO₂ is rarely found until FEV₁ is below 30% of predicted value (70, 90), or below 1 litre (106).

Arterial pH is usually moderately decreased to about 7.30 but very low values, below 7.00,

are on record (118, 130, 137). The findings are usually those of an acute respiratory acidosis (39, 68) but some patients may have a metabolic acidosis (27).

The beta-adrenergic agents

Adrenaline is the classic drug in the treatment of asthma. It has a powerful bronchodilatory action, but owing to its non-selective action on both alpha- and beta-receptors it may very often have undesirable side effects. It has the shortest duration of action of all the sympathomimetic amines, and with the short or long acting specific beta₂-stimulants now available there are no grounds for including adrenaline in a therapeutic regimen for asthma.

The therapeutic aim is to provide relief from airway obstruction. Studies in fatal cases of asthma (13, 49, 108, 131) have shown the typical findings to be mucus plugging of the bronchi, shedding of the epithelium, eosinophil infiltration and thickening of the basal membrane, changes on which it is unlikely that therapy can have any immediate effect. What the beta-adrenergic agents can do is to act upon bronchial smooth muscle, which presumably contracts during the attack. In addition, the beta-adrenergic agents have an inhibitory effect on the liberation of mediator substances and may have a stimulating effect on mucociliary clearance (11, 91). The clinical significance of these effects is uncertain.

Generally speaking, the patient in status asthmaticus will have used a bronchodilator spray repeatedly before admission and gained very little benefit from it. In view of the pathological findings in patients dying in status asthmaticus it can hardly be surprising that inhalation therapy is less effective, and it seems reasonable to administer a bronchodilator parenterally, as a subcutaneous, intramuscular or intravenous injection. The intravenous route has the advantage of complete absorption and immediate delivery.

The specific beta₂-adrenergic agonists, salbutamol, terbutaline and fenoterol have been the most widely used and they are for all practical purposes identical in action.

Bolus injection of salbutamol was given by Fitchett et al. (37) to patients with severe exacerbation of asthma. A dose of 100–300 μg had maximal effect within 5–10 min in most patients and within 30 min in all of them. Doses of 500 μg had no further effect.

Continuous intravenous infusion of salbutamol has been employed in a large number of asthmatic patients. Infusion rates of 1–2 $\mu\text{g}/\text{min}$ are relatively ineffective, and 2.5–5.0 $\mu\text{g}/\text{min}$ are preferred as the initial dose. The dose may be increased to 10 $\mu\text{g}/\text{min}$ if no response is obtained after 30 min. Higher doses up to 25 $\mu\text{g}/\text{min}$ lead to little further improvement (81). The average half-life of intravenous salbutamol is about 5–6 h and the time to reach steady state plasma levels about 10–12 h, but most of the clinical effect is achieved within 0.5–1 h (81).

The most rapid increase in plasma concentration is obtained by starting with a bolus injection of 250 μg intravenously and continuing with intravenous infusion of 2.5 or 5.0 $\mu\text{g}/\text{min}$. This is the same principle as has been widely used in the administration of aminophylline to patients with severe acute asthma and it also seems a reasonable way to administer a β_2 -adrenergic agent. The infusion rate can be doubled if the response after 30 min is unsatisfactory.

Subcutaneous injection of salbutamol provides an adequate response after 5 min but it takes up to 30 min for peak activity to be reached. A dose of 500 μg has been found to give optimum response, but doses of 750 and 1000 μg can be given if necessary (20).

A comparison of intravenous and aerosol salbutamol (200 μg i.v. vs 5 mg by intermittent positive pressure breathing (IPPB)) showed the intravenous administration to be superior in 10 patients in status asthmaticus (139). Once the patient began to raise sputum, inhaled salbutamol proved as effective as intravenous.

