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A 25-Year Perspective of Status Asthmaticus

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Introduction

Acute severe asthma in children remains one of the leading causes of admission to the hospital, although last reported in 1972.[1] This disease was the seventh most common diagnosis at 5 children's hospitals, fifth at 5 large general hospitals, and ninth at 10 median-sized general hospitals. While these data reflect the magnitude of the problem, there remains great diversity of the criteria for admission, as well as management before, during, and after hospitalization.

A prospective study of hospital admissions of asthmatic children has documented many of my preconceived notions about these patients.[2] The mean number of admissions was 5.7, and 46% of school-aged patients had missed 4 weeks or more during the previous 12 months because of asthma. The frequency of readmission was four times higher in the socioeconomically disadvantaged as implied by a lower number of homes owned, larger families, and relative overcrowding. This study also suggested that the difference may be related to less drug usage as well as different admission criteria. The perceived ability or inability of the parent or patient to provide adequate care at home obviously must also play a role.

The mortality statistics for asthma have remained largely unchanged for over 30 years,[3] in spite of major advances in treatment. Many patients now die "suddenly" outside the hospital. Yet, a surprising number still progress to death under medical supervision. This editorial suggests a need for the adoption of three principles to control asthma; education of patients, careful supervision, and prompt recognition and treatment of deterioration. All three are cornerstones of the successful management of status asthmaticus.

Whenever an acute, severe attack of asthma occurs, the parent and/or patient must be encouraged to seek help quickly. The results of delay have been well documented in an adult patient seen 4, 55, and 90 hr after the onset of three attacks.[4] The treatment was the same for each episode, but the rate of recovery was significantly different. Therapy started at 4 hr resulted in 100% of the predicted forced expiratory volume in 1 sec (FEV_1) after 10 hr, and in 100% of the predicted maximum midexpiratory flow (MMEF) after 20

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hr, whereas these parameters remained abnormal after 5 days when therapy was started 90 hr after the onset of symptoms. Also, a 10-year evaluation of a self-referral emergency admission service for patients known to suffer from life-threatening asthma appears to have reduced the frequency of sudden unexpected death at home.[5]

An increase of 167% in the number of children admitted to the hospital in a region of London between 1970 and 1978 has been reported.[6] There was a more than fivefold increase in self-referrals, and a higher readmission rate for these patients. It was suggested that this indicates an inadequacy of ambulatory care. Yet, during a staff development period the Children's Hospital of Pittsburgh (CHPgh) had shown a similar increase with a doubling of admissions between 1958 and 1968,[7] even with a significant increase in the quality of the primary care provided these patients. At the Children's Hospital of Los Angeles, with an established training program, between 1969 and 1976 the number of admissions for asthma ranged between 408 and 595 with no significant increase and no significant change in the number requiring the intensive care unit, being between 0.7% and 1.9% of the status group.[8] Thus, it should be obvious that the background of the unit reporting is essential to the interpretation applied to the results in this multifactorial situation.

The purpose of this chapter is to review the issues involved in the decision-making process that are likely to prevent the progression of acute severe asthma to early and then advanced status asthmaticus with acute respiratory insufficiency or with acute respiratory failure and then death. The data selected for this review have been mostly obtained from the pediatric literature because this issue is devoted to problems in children. Selected adult data are utilized where pediatric data are lacking. However, it is essential that the reader realize that certain therapeutic modalities must be used with great care in adults.

Incidence

The true incidence of status asthmaticus is unknown for several reasons: (1) the absolute number of asthmatic children in a community served by a pediatric facility is unknown and varies for many reasons, (2) the criteria for the diagnosis are not uniform, (3) the number of medications a patient might receive before arrival in the emergency room varies between none to seven or eight, (4) previous data are difficult to use because some facilities, like the CHPgh, had no multidisciplinary intensive care units (ICUs) until 1967 yet had an emergency room holding area, and (5) most general hospital pediatric facilities always have empty beds, whereas others like CHPgh rarely do.

