Management of status asthmaticus

HARRY A. REES

University Department of Medicine, Royal Infirmary, Edinburgh

Mortality

Status asthmaticus is a term which is universally used but not uniformly defined. It is generally taken to mean an acute episode of 'bronchospasm', severe enough to cause distress to the patient and which is not relieved by conventional 'bronchodilator' therapy.

Is status asthmaticus a transient event in the life of the asthmatic patient; can it be treated as a minor incident? I think the following data will convince you that nothing is farther from the truth. It consists of the deaths in the Cardiff area for the years 1951 to 1964 and I am grateful to Dr D. A. Williams for generously making it available to me. There were 111 deaths over this period (Fig. 1), an average of

FIG. 1. Deaths from asthma in the Cardiff area from 1951 to 1964. Thirty-eight at home, seventy-three in hospital (total 111).

1.8 per 100,000 population per annum and which is comparable to the annual death rate from asthma in America of 1.6 per 100,000 (Derbes & Engelhardt, 1946) but is much less than that reported by Williams (1953) of 7.07 per 100,000 for England and Wales. It appeared by 1960 that the problem was well under control, but there has since been an upward trend in mortality. This is also seen in the Reports of the Registrar General for England and Wales. Although death occurred at all ages in the Cardiff group, only 5% were under the age of 20 years (Fig. 2). Thirty-nine per cent occurred between 20 and 50 years and 51% between 51 and 70 years. The ratio of male-female deaths was 1:2 at most ages. Most had long histories of asthma with frequent episodes of status

asthmaticus, but of great interest were a few who died during an attack which did not appear to be severe and in some cases certainly not as severe as previous ones. Most of us have had this startling experience. It is surprising that at post-mortem the lungs of these patients who died suddenly should show the same appearance as those dying in status asthmaticus (Walton, Penner & Wilt, 1951; and personal observation), and serves to illustrate the fallibility of clinical assessment in certain cases of status asthmaticus.

FIG. 2. Sex and age distribution of deaths. ○, Female; ×, male; ●, total.

Detailed study of mortality statistics, though instructive, does not enable us to pick out the individual who is at particular risk from status asthmaticus.

Prevention

It follows that if the frequency and severity of status asthmaticus could be reduced, then there should be an accompanying fall in mortality. Although there are no adequately controlled studies it seems likely that the judicious use of long-term corticosteroids and/or ACTH has helped to reduce the frequency of status asthmaticus. It should be emphasized that this form of therapy should only be employed in intractable asthma when all other measures have failed. It was possible, using this regime, to reduce the frequency from 42% to 4.4%

in a group of 317 patients receiving long-term corticosteroid and/or ACTH therapy for longer than 3 months (Rees & Williams, 1962). Some workers favour an intermittent regime for so many days each week and this approach may be better in children. Although it should be possible to prevent status asthmaticus with large doses of steroids used continuously, the accompanying serious side-effects preclude this. Therefore the aim should be to use the smallest dose of steroid which enables the person to lead a useful life and not to try to get him/her completely free of bronchospasm. In most cases this is 5–10 mg of prednisone taken with 'bronchodilators'. Patients on long-term corticosteroids should be reviewed frequently (Rees & Williams, 1962).

When increased 'bronchodilator' therapy fails to control increasing 'bronchospasm' we have found it useful to instruct the patient to increase the dose of prednisone to 40 mg/day. Those subject to infective asthma are either given a reserve supply of an antibiotic to take at the first sign of a chest cold, or advised to increase the dose if they are receiving long-term antibiotics. Ideally all patients in status asthmaticus should be admitted at the onset of the episode, but this may be impracticable. If, therefore, the 'bronchospasm' remains unaltered after 24 hr of increased steroids and, possibly, antibiotics, the patient is advised to contact the general practitioner, who should arrange for hospital admission. We feel to persevere with treatment at home for longer than 24 hr may be dangerous. Of the 111 deaths in the Cardiff area, one-third occurred either at home or in transit to hospital and it is possible that some of these may have been avoided.

You may well ask why mortality is rising despite the wider use of corticosteroids? The problem is complex and there are several possible explanations other than ineffectiveness of long-term steroid therapy. It may be that the incidence of bronchial asthma is changing and that some asthmatic patients who would have died some years before have had their lives prolonged by the use of corticosteroids. Whatever the explanation, this further increase in deaths stresses that status asthmaticus is a serious and sometimes fatal condition.

Other novel measures such as glomectomy (Curran *et al.*, 1966), hypnotherapy (Maher-Loughnan *et al.*, 1962) and treatment in a pressure-chamber (Tromp, 1964) have only a limited application.