In another study of 16 patients with acute severe asthma, inhalation of 10 mg salbutamol was found as effective as intravenous infusion of 900 μg (20 $\mu\text{g}/\text{min}$ for 45 min) (65), and had no side effects. The divergent findings may be due to the much longer inhalation time (45 min) used in the latter study. In a third study

of 22 episodes of severe acute asthma (6) 10 mg salbutamol administered by IPPB was compared to an intravenous injection of 500 μg , both given over 3 min. Inhalation was deemed more effective, mainly judged by the effect on pulsus paradoxus. The effect on PEF showed no statistically significant difference between the two types of treatment. What the authors actually compared was inhalation followed by intravenous injection 1 h afterwards, with the same treatment given in the opposite order. It is not unlikely that the initial intravenous injection can make the following inhalation more effective, whereas the initial inhalation is less efficacious and may not improve the effect of the later intravenous injection.

It has been sufficiently demonstrated, however, that inhalation therapy may be efficacious even in severe acute asthma. Cooke et al. (25) used inhalation of 0.5% salbutamol as a standard treatment for 276 patients admitted with asthma. The inhalations were given by IPPB for 3 min and repeated every 2–4 h. Most patients were found to respond rapidly, and in some cases dramatically, to the inhalation.

From these recorded experiences it seems fair to conclude that inhalation of a β_2 -agonist is usually effective even in patients with severe asthma, and that a prolonged inhalation of 45 min duration is likely to be more effective than a short one. In the very severely ill patient, intravenous administration is preferable.

The employment of intermittent positive pressure breathing has never convincingly been demonstrated to be better than ordinary inhalation (26, 66, 98). The simple pressure-packed aerosol is generally effective, but nebulization may be slightly better for patients with acute asthma (15). The merit of the nebulizer is presumably that the inhalation can be prolonged, so that the initial portion of the drug will have produced a bronchodilatory effect when the last portion is being inhaled, thus causing it to reach parts of the airways which were not initially accessible. The maximum dose deposited in the lungs is about 10% of that initially present in the nebulizer (114).

IPPB has been claimed to carry a definite risk of inducing pneumothorax in the asthmatic pa-

tient (57). It was used in 276 patients (25) with only two cases of pneumothorax, so the risk does not seem to be high.

Theophylline

Theophylline has for many years been among the first drugs administered to a patient admitted to hospital with an attack of severe asthma. It is usually given intravenously as a bolus injection and should be given slowly over an interval of 10 to 20 min if toxic concentrations are to be avoided. The therapeutic blood levels were found by Turner-Warwick (133) to be at a plasma concentration of 10–20 mg/l and this has been substantially corroborated by all later observers (53, 86, 99). Some effect may be noticed already at 5 mg/l (78, 86), and adverse effects begin to appear when the concentration reaches 20 mg/l. They are headache, anorexia, nausea, vomiting, abdominal discomfort, nervousness, anxiety, arrhythmias and convulsions, in that order of appearance. Atrial tachycardia and ventricular arrhythmias, cerebral seizures, respiratory or cardiac arrest may be produced by a rapid intravenous injection, especially when given through a centrally placed intravenous catheter. The drug should always be infused into a peripheral vein, and rapid intravenous injection is never warranted.

Theophylline is distributed in the organism in a volume of about 0.5 l per kg (41, 95, 105). The estimated values range from about 0.30 to 0.70 l/kg, not affected by age and usually not by sex, although Fixley (38) found lower values for seven females (average 0.41 l/kg) than for five males (average 0.48 l/kg). The apparent volume of distribution appears smaller in obese persons (41), and the use of the ideal weight (or the person's earlier weight when non-obese) is preferable in these cases.

The initial dose of theophylline can be calculated with reasonable accuracy from the estimated distribution volume. If this is taken as half the body weight, a blood concentration about 10 mg/l will require a dose of 5 mg/kg, i.e. about 300 mg for a 60 kg person and 350 mg for a 70 kg person. It should be remem-

bered that aminophylline contains 75–85% theophylline (95).