The occurrence of status asthmaticus is impossible to describe without a uniformly accepted definition. Therefore, most authors have neglected this subject and have limited their data to those for patients with life-threatening asthma. The most helpful data are for the month of May 1979 at the Children's Hospital National Medical Center in Washington, D.C. (CHNMC).[9] This is a long-established center with a stable inner-city clinic as well as a significant private patient population.

Previous to 1965, it was generally the patient unresponsive to three injec-

tions of epinephrine who was diagnosed as having status asthmaticus. Most children were not receiving around-the-clock therapy with theophylline. Now most of our patients have already received theophylline when first seen,[10] as had 67% of the CHNMC patients.[9] Interestingly, 23% of the known asthmatics had no medication prescriptions. Not infrequently patients are admitted with acute severe asthma after running out of medication or have recently stopped taking it. If unresponsiveness to a series of three epinephrine injections (0.01 mg/kg every 20 min) is the major criterion for the diagnosis of status asthmaticus, both with and without prior theophylline administration, then 24% of acutely ill patients are likely to be admitted based on the CHNMC study. At LaRabida Children's Hospital, the unresponsive group was 23% of those coming to the emergency room.[11] This therapy differed from that at the CHNMC in that epinephrine was alternated with either isoproterenol or isoetharine by ultrasonic nebulization, with a mean of 4.7 such treatments before admission.

Risk Factors and Predictive Indexes

Most pediatric allergists agree that the risk profiles in childhood status asthmaticus should include males with severe or chronic disease, asthma since infancy, sudden changes in pattern, repeated episodes of status asthmaticus, barrel-chest deformity, short stature, underweight, steroid dependency, and poor coping style.[12] In addition to these, the following have also been suggested: previous failure of usually effective therapy and short-term drug relief of symptoms. Thus, the occurrence of these characteristics suggests the need for very careful observation during each episode.[13]

A definition of status asthmaticus should identify those at risk who will require hospitalization for intense monitoring and comprehensive therapy. Yet, a list of criteria and/or definitions is no substitute for sound clinical judgment based on previous experience with an individual patient and his or her family. Moreover, careful, frequent observations over several hours is the best way to prevent advanced status asthmaticus as well as to identify patients who might need ventilatory support.[14] A patient seen early in his attack will have a $PaCO_2$ below 33 mmHg and will be at low risk (11%) of subsequent $PaCO_2$ elevation. For those with a $PaCO_2$ in the normal range, the risk of progression to respiratory failure is 40%. Nine percent require immediate intubation. In a study on 445 adults in an ICU, two types of asthmatics not at risk were described: (1) no change in the $PaCO_2$ level and no hypercarbia (41%), and (2) initial hypercarbia that did not persist (17%). Two types of at-risk asthmatics were seen: (1) fluctuating $PaCO_2$ with frequent hypercarbia (14%), and (2) $PaCO_2$ increasing and hypercarbia persisting (29%). These authors have suggested the use of the terms "early status asthmaticus" and "advanced status asthmaticus."

Another predictive index is the heart rate. While sinus tachycardia is commonly attributed to drug therapy, this may be an error because tachycardia greater than 110 beats/min indicates a severe episode and often subsides when the attack is brought under control with more vigorous drug therapy.[15] Determination of the pulse rate is an excellent procedure that should be taught

to parents for use at home. For years we have suggested measurement of sleeping respiratory rates to help parents judge the severity of respiratory illnesses.

Many emergency rooms have been using pulmonary function screening tests to judge the severity of respiratory diseases. The peak expiratory flow rate (PEFR), measured with a mini-Wright peak flow meter, and the forced expiratory volume in 1 sec (FEV_1) have been shown to have excellent correlation at various stages of treatment of acute asthma in adults. Thus, the PEFR may be substituted for the FEV_1 in the emergency room.[16]

Martin et al. suggested that the PEFR might be used to screen those suspected of needing arterial blood gases (ABG), because there was a small but significant correlation between ABG parameters and the PEFR. No adult patients with a PEFR of greater than 25% of the predicted normal value had a $PaCO_2$ greater than 45 mmHg or a pHa less than 7.35. These authors felt that ABG parameters could thus be eliminated in at least 40% of patients with acute asthma. Such data may not be applicable to children for two reasons: (1) There may be significant metabolic acidosis, and (2) some asthmatic children have a higher actual PEFR than predicted, and the determined value may be significantly lower than 25% of the "best value" but higher than 25% of the predicted value.