Therapy of acute attack

My terms of reference are the 'medical' treatment, and the Liverpool group will discuss their results with assisted ventilation. In an attempt to gain a better understanding of status asthmaticus we have been monitoring the arterial gas tensions and pH

(Rees, Millar & Donald, 1967). It is in the light of these findings that I propose to discuss conventional therapy, which is listed below:

1. Oxygen
2. Bronchodilators
3. Corticosteroids and/or ACTH
4. Antibiotics
5. Fluid replacement
6. Sedation
7. Other measures

1. Oxygen

The main limiting factors to the administration of oxygen for the relief of hypoxaemia in patients with chronic lung disease are the loss of chemoreceptor drive when the hypoxaemia is relieved, and the possibility of atelectasis. All the patients we studied were hypoxaemic, and the patient illustrated in Fig. 3 is an example. Arterial oxygen tensions (P_{aO_2}) as low as 30 mmHg were common in those who were obviously severely ill. In the severely ill patient it is likely that the cardiac output is reduced, which will interfere with the delivery of the available oxygen to the tissues. Some of this group were hypercapnic. They were also acidotic from respiratory and metabolic causes. In a situation where life is jeopardized by lack of oxygen, the possibility of atelectasis is more theoretical than real. It would appear that vast shunting of blood may occur through the lungs of patients in status asthmaticus. This is, perhaps, not surprising in view of the widespread bronchiolar plugging which is well seen at post-mortem.

Where facilities exist for monitoring arterial gas tensions, it is relatively easy to adjust the concentration of oxygen that is administered. Controlled oxygen through an Edinburgh or Venturi mask or nasal spectacles is indicated for the hypercapnic patient. It is not known what constitutes a safe level of P_{aO_2} or, more important, what is a safe level of tissue oxygen tension. We aim to maintain the P_{aO_2} above 50 mmHg and in most cases this can safely be achieved with oxygen delivered through a Polymask. It is advisable to bubble the oxygen through water in an attempt to maintain hydration of the airways and so to prevent the bronchiolar plugs of mucus, etc., becoming tenacious. The flow rate at the mask is lower than that registered on the flowmeter, particularly at the lower ranges, because of the resistance to oxygen as it bubbles through the water. Most hospitals have apparatus for measuring PCO_2 and pH and if it is not possible to obtain arterial blood, then properly 'arterialized' venous blood (Harrison & Galloon, 1965) may be a useful guide. Alternatively, mixed venous PCO_2 may be measured by the rebreathing technique (Campbell & Howell, 1962) and if the concentration of bicarbonate is also determined the pH can be deduced from

the Henderson-Hasselbalch equation. Where no facilities exist for making measurements of the PCO_2 and/or pH, then increasing flow rates of oxygen should be administered, starting at 1 l/min and assessing the clinical response closely. At the first sign of drowsiness the administration of oxygen should be temporarily discontinued while respiratory stimulants are given and oxygen then restarted at lower flow rates.

Rector *et al.* (1960) have shown that it takes up to 4 days for maximal reabsorption of bicarbonate to occur in dogs. The chronic asthmatic patient, who is normally hypo- or normocapnic, is unstrategically

great, this form of therapy may be proved to be beneficial.

Of great interest and hitherto unrecognized, is the fact that the hypoxaemia persists on breathing air for many days (Figs. 3 and 4) in the face of apparent clinical improvement. Additional hypoxaemia from further acute bronchiolar obstruction could be lethal. The persisting hypoxaemia indicates the need to continue oxygen therapy for 2 weeks in most cases and the importance of having the patient in hospital under surveillance for 3 weeks. I have dealt with oxygen therapy at considerable length; I make no apology for it—it is of vital importance.

FIG. 3. Results of arterial gas tensions and pH in one patient (J.L., female, 20 years old) during and following treatment of acute status asthmaticus. PO_2 (●), PCO_2 (○), pH (×).

placed to meet any rapid increase in $Paco_2$. We have therefore set arbitrary safe limits of $Paco_2$ of 50 mmHg and of pH=7.30, the latter probably being more important than the former. However, each case has to be judged on its own merits and such features as physical exhaustion, rapidity of rise in $Paco_2$, fall in pH, have all to be considered before deciding to institute assisted ventilation. Hypercapnia is a grave prognostic sign and this has previously been noted by Williams & Zohman (1960) and Feldman (1962). Where severe hypercapnia, i.e. $Paco_2$ of 60 mmHg and/or severe acidosis, i.e. pH < 7.25, exists on admission, then there should be no delay in starting assisted ventilation. However, we do not feel that assisted ventilation is needed as frequently as reported by Marchand & Van Hasselt (1966). Assisted ventilation is not without its complications, such as difficulty in maintaining an adequate circulation, infection, etc. Nevertheless, we feel that in a situation where the risk of death is so