The difficulties in administering theophylline are due to the rather narrow therapeutic range of plasma concentration and the widely varying elimination rate of theophylline in different persons. Theophylline has a mean half-life in adults of about 4.5 h, with a range between 3 and 16 h (53, 87, 95, 99). It is lower in children; mean value 3.6 h, range 1.4 to 9.5 h (31, 53, 78, 86, 99). The half-life is significantly shorter in smokers than in non-smokers (17, 46, 50, 104, 105). Patients with hepatic cirrhosis have a prolonged plasma half-life; the mean value in nine patients was found to be 25.6 h (100).

Other drugs may also interfere with the elimination of theophylline. Erythromycin is a potent inhibitor (63), whereas phenobarbitone has a tendency to increase theophylline elimination. This can be of practical interest since phenobarbitone, on no rational basis, is commonly included in combination products used for asthma.

Thus, though the loading dose of theophylline can be estimated with an acceptable accuracy, the maintenance dose is difficult to calculate, and for longer treatment an estimation of serum theophylline is necessary. If rapid relief of the symptoms is aimed at, a loading dose is mandatory. An improvement can be measured within 15 min after a loading dose (78), whereas it may take several hours before an improvement is noted during continuous infusion.

Mitenko & Ogilvie (86) recommended an intravenous loading dose of aminophylline of 5.6 mg/kg, given over 20 min and followed by an intravenous maintenance infusion of 0.9 mg/kg per hour. This scheme has been widely used but has met with some criticism. It is based on studies of nine asthmatic patients (17–56 years) and aimed at producing a plasma theophylline concentration of about 10 mg/l. Later it has become apparent that many older or seriously ill patients reach higher plasma concentrations which may produce adverse effects. Powell et al. (105) estimated that about 40% of their acutely ill patients would reach plasma theophylline concentrations above 20 mg/l. It is suggested

that older patients should receive a 25% reduction in infusion rate and patients with congestive heart failure or liver disease a 50% reduction (55).

The difference between smokers and non-smokers with respect to theophylline elimination has not always been taken into account. Smoking was found to increase theophylline clearance by about 60% (104). A lower maintenance dose in non-smokers will be appropriate, and 0.4 mg/kg/h of theophylline (0.5 mg of aminophylline) has been recommended (46). Inter-individual variation in theophylline clearance was found significantly higher in patients than in healthy control subjects (105) and the clearance in general was considerably lower than in the patients studied by Jenne et al. (53) and Mitenko & Ogilvie (87). Powell et al. (105) recommend a standard infusion rate of 0.5 mg theophylline/kg/h, varying from 0.2 to 0.8 mg according to the clinical situation (smoker, congestive heart failure, pneumonia, liver disease, etc.). An estimation of plasma theophylline must be made preferably between 18 to 36 h of starting the maintenance dose. The new infusion rate should be the old rate multiplied by the ratio of the target concentration to the measured concentration (105).

If a patient has previously been taking oral theophylline preparations in therapeutic doses the loading dose should be reduced and may be cut to half the estimated value. The maintenance dose is of course unchanged.

Theophylline vs beta-adrenergic agents

Theophylline and the beta-adrenergic agents are both effective in the treatment of asthma. Intravenous aminophylline and intravenous salbutamol have been compared in several studies, usually as mg to μ g, i.e. 250 or 500 mg aminophylline compared to 250 or 500 μ g salbutamol. The results have been equally good in the reported series of about 100 patients (5, 35, 43, 138).

Theophylline has for many years been a favourite drug in status asthmaticus. Knowledge of the pharmacokinetics led to the scheme of intravenous treatment, which soon became very

popular. It secures a rapid action and maintains a plasma concentration in the therapeutic range if the patient does not differ too much from the average as regards elimination rate of theophylline. This, of course, is the salient point. The loading dose of theophylline can be estimated with acceptable accuracy from the body weight (or lean body weight, for the very obese), but the maintenance dose is much more difficult to estimate reliably. The therapeutic range, a plasma concentration of 8 to 20 mg/l, is rather narrow, and higher values rapidly give rise to toxic symptoms, some of them serious. Earlier administration of theophylline to the patient may add to the difficulties in the estimation of a correct dose.