One of the best predictive index systems has recently been described for *adults*.[18] One point was given for each of the following presenting factors: pulse rate $\geq$120/min, respiratory rate $\geq$30/min, pulsus paradoxus $\geq$18 mmHg, PEFR $\leq$120 liters/min, moderate to severe dyspnea, accessory-muscle use, and wheezing. The index scores of the admitted group (5.1 ± 1.0) and the relapse group (4.9 ± 1.0) were statistically significantly worse ($p < 0.001$) than those of the group treated successfully in the emergency room. This system has the advantage of being less subjective than most other scoring systems reported in the literature. In our hands, the other systems lost their accuracy with changes in shifts or nurses and/or house staff. Even when obtained and recorded hourly, such scores are a poor substitute for frequent, 30- to 60-min observations by a concerned, experienced physician.

Epinephrine

Epinephrine remains the drug of choice in the early treatment of acute bronchial asthma. Aqueous epinephrine, 1:1000, contains 0.01 mg (10 μg) per 0.01 ml. The usual dose is 0.01 mg/kg, maximum 0.2 ml, which may be repeated twice, 20 min apart.[19] Although this dose has been used for over 20 years, more recently supportive data have scientifically documented its efficacy.

Because this issue contains an article on β-adrenergic agents used in asthma, emphasis will be limited fundamentally to personal opinions about their use in status asthmaticus. During history taking specific questions must be asked about medications used to control asthma at home. While this is now especially true in regard to long-acting theophylline preparations, it must also become true of aerosolized bronchodilators. Although abuse of the longer-acting new agents seemed less likely to occur, abuse of salbutamol (albuterol) has already been reported.[20]

Considerable clinical experience has been gained over the past 20 years with the routine use of epinephrine suspension, 1:200 (Sus-Phrine), in a dose of 0.005 ml/kg at 8- to 12-hr intervals by subcutaneous injection, with a maximum single dose of 0.2 ml.[19] We have occasionally used it every 6 hr. This eliminates the trauma of frequent injections in children. Because 20% of this preparation is in an aqueous state for immediate utilization and the remainder is slowly dissolved, this is an excellent way to obtain both instantaneous and sustained relief of bronchospasm. If used initially in place of aqueous epinephrine and insufficient relief (less than 50%) is observed in 30 min, one dose of aqueous epinephrine, 1:1000, can also be given. We use the suspension most often as a replacement for the third dose of epinephrine.

Adults with acute asthma randomly treated with a subcutaneous injection of 0.1, 0.3, or 0.5 mg epinephrine in a double-blind fashion had no significant difference in the PEFR among the three doses at 10, 20, and 40 min. Yet, there was a significant difference at each time point.[21] Why give more, when less works just as well? In a similar open study, randomly selected adults received three repeated doses of 0.1, 0.3, or 0.5 mg epinephrine at 20-min intervals. In these more severely ill patients the 0.1-mg initial dose resulted in no significant improvement, but this effect was overcome with statistically significant improvement occurring after each additional dose.[22] There was no apparent advantage to the 0.5-mg dose; it appears that the best dose is 0.3 mg, to minimize side effects.