2. Bronchodilators

(a) *Adrenaline*. This may be given subcutaneously in doses of 0.5–1.0 ml, 1:1000 solution over 10 min. Broom (1961) has advocated larger and more frequent doses intramuscularly but it has been well demonstrated by Whelan & Young (1953) that, despite the continued intravenous infusion of adrenaline, the maximal response was obtained at 10 min and thereafter a return to the pre-injection state occurred. In view of the rapidity of action when given subcutaneously there is no point in taking the potential risk of producing arrhythmias by giving it intravenously. To our immense surprise, we found that adrenaline produced no real change in Pao_2 even when there was subjective, and (in some cases in whom forced expiratory volume in 1 sec could be recorded) objective relief of airways obstruction (Fig. 5). There was no correlation between the so-called adrenaline-fast state and the level of systemic arterial pH. Furthermore, we have found that even

when the pH has been corrected using sodium bicarbonate, as advocated by several groups including Mithoefer, Runser & Karetzky (1965), the injection of adrenaline has produced no real change in the

patients had been using an isoprenaline inhaler at frequent intervals shortly before admission. The suggestive findings of Lockett (1965) using a Starling preparation, that a combination of isoprenaline and

FIG. 4. Serial arterial oxygen tensions measured in the same patients breathing air.

FIG. 5. Changes in arterial oxygen tension (●) and forced expiratory volume (▲) in 1 sec and vital capacity (□) in three patients after 1.0 ml of 1:1000 adrenaline s.c. (Ad) and 0.5 g of aminophylline i.v. (Am).

P_{aO_2} . That is not to say that the correction of acidosis may not have other merits. During the continuous monitoring of the electrocardiogram for 1 hr or so, when adrenaline has been given, atrial ectopic beats were frequently seen. Many of the

adrenaline may produce cardiac arrest makes it prudent to avoid this combination, although there is, as yet, little convincing clinical evidence for this view. It does seem rational to expect a myocardium that is inadequately oxygenated to be more 'irritable' and

thus to be more susceptible to arrhythmias. Dramatic falls in mean systemic arterial pressure of up to 50 mmHg have been noted and this could prove dangerous.

In view of all these findings, I feel that adrenaline—a time-honoured therapy—should be discontinued.

(b) *Aminophylline*. We found that the intravenous injection of 500 mg of aminophylline produced changes in the P_{aO_2} similar to those produced by adrenaline. Nausea and sickness were noted in the occasional patient but there were no arrhythmias. The differentiation of left ventricular failure from asthma in the elderly patient can be difficult, even to the experienced, and it is in this situation that aminophylline is particularly useful. Suppositories (one or two) at night are also effective. The oral dose required to produce relief provokes severe gastric irritation and vomiting. In a situation where the work of breathing is greatly increased (McIlroy & Marshall, 1956) any decrease produced by relieving airways obstruction is valuable.

Other oral 'bronchodilators' such as isoprenaline and ephedrine are not particularly helpful in the acute situation.

3. Corticosteroids and/or ACTH

As many patients will have been on long-term corticosteroid therapy it seems more rational to give corticosteroids rather than ACTH. The dosage usually used is 60–100 mg of prednisone during the first 24 hr and adjusting it thereafter according to clinical progress. Some workers favour hydrocortisone given intravenously, 50–100 mg every 6 hr, and it is often useful to give 100 mg intravenously at the start of therapy with oral prednisone. Grant (1966) favours much higher initial doses of corticosteroids. Others have found ACTH 40 units, every 4–6 hr given intramuscularly, or 60 units in 1 litre of fluid given intravenously over 6 hr, followed by intramuscular therapy, to be useful. Although corticosteroids and ACTH take many hours or days to produce any effect, it is likely that they play an important part in therapy. As loss of potassium may occur with large doses of steroids and ACTH, watch must be kept on the serum potassium level and supplements given orally if necessary. Scribner, Freemont-Smith & Burnell (1955) have also shown that overall potassium depletion exists when acidosis is present, even though the serum level may be normal.

4. Antibiotics

Ideally sputum should be cultured and therapy instituted accordingly, but in the situation of status asthmaticus this approach is impossible. Unless the precipitating factor is obviously allergic or psychological, it is wise to give a bactericidal antibiotic such

as penicillin and streptomycin or ampicillin. Three patients given terramycin with high dosage of corticosteroids developed severe pneumonia from a hospital penicillin-resistant staphylococcus, whereas no other patient on bactericidal drugs did. This, of course, is a clinical impression and as such has to be interpreted cautiously. It is worth noting that sputum containing large numbers of eosinophil cells may be yellow.