With the specific beta₂-adrenergic agents now available, it is possible to accomplish whatever theophylline can do, with very little risk of serious side effects. These drugs may also be given intravenously to obtain a rapid effect, e.g. 250 μ g of salbutamol or terbutaline, followed by intravenous infusion at a rate of 5 μ g/min, increased if necessary to 10 or 20 μ g/min.

Earlier administration of a beta-adrenergic agent to the patient will rarely cause any difficulty. The only side effect likely to be met with is tremor, which is due to a direct effect on skeletal muscle beta₂-receptors (64). It is not usually troublesome in the acute situation, when the patient can be told that it is caused by the medication and will disappear when the treatment is no longer necessary.

There is very little direct effect on the heart except a tendency to increased heart rate, which is mainly caused by peripheral vasodilatation, but the treatment may also cause a fall in heart rate when the asthma improves.

No serious side effects have been reported from the beta₂-adrenergic drugs in asthma. They have also been used for the treatment of premature labour, and there are reports of pulmonary oedema developing during this treatment (30, 93, 110, 132). In this situation the drugs have usually been administered for a considerably longer time than in the case of asthmatic patients, and the tendency to sodium and water retention at the end of pregnancy is likely to be an important contributory factor.

Both aminophylline and the β_2 -adrenergic substances are effective drugs in status asthmaticus. Aminophylline, however, is much more likely to produce serious side effects, whereas the β_2 -adrenergic agents can usually be administered with few side effects, and their dose can safely be regulated from the clinical response. Today, the β_2 -adrenergic agonists must be considered as first choice in the treatment of the severely ill asthmatic. If the response during the treatment is not satisfactory it will always be possible to add aminophylline, which in combined treatment can be given in a low dose with little risk of side effects, e.g. 0.5 mg/kg $\times$ h. The combination of aminophylline and a β -adrenergic agent is pharmacologically rational, both drugs acting in different ways to increase the intracellular concentration of cyclic AMP. It has been shown to have an additive, but rarely a synergistic, effect (12, 29, 76, 128, 140). However, in a series of 56 patients (54) no significant difference was found between treatment with adrenaline 0.3–0.5 mg at 30 min intervals and the same treatment combined with infusion of aminophylline.

Glucocorticoids

The action of the glucocorticoids in asthma is still incompletely understood. They have very little effect on immediate hypersensitivity (IgE mediated type I reaction), but they do suppress the delayed response (immune-complex mediated type III reaction). They do not seem to have any important effect on the control of chemical mediators that may be related to asthma in man.

Our knowledge of corticosteroid action has been reviewed recently by Claman (18), Middleton (84), NIH conference (94), Chan & O'Malley (16), Collins & Jones (24) and Svedmyr (129). The glucocorticoids are bound to a specific cytoplasmic receptor protein in the target cell. The steroid-receptor complex is transported to the nucleus, bound to the genome, where it induces the production of a specific messenger-RNA which is transported to the cytoplasmic ribosomes. Here it leads to the synthesis of the specific proteins believed

responsible for the corticosteroid effects. Obviously this process must take some time and this is consistent with the period of latency between the administration of a corticosteroid and the time when its effects can be demonstrated clinically.

Cortisone was the subject of the first controlled trial in status asthmaticus, carried out in 1956 by the British Medical Research Council shortly after the drug had become generally available (82). It comprised 32 patients all given conventional treatment with subcutaneous adrenaline, intravenous aminophylline and isoprenaline inhalation for 24 h, at which point those who had still not responded were randomly allocated to receive either cortisone or placebo. The dose of cortisone was 350 mg for the first 24 h, 200 for the next, and then gradually reduced by 25 mg daily. The treatment lasted for 9 days and the total dose administered was 50 tablets or 1250 mg cortisone acetate. The patients were clinically assessed twice daily with evaluation of the degree of bronchial obstruction in 5 grades and counting of pulse rate and respiration rate. Objective measurements of lung function or of arterial blood gas tensions were not performed. The cortisone group began to show an advantage over the control group by day 2. This difference became marked by day 4 and continued until the end of the trial. Eleven out of 15 in the cortisone group and four out of 17 in the placebo group obtained complete relief. This is a highly significant difference, evaluation by chi-square test gives $\chi^2 = 7.9$, $0.01 > P > 0.001$. Thus the study demonstrated that glucocorticoids are effective in status asthmaticus and that it takes time for them to reach their full effect. When glucocorticoids are compared to placebos or to other drugs used in status asthmaticus, 24–48 h should be the shortest period for any valid comparison.