In a randomized, double-blind placebo control study, adults with acute asthma received one of two regimens: Three injections of 0.3 ml of 1:1000 epinephrine at 20-min intervals (0.9 mg epinephrine) plus an aerosol placebo every 10 min six times or three placebo injections at 20-min intervals plus a single inhalation of epinephrine aerosol (0.16 mg/puff) every 10 min for 6 doses (0.96 mg epinephrine). Although the mean data showed no statistical difference at the end of 1 hr, there was a definitely superior response to the injected epinephrine in a small subset with a PEFR of ≤ 120 ($p < 0.005$ at 60 min).[23]

In another study 20 children were treated for acute asthma with terbutaline. There was a 50% increase in the PEFR 5 min after the injection, with an increase of 90% 30 min after treatment.[24] A dose of 0.01 ml/kg, with a maximum of 0.25 ml, has been recommended and may be repeated in 20 min. The response has lasted as long as 4–5 hr. Yet this response, except for the duration, was similar to that to epinephrine. In a prospective single-dose, double-blind study in children with acute asthma 3, 6, or 12 μg/kg of terbutaline sulfate was compared with 10 μg/kg of subcutaneous epinephrine. Terbutaline was not significantly more effective at the 12 μg/kg dose, but it caused clinically imperceptible tremors, whereas this dose of epinephrine produced unpleasant headaches and excitation in a few patients.[25]

Additional Recommendation

Any child who has required epineprhine by subcutaneous injection 2 days in succession should be admitted to the hospital to receive more aggressive medical care.

Sodium Bicarbonate

By the early 1960s it had become increasingly apparent that techniques were being developed to assess the acid–base balance of those in acute respiratory failure more accurately and conveniently. With the developments in open heart surgery came life support systems not previously available. Before then life-threatening asthma was treated with rectal ether and a touch of empirical sodium lactate. Our first patient who required controlled ventilation caused us to think seriously about control of metabolic and respiratory acidosis.

The magnitude of the problem seemed tremendous. A decrease of 0.3 of a pH unit, that is, a drop from 7.4 to 7.1, represents a doubling of the hydrogen ion concentration. The only experience, largely without adequate or frequent monitoring of pHa, PaO_2 and $PaCO_2$, was during cardiopulmonary resuscitation (CPR). Sodium bicarbonate ($NaHCO_3$) was being used with increasing frequency, often on an empirical basis.

In 1964 the CHPgh group was using and recommending sodium lactate, and in 1965 $NaHCO_3$, to correct metabolic acidosis when the pHa was below 7.2.[26] While this seemed reasonable at the time, there were during the next 2 years three patients who required controlled ventilation even after this regimen.[27] By 1967 our protocol had been changed to the following: "2 mEq/kg over 5 minutes and repeat this amount more slowly during the next 45 minutes. If the hourly pHa is less than 7.35 and the Na less than 145 mEq/L, the $NaHCO_3$ should be repeated hourly, as above, if necessary."[19]

The use in adults of 88 mEq of $NaHCO_3$ was first reported in 1965 after it was given to an epinephrine-unresponsive, aminophylline-treated, unconscious known asthmatic with a pHa of 6.91 and a $PaCO_2$ of 150 mmHg.[28] Within 10 min the patient was conscious, with a pHa of 7.10 and a $PaCO_2$ of 95 mmHg. Following an additional 88 mEq and without additional bronchodilator, the patient had a pHa of 7.37 and a $PaCO_2$ of 48 mmHg, after 2 hr. A second patient, as seriously ill, also responded within 8 hr. Controlled ventilation was not used for either patient.

Karetzky and Mithoefer also measured sodium and bicarbonate excretion by the kidney following $NaHCO_3$ infusion.[29] Wide variation among individual patients was recorded. The type of response appeared unpredictable, because of multiple variables. This group of three patients was too small to assess the significance of delayed excretion in one patient.

Six more cases were reported later by this group, including the recovery of a 12-year-old with a pHa of 6.66 and a normal lactic acid concentration of 1.3 mEq/liter.[30] In two of the patients artificial respiration was avoided by correction of acidemia. Two of the patients had associated congestive heart failure, which was not adversely affected by a total dose of 88 and 352 mEq of $NaHCO_3$, respectively. The bronchospasm in the former responded without the use of a bronchodilator.