5. Fluid replacement

Dehydration is often overlooked. When one takes into account the poor fluid intake because of severe dyspnoea, the excessive loss during respiration and often increased loss through the skin of a feverish patient, then there is more than sufficient cause for the dehydration. Close check should be made on the urinary output and the intake adjusted accordingly. It may be necessary to give intravenous fluids—preferably 5% dextrose, rather than saline, even though I do not believe congestive cardiac failure occurs in asthma uncomplicated by chronic bronchitis or bronchiectasis. Transient right ventricular strain may be noted on the electrocardiogram. In view of the marked tachycardia which is usually present, it is prudent to give fluid slowly at a rate of 1 litre every 6 hr, and make every effort to get the patient to take fluid by mouth. I used to be taught that a nurse should never walk past a patient with pneumonia without making him take a drink and this should apply equally to a patient in status asthmaticus.

6. Sedation

There is no known sedative which can be guaranteed not to produce respiratory depression. However, many of the patients are physically exhausted and have not slept for several nights. In this situation and when the P_{aCO_2} is low or normal, sedation with promazine 50–100 mg intramuscularly, or amylobarbitone sodium 100–200 mg orally, may ensure a much-needed rest. In certain cases where the P_{aCO_2} is raised and monitoring facilities are available, I feel sedation is permissible. Such patients are agitated and make increased metabolic demands on an oxygen supply which is already precarious. Under these circumstances a calculated risk is justifiable provided close watch is kept and respiratory stimulants and/or assisted ventilation instituted if necessary.

Opium alkaloids, of which morphia is commonly used, cause release of histamine (Nasmyth & Stewart, 1950) as well as respiratory depression and should never be used.

7. Other measures

It is not surprising that a large number of remedies have been tried in a situation which may be resistant to conventional therapy.

(a) Humidification with steam may be helpful, particularly in children who are in an oxygen tent. The bronchial mucosa is dry and water vapour may well help to rehydrate it.

(b) Bronchial lavage has its supporters, including Marchand & Van Hasselt (1966), but I find it difficult to imagine how anything less than an Atlantic storm could loosen the tenacious plugs which obstruct the bronchioles.

(c) Tracheostomy with aspiration of plugs has occasionally proved useful (Hugh-Jones, 1958) but again the problem of accessibility of the plugs exists.

(d) Inhalation of adrenaline or isoprenaline using a Collinson's apparatus or Wright's nebulizer are sometimes used. These drugs may also be administered under positive pressure using a Bennett or Bird ventilator.

(e) Clinical experience with the new mucolytic agent acetyl-cysteine (Airbron) has proved encouraging but its efficacy has yet to be proved.

(f) General anaesthesia has its advocates (Tausig, Papper & Barach, 1952) and more recently rectal ether described in 1931 by Maytum has been again put forward as effective therapy.

(g) I feel that hypnotherapy is impracticable and might even be dangerous.

Summary

1. The mortality from asthma appears to be rising again, after falling in the late 1950s. Many workers ascribed this fall to the use of long-term corticosteroid therapy. It may well be that factors, other than decreased effectiveness of long-term steroid therapy, are responsible for the present increase.

2. The management of status asthmaticus may be divided into: (a) prevention, and (b) therapy of the acute attack.

(a) It should be possible using large doses of steroid therapy to prevent status asthmaticus altogether but only at the expense of serious side-effects. However, the careful use of small doses of steroids on a long-term basis (i.e. longer than 3 months) can significantly reduce the incidence of status asthmaticus.

Should an attack not respond to 24 hr of intensive therapy at home, then hospital admission is advisable, as it is felt that some of the deaths that occur at home are preventable.

(b) The treatment of the acute attack is discussed in the light of the experience gained in monitoring systemic arterial gas tensions and pH during the acute episode and for the ensuing days. Hypoxaemia was invariably present and often severe. PaCO_2 was low or normal in most of the patients, but in the few patients in whom it was raised it was a grave prognostic sign. The pH was also low in these patients.

We found to our immense surprise that adrenaline and aminophylline did not produce any substantial change in the PaO_2 levels. Evidence is put forward that adrenaline is best avoided and aminophylline used as a 'bronchodilator', although its effects were not dramatic.

As well as giving large doses of steroids attention must be paid to the maintenance of fluid balance, and antibiotics used where necessary. Sedation in selected cases is probably both beneficial and justifiable.