Another controlled study on glucocorticoid therapy was carried out by Pierson et al. (101) on 45 children in status asthmaticus. Fifteen children received placebos and 30 glucocorticoids. They were assessed by lung function tests (FEV and FVC), arterial blood gases and by a clinical score of physical signs. The patients in

the glucocorticoid-treated group showed a significantly greater improvement in their arterial oxygen tension during the first 24 h (mean values 58.5 rising to 78.1 mmHg against an increase from 57.9 to 64.4 mm in the control group). The clinical score and the lung function tests improved in an identical manner in the two groups.

These two studies (82, 101) form the basis of the present day employment of glucocorticoids in severe acute asthma. There have been two other controlled studies, which somewhat disturbingly have been unable to demonstrate beneficial effects of the glucocorticoids.

McFadden et al. (72) treated 38 acutely ill asthmatic subjects with either placebo, 250, 500 or 1000 mg hydrocortisone intravenously, followed by inhalation of isoprenaline at hourly intervals for 6 h. No difference was found in the course of the four groups, who were followed with measurements of forced expiratory volumes and of airway resistance and conductance in a body plethysmograph. All asthma attacks had ended clinically before the study was terminated, and these patients obviously did not have severe asthma. Their major improvements in lung function tests were seen at 1–2 h, i.e. before any effect of hydrocortisone would be evident.

In a recent study on children in status asthmaticus, Kattan et al. (59) compared 10 children given hydrocortisone (7 mg/kg intravenously with 6 h intervals) to a control group of nine children. Both groups received treatment with intravenous aminophylline and inhaled salbutamol. The children had moderately severe asthma with an average clinical score of 6–8 on a 0–12 scale. They were clinically assessed after 12, 24 and 48 h and no difference between the groups could be demonstrated at any time. Improvements were marked in both groups and PEF reached values about 60% of predicted after 36 h. The response was very similar to that found by Pierson et al. (101), and it is unfortunate that estimations of blood gases were only performed initially and not repeated in the study of Kattan et al.

These two studies (59, 72) clearly demonstrate that airway obstruction in children in

status asthmaticus can be improved by the usual bronchodilatory treatment with beta-adrenergic agents and theophylline. If glucocorticoids give an added effect, as we believe them to do, it seems predominantly to be by an action peripherally in the lungs, such as may be reflected by an increase in arterial oxygen tension.

The most important effect of the glucocorticoids in asthma is presumably their anti-inflammatory action, which involves both an effect on the blood vessels leading to a decreased permeability, and a reduction in the number of inflammatory cells, neutrophils and macrophages as well as eosinophils. Besides, the glucocorticoids seem able to potentiate the action of beta-adrenergic agents. It is a common clinical observation that the severely affected asthmatic patient who does not respond to the beta agonists, may regain responsiveness during glucocorticoid treatment (3, 34, 120). Normal subjects with an induced resistance to beta agonists may have their bronchodilator sensitivity restored after treatment with hydrocortisone (48). No such effect was evident in the three studies on children in status asthmaticus (59, 72, 101), and children may perhaps differ from adult asthmatics with regard to this action of the glucocorticoids.