Administration of $NaHCO_3$, 50–100 mEq, to mild asthmatics usually responding to only a single dose of epinephrine resulted in no significant improvement in the FEV_1, although most patients reported slight relief.[31] Yet there was a significant decrease ($p < 0.01$) in the PaO_2 (2–22 mmHg, mean

9.7 mmHg). The pH increased by a mean of 0.06 units (range 0–0.12). Yet, this study, although apparently prospective, lacked controls and crossover data with a placebo and epinephrine alone. Nonetheless, it is obvious that $NaHCO_3$ should be given only if the patient is receiving O_2.

A dose of 2.5 mEq/kg of $NaHCO_3$ was found to be sufficient to maintain the pHa for 30 min in dogs made apneic and with ventricular fibrillation for 5 min, followed by CPR.[32] The short duration of the effect suggested the need for more $NaHCO_3$ after CPR.

Another experimental model was also evaluated by the CHPgh group. In vitro acidosis had a profound effect on the ability of epinephrine and aminophylline to relax guinea pig tracheal smooth muscle, but this effect was almost instantaneously reversed with a conversion of the pH from 7.0 or 7.2 to 7.4.[33,34]

Additional clinical studies at CHPgh between 1968 and 1971 have emphasized the need for "vigorous pHa control" with the use of oxygenation and $NaHCO_3$.[35] During a prior 4-year period with a low dose or no $NAHCO_3$, intubation and controlled ventilation were necessary in 2.6% of patients with status asthmaticus, whereas later with vigorous early normalization of pHa, the incidence was only 0.6%. The dose used was 1–2 mEq/kg body weight intravenously over 5 min with a repeat dose within 10–15 minutes if wheezing persisted. In severe status asthmaticus these two doses were given empirically without a waiting blood gas data, although determinations were available in the ICU. Subsequent $NaHCO_3$ titration was utilized to restore and to maintain the pHa between 7.4 and 7.45. During 1970, 11 patients with advanced status asthmaticus received 4–13 mEq/kg during the first 6 hr (mean 8 mEq/kg). Two of these patients with pulmonary infection and inspissated secretions required controlled ventilation.

Several complications deserve mention. Death occurred in one patient because she was receiving inadequate therapy. Hypokalemia always occurred when the dose was greater than 3 mEq/kg/6 hr. This was corrected by adding potassium chloride (KCl) to the intravenous fluids. When more than 8 mEq/kg/6 hr was given, up to 60 mEq/liter of KCl was necessary. Hypernatremia was mild and transient and occurred only when more than 8 mEq/kg/6 hr was required. The highest serum sodium level was 155 mEq/liter, and it returned to 146 within 5 hr. Hypocalcemia was slight and did not require replacement therapy. Hyperosmolality occurred in patients who received more than 10 mEq/kg/6 hr, but was slight. Severe alkalemia was avoided by careful titrations and frequent pHa determinations. All $PaCO_2$ values obtained 15–20 min after $NaHCO_3$ administration were lower than the initial values, yet earlier hypercarbia because of $NaHCO_3$ was not evaluated. Moreover, the use of $NaHCO_3$ continues to be credited by this group, since the incidence of mechanical ventilation has remained at 0.6% for 10 years and intravenous isoproterenol has not been used for any of the patients.[36]

After 12 years at CHPgh I moved in 1968 to Jefferson Medical College (JMC). This component of the protocol for the treatment of status asthmaticus has remained unchanged. An additional large service, not as large as that at the CHPgh, is different in that we have had for 11 years a chronic asthma

care program at the Children's Heart Hospital (CHH) with a daily census of 25–30 intractable asthmatic children. Many of these patients previously required intravenous isoproterenol and/or controlled ventilation, and a few, several times. During this 14-year period, none has required intravenous isoproterenol, and in 1982 the first child required controlled ventilation, essentially because of inattention to the $NaHCO_3$ regimen. Moreover, there has not been an in-hospital death because of status asthmaticus with this service in 25 years,[37] a fact I have been very hesitant to publish.