Above all else, the most important life-saving therapy is the administration of oxygen, bearing in mind that hypoxaemia often persists for weeks. The patient should be kept in hospital, under surveillance, for 3 weeks after the acute episode and oxygen administered if indicated.

Acknowledgments

The work on arterial blood gases was carried out in the University Department of Medicine (Professor K. W. Donald) with the financial support of the Asthma Research Council.

It is a pleasure to acknowledge the help of Dr J. S. Millar, Medical Research Council Scholar, and of the physicians of the Royal Infirmary and City Hospital, Edinburgh, who allowed me to study their patients.

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Discussion to the paper by H. A. Rees

GRANT. I share Dr Rees' impression, not yet confirmed by statistics, that there has been an increase in mortality from bronchial asthma during 1965 and 1966. My own experience suggests that a high proportion of recent deaths took place in patients' homes, or in transit to hospital. When patients reach hospital alive, status asthmaticus can usually be controlled by massive doses of corticosteroids, without recourse to more elaborate measures. Up-to-date and detailed information about deaths from asthma are urgently required, particularly in respect of those occurring outside hospital. I suspect that many of these deaths result from delay on the part of the patient or the relatives in summoning medical assistance, and from errors of judgment on the part of the general practitioner in not administering large enough doses of corticosteroid and in not expediting the patient's admission to hospital. These factors cannot account for an increase in the death-rate from bronchial asthma, if this has in fact occurred. I doubt the credibility of Dr Rees' suggestion that the nature of the disease has changed, and put forward the view that individual patients receiving long-term treatment with corticosteroids may have become relatively resistant to these agents, with the result that whenever they 'escape' from control, they tend to deteriorate more rapidly than untreated patients, unless the dose is promptly and massively increased.

With regard to the management of status asthmaticus in general practice, I consider that if a patient does not show a distinct improvement within 6 hr, admission to hospital is imperative. I feel that in certain cases even a delay of this duration may be dangerous. Corticosteroids do not begin to exert any useful effect for about 8 hr. During this critical period a patient may continue to deteriorate, and therapeutic measures other than corticosteroids may then have a decisive influence on the outcome. In most instances oxygen therapy, adequate hydration and the frequent administration of an isoprenaline aerosol by intermittent positive-pressure ventilation (IPPV) via a facemask, using a patient-triggered ventilator (Bird or Bennett), are sufficient to tide the patient over this dangerous phase, and it is rarely necessary to resort to oro-tracheal intubation and full-scale IPPV. Facilities for this procedure should, however, be readily available in every unit undertaking the treatment of status asthmaticus, as they may be urgently

required for the resuscitation of patients admitted *in extremis*, and for those who continue to deteriorate after admission. I agree with Dr Rees that a Paco_2 of more than 50 mmHg is an absolute indication for starting artificial ventilation, but consider that in gravely exhausted patients there may be a case for embarking on this treatment even when the Paco_2 is normal or only slightly increased. One of the great benefits of artificial ventilation is that it allows the patient to be deeply sedated without risk, and this in itself may tip the scales in his favour.

I accept the view of Dr Rees that adrenaline, whether administered subcutaneously or intravenously, has no place in the treatment of status asthmaticus. The experimental evidence that adrenaline, particularly when combined with isoprenaline, could induce ventricular fibrillation, may not necessarily be applicable to human subjects, but as adrenaline is in practice seldom effective in status asthmaticus, there would seem to be no real justification for using it. I believe that aminophylline administered intravenously is in a slightly different category. Unlike adrenaline it does not produce cardiac arrhythmias and although, as Dr Rees has shown, it may not increase the PaO_2 , it may in some cases produce partial relief of airways obstruction, and a consequent reduction in the work of breathing. In this respect, however, neither adrenaline nor aminophylline is as effective as an isoprenaline aerosol administered by IPPV.

AMBIAVAGAR. Two points made in the preceding paper are worth amplifying. In describing *deaths* from asthma, it was stated that a sudden death due to cardiac arrest, sometimes preceded by a period of hypotension, was characteristic of this disease. These deaths, which all authorities agree are usually unexpected, occur during a period of gradual suffocation—and asthma is perhaps the only known circumstance where gradual suffocation occurs. The incongruity of this point, sudden unexpected cardiac death during a period of *gradual* suffocation led us to investigate the cardiovascular abnormalities present during asthma. Clinical signs and electrocardiograms show that acute right ventricular strain occurs and cardiac catheterization showed several abnormalities.

Fig. A1 is a composite trace of the cyclical intrapleural pressure changes during asthma of this severity, the