There are a number of observations on adult asthmatics regarding the time required from the administration of a glucocorticoid to any observable effect on lung function, usually estimated by PEF or FEV. The earliest effect was observed 1 h after intravenous injection of hydrocortisone or prednisolone in patients with chronic bronchial asthma (32, 33), and the same authors found the maximum effect 5 h after hydrocortisone and 8 h after prednisolone. Klausmeyer & Hale (62) found the earliest response to intravenous methylprednisolone at 2 h, with a peak response at 4–6 h. In patients with severe acute asthma it took 6–8 h for a significant improvement in FEV or FVC after hydrocortisone, and 140 to 170 h for maximum improvement in FEV or PEF (23). After a single oral dose of prednisolone it took 3 h for a significant improvement to be demonstrated in patients with chronic bronchial asthma (32) and

maximum effect was not seen until 9–12 h after the start of treatment. In status asthmaticus, where the response seems to occur slower than in chronic bronchial asthma, it seems obvious that the initial doses of glucocorticoid are best given intravenously.

The optimal dose of the glucocorticoids cannot be said to have been established, but in the treatment of severe asthma the majority have settled for a dose about 3–4 mg/kg body weight with intervals of 4–6 h. The dose of 4 mg was suggested by Collins et al. (22), who later found 3 mg/kg to be satisfactory (23). In practice 200 mg hydrocortisone is the usual dose administered to an adult patient. Very high doses of a glucocorticoid (methylprednisolone) have not been found to offer any advantages in controlled studies of the treatment of severe asthma, either in adults (9) or in children (45).

Treatment with corticotropin or tetracosactrin can be as effective as intravenous hydrocortisone (23), but it cannot be recommended for patients who have previously been treated with corticosteroids. The dose is supramaximal and the effect varies with the response of the adrenals. Their response cannot be regulated as the doses of hydrocortisone can, and the side effects are much more pronounced, including hypertension and fluid retention, which may be troublesome in elderly patients. The onset of the effect is also slower than after intravenous hydrocortisone (23).

The recommended doses of hydrocortisone may well be higher than necessary in many cases, but for a short period of treatment as usually will be the case, no harm is done. Collins et al. (22) settled for the dose of 4 mg/kg after estimations of plasma 11-hydroxycorticosteroid, the aim being to keep the plasma cortisol concentration above 1 mg/l. This is a level which Dwyer et al. (28) considered necessary for a satisfactory clinical response, based on a study of five steroid treated asthmatic patients, who did not show clinical improvement until plasma cortisol had reached values above this level. These authors do not seem to have taken into account the time necessary for an effect of cortisol to be clinically manifest. Cayton & Howard (14) did not find plasma

cortisol levels a useful guide to therapy.

It is a reasonable assumption that a fairly high plasma concentration of a glucocorticoid is desirable in severe acute asthma, but it does not seem necessary for it to be continuously high. In the long term treatment of asthma a single dose of prednisone or prednisolone every 24–48 h is usually sufficient. The glucocorticoids perform their action long after the plasma concentration has fallen to zero or very low values. It has been advocated to administer the glucocorticoids as a continuous intravenous infusion (2, 3), but the rationale is not convincing.

Supporting measures and some drugs of questionable value

Even the asymptomatic asthmatic may have abnormal lung function and ventilation-perfusion disturbances (67, 71, 135). The severely ill patients with asthma always have a decreased arterial oxygen tension and will usually need treatment with oxygen. It can be administered without risk of a rise in carbon dioxide tension in the great majority of cases, e.g. with a Venturi mask delivering 28 or 35% oxygen.

Recently it has been convincingly demonstrated that heat loss from the intrathoracic airways is the initiating stimulus for airflow obstruction induced by exercise in asthmatic subjects (73, 74). Inhalation of air saturated with water vapour and heated to body temperature will prevent the reaction. A case can thus be made out for supplying the patient in status asthmaticus with hot and humid air enriched with oxygen. One very simple and effective method for doing this was described by Lomholt (69).