In addition to the previously cited uncontrolled observations, good data on the efficacy of $NaHCO_3$ in controlling pHa have appeared. In evaluating the role of hydrogen ion in the production of exercise-induced asthma, six asthmatics were exercised to exhaustion. All subjects developed significant acidemia, which was most extreme 4–5 min after the completion of exercise (pHa 7.29). This decrease in pH was completely eliminated by the infusion of a 1 mEq/ml solution of $NaHCO_3$ in amounts based on the calculated decreases in HCO_3 in the first experiment and estimates of the size of the extracellular fluid compartment based on body weight. The mean dose was 178 ± 36 (SD) mEq, or 2.96 mEq/kg assuming an average adult weight of 60 kg.[38]

Many pediatricians are rightly concerned about the use of $NaHCO_3$ as a rapid hypertonic (1.0 M) intravenous infusion into neonates with respiratory distress syndrome.[39,40] The complications seen in infants have not been found in patients with asthma. There may be only a relatively "closed system" in asthmatics, in that the nonmetabolic increase in CO_2 can be rapidly eliminated as illustrated by the CHPgh studies.[35] Moreover, in asthma a slow infusion of a 2:3 isotonic infusion (isotonic = 3 mEq/kg) is given instead of a rapid infusion of hypertonic $NaHCO_3$ as is given to infants.

However, the use of $NaHCO_3$ has received wide acceptance in the pediatric allergy literature by directors of established training centers. Most agree that, when the pHa is below 7.3 and the base deficit is greater than 5 mEq/liter, $NaHCO_3$ is recommended. The aim is to restore the extracellular pHa to 7.35–7.45. Therefore, the following formula is based on the assumption that the extracellular fluid space represents 30% of body weight:

$$\text{Amount of } NaHCO_3 \text{ in mEq to give} = \text{amount of negative base excess} \times 30\% \text{ of body weight in kg.}$$

This recommendation received only mild endorsement by the Section on Allergy and Immunology of the American Academy of Pediatrics in a statement that it "may be helpful" to correct the metabolic component of the acidosis.[41] My recommendation remains unchanged: up to 4 mEq/kg/hr if the pHa is less than 7.35.

While it has been recommended that patients who require alkalization should be admitted to the hospital,[35] our service has had extensive experience with the use of $NaHCO_3$ in the emergency room. Some patients need to be admitted, but many have been discharged. $NaHCO_3$ was not used early with a pHa between 7.35 and 7.3 in the emergency room studies reported in the section on incidence.[9,11,18]

Table 1. Intravenous Dosing With Theophylline in Children

Dose[a]	Without serum levels	With serum levels
Loading dose (over a 20-min period)		
Oral theophylline within 6 hr	2 mg/kg[b]	3–5 mg/kg
No previous theophylline	4 mg/kg	6 mg/kg
Maintenance dose		
Continuous infusion	0.75 mg/kg/hr	0.8–1.25 mg/kg
Maximum dose (if clinically unresponsive)		
For 1–6 hr	1 mg/kg/hr	—
Dose not to exceed	22 mg/kg/24 hr	28 mg/kg/24 hr

[a]Doses expressed as theophylline (78.9% of aminophylline, assayed as theophylline dihydrate). Aminophylline dose = theophylline dose/0.8.
[b]Kilograms of ideal body weight.

Theophylline

Another article in this issue is devoted to theophylline, but I will comment on my experience and my interpretation of the relevant literature.