Asthmatic patients often produce very viscid sputum (60) and mucolytic agents might be helpful. Iodine is the classical remedy but its effect has never been convincingly demonstrated in man. Bromhexine has been shown to produce a disintegration of the mucopolysaccharides in sputum (10). It was found to have some effect in chronic bronchitis (21, 44), but a multicentre trial on 42 patients could not demonstrate any difference from a placebo (8). Rudolf et al. (112) used it in a controlled study

of 14 patients with severe asthma, given in the high dose of 24 mg 3 times daily. No effect on sputum production, PEF or arterial blood gases was shown.

The beta-adrenergic agents have been shown to stimulate ciliary function and accelerate mucus clearance within the human tracheo-bronchial tree (11, 40, 83, 91). In healthy subjects, a marked increase in mucociliary transport velocity was demonstrated after the administration of terbutaline. A similar effect, but less pronounced, could be demonstrated in asthmatic subjects (91). This effect offers an extra argument for employing the beta-adrenergic agents in the treatment of severe asthma.

Status asthmaticus often seems to be precipitated by infections of the upper airways, usually virus infections. Respiratory syncytial virus and rhinoviruses are the prominent causes in children (75). The rhinoviruses also seem to be important precipitants of asthma in adults (85), but infection as a factor causing exacerbations of asthma in adults may be less important than in children. Clarke (19) could demonstrate an association in only 12 of 111 exacerbations (10.8%) in adult asthmatics, and bacterial infection was found in only five of the 111 exacerbations. Bondi & Williams (7) found pathogenic bacteria in sputum in three of 59 patients. The routine employment of antibiotics does not seem warranted.

Acid-base disturbances are not rare in severe cases of asthma. The great majority are cases of respiratory acidosis (39, 68), and they are usually best treated by placing the patient in a respirator, where the acidosis is easily controlled by an increase in pulmonary ventilation. Administration of sodium bicarbonate may be indicated in very rare cases of severe metabolic acidosis, especially if cardiac or respiratory arrest has occurred. There have been reports of a favourable effect of sodium bicarbonate also in severe respiratory acidosis (88, 89), in one case with the extremely low value of 6.66 in arterial pH. The authors point out that the correction of acidaemia restores the responsiveness to the beta-adrenergic agents, and that mechanical ventilation may be avoided by this approach. This seems a risky policy and one

would feel that such patients were better treated by mechanical ventilation at a much earlier time. Moreover, Reisman et al. (109) could not demonstrate a restored responsiveness to adrenaline after correction of acidaemia by assisted ventilation. A nonresponsive phase with very little improvement in FEV after bronchodilatory therapy is commonly found in the patient with severe asthma. The time taken to achieve a responsive phase ranged from 1 to 18 days in the 58 patients studied by Rebusck & Read (106).

Dehydration may be a feature of status asthmaticus. Straub et al. (127) found an increase in haematocrit and a decrease in blood volume in nine patients. Baker et al. (4) found plasma antidiuretic hormone to be elevated in seven patients in status asthmaticus. This carries a risk of hyponatraemia and water intoxication with rehydration. The very high negative pleura pressure may precipitate pulmonary oedema (125). Rehydration is usually accomplished with the fluid replacement which occurs when a treatment with intravenous infusion is established. Isotonic glucose should be preferred to electrolyte solutions, owing to the slight risk of inducing pulmonary oedema.

Sedatives are potentially dangerous and not helpful in the treatment of severe asthma. They can only be safely used when the patient is in a respirator.

Cholinergic innervations of bronchial smooth muscle is well demonstrated in the larger airways down to the terminal bronchioles (126), and normally there is a slight smooth muscle tone due to efferent vagal activity. Cholinergic agents increase the tone of bronchial smooth muscle, anticholinergic agents act competitively with acetylcholine on the muscarinic receptors and may block the effect.

The parasympathetic nervous system has only a minor influence on antigen mediated bronchoconstriction in humans (36). Atropine and its derivatives act by reducing the resting bronchomotor tone. Used systemically they cause a number of undesirable side effects, but the inhalation of atropine methylnitrate or of ipratropium bromide leads to a local action in the lung, with negligible systemic effects. They act mainly on the larger bronchi (47, 52) and in

general these drugs seem more effective in patients with chronic, non-specific obstructive lung diseases than in asthmatic subjects (77, 97, 102, 117). Patients with severe asthma, requiring steroid therapy, did not respond to atropine (1) and the atropine derivatives do not seem to be useful in status asthmaticus.

The prostaglandins, PGE_1 and PGE_2 , are theoretically useful therapeutic agents in asthma. They have a bronchodilatory effect and are also able to inhibit the anaphylactic release of histamine and slow reacting substance (SRS-A) (80). They stimulate the formation of cyclic AMP, acting on a receptor different from that of the beta-adrenergic agonists, and might be effective in patients unresponsive to the beta agonists. Aerosol administration of prostaglandin E to asthmatic subjects has been shown to cause bronchodilation (79, 124), but the effect has been limited by local irritation, a short duration of action and host defense mechanisms.

Antagonists of SRS-A have so far not been found clinically useful. The chemical structure of the slow reacting substances has recently been clarified. They are derivatives of eicosatetraenoic acid, labelled leukotrienes (115), SRS-A being a mixture of leukotriene C and D. There is reason for hope of the development of new and clinically useful antagonists.

Artificial ventilation

Most patients in status asthmaticus will respond to medical therapy with bronchodilators and glucocorticoids. Patients needing artificial ventilation are rare. They may indicate a therapeutic misadventure, such as the administration of sedatives, or the failure of conventional therapy. Mechanical ventilation is the last resort for the severely ill patient with acute asthma. On the other hand, status asthmaticus presents an ideal setting for mechanical ventilation, an acute, potentially fully reversible respiratory failure, which usually requires only 24–72 h in the respirator before the medical treatment has become effective enough for the patient to be let out again.

Nevertheless, it is a procedure connected with an appreciable mortality. In the larger series published during the last 10 years the average mortality rate was about 20% (51, 118, 119, 136, 137). Another interpretation of this figure is, of course, that 80% of patients about to die in status asthmaticus can be rescued by artificial ventilation. What the figures do tell us is that the patient in status asthmaticus is seriously ill and may die from his illness, and if he is thought to be in a high risk group he is also likely to be placed in a respirator.

The aim of the treatment is to relieve the exhausted patient of the excessive work of breathing, to restore normal blood gases, to allow removal of retained secretions and sometimes to allow the use of sedatives. Criteria for starting ventilation, as given by Webb et al. (136) are evidence of deteriorating pulmonary function, i.e. falling P_aO_2 and rising P_aCO_2 , the danger levels being an oxygen tension about 5–6 kPa and carbon dioxide tension about 7 kPa, evidence of deteriorating cardiac function with a rising heart rate (above 140 min), onset of dysrhythmia, presence of pulsus paradoxus, and general evidence of exhaustion, slurring of consciousness, fall in urinary output and onset of acidosis.

The ventilation is best performed with nasotracheal intubation and the use of a volume pre-set, time-cycled respirator. With a pressure cycled respirator it will usually be difficult to give sufficient ventilation. The airway pressures needed are on the average 50–60 cm H_2O , but pressures of 70–80 cm have been necessary (51, 136). Respiratory rate should generally be kept low, about 12–14/min, with expiration occupying at least 50% of the cycle. The expiration should have come to an end before the next inspiration starts. These patients are hyperinflated and it is important that they do not get further inflated during the treatment. Oxygen should be added to the inspiratory air in sufficient quantity to maintain the arterial tension at normal levels. The carbon dioxide tension should not be brought down precipitously, a fall of about 1 kPa/h is considered optimal (136). The patient can usually be kept intubated for about a week before tracheostomy

has to be considered, and most patients will be out of the respirator by that time.

It is rarely necessary to use mechanical ventilation in the treatment of status asthmaticus. Westerman et al. (137) found it required in six of 2000 admissions for severe asthma, i.e. 0.3%. In this small minority it is a treatment which may be life saving, and the published figures for the mortality suggest that it has many times been undertaken too late.

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