Since 1960 CHPgh patients with status asthmaticus have received 4 mg/kg of aminophylline every 6 hr by constant intravenous infusion.[26,35] After 1968 some received it every 4 hr. JMC patients received this constant infusion, 4 mg/kg of aminophylline, every 6 hr, but in 1968, 2 mg/kg as a loading dose was added to the regimen if no theophylline had been taken previously. Moreover, a very sick child was often treated with 1 mg/kg/hr for several hours.[19] The efficacy of aminophylline was confirmed by a double-blind trial reported in 1971.[42] In 1973 the JMC protocol was changed to include a loading dose of 4 mg/kg if none had been taken and retained in the previous 6 hr, followed by a continuous infusion of 4 mg/kg over each 6-hr period (up to 20 mg/kg/24 hr). In 1976 the JMC protocol was changed again with the introduction of the availability of serum theophylline concentration determinations. Although the previous dose was encouraged, a loading dose of 5.6 mg/kg was permitted when the serum level was determined. A maintenance dose of 1.25 mg/kg/hr could then be used provided steady state levels were obtained every 6–12 hr. Based on clinical experience, in 1978 the doses were slowly elevated as illustrated in Table 1. It should be noted that these doses are slightly less than current recommendations of others,[41] because it is easier to increase the dose than to decrease it. This drug is much too important to permit overdosing to place it back on the shelf again, since letters to the editor that correct recommendations receive scant attention.[43] At this time, the dosing requirements for our patients were placed on 3 × 5 cards after each acute episode, an excellent immediately available resource for dosing.[44]

Corticosteroids

There is an article on corticosteroids in this issue, and accordingly I will relate only my use of steroids and its rationale. For several years at JMC, 7 mg/kg of body weight[45] of hydrocortisone sodium succinate (Solu-Cortef) was given

when steroids had been previously required, when an attack was very severe, when the PaO_2 was less than 60 mmHg, or when the patient had not significantly improved after treatment with the above regimen within 6 hr. This was followed by 4 mg/kg every 4 hr. Occasionally a very sick patient received it every 2 hr to provide a serum level of 150 μg/ml.[46] The CHPgh used 5 mg/kg body weight of hydrocortisone repeated every 6 hr or methylprednisolone at a dose of 1 mg/kg/6 hr.[35]

Over the past few years, several observations have caused the regimen to be changed. As sicker asthmatics entered the CHH, more had received steroids recently and most were sicker, having a decreased PaO_2 during status asthmaticus. The implication of the observation of significantly higher PaO_2 values in patients treated with corticosteroids also was of influence.[45] The first change was more rapid administration to avoid the risk of prolonged hypoxemia. Corticosteroids can always be discontinued in 12–48 hr without problems.

The second major change has been the gradual replacement of hydrocortisone by methylprednisolone sodium succinate (Solu-Medrol). Substitutes are *not* permitted, because Solu-Medrol is known to be paraben-free, while many generic substitutes are not. This change came about because of the need to use larger doses of steroids and the occurrence of water retention in several patients on maintenance fluids. Methylprednisolone is known to have much less tendency to induce sodium and water retention.

In adults, 3 days of treatment with methylprednisolone, 125 mg every 6 hr, appears adequate for most refractory asthmatics. Some patients relapse when the dosage is tapered over the next several days.[47] A double-blind randomized study of the use of methylprednisolone in status asthmaticus showed that 125 mg every 6 hr elicited statistically significant improvement in indexes over the low dose (15 mg every 6 hr) on all 4 days ($p < 0.01$) and better improvement than the medium dose (40 mg every 6 hr) on day 1 ($p < 0.05$).[48] Yet there was no apparent advantage to the use of extremely high doses (300 mg/m^2) every 6 hr in a small group of children of which only 10% were at risk of developing advanced status asthmaticus.[49]

Current Recommendations

Upon admission Solu-Medrol (methylprednisolone sodium succinate), 2 mg/kg body weight, should be given intravenously slowly over 10 min and 1 mg/kg every 6 hr. In *severe cases* (advanced status asthmaticus), 4 mg/kg followed by 2 mg/kg body weight should be given every 6 hr for 24–48 hr.

The Role of Oxygen Therapy

Although it is natural to anticipate a low PaO_2 during acute asthma, a review of the literature on subclinical asthma[50] revealed that significant hypoxemia occurs in relatively normal asthmatic children. Such patients are likely to become more hypoxemic during sleep and status asthmaticus. Essential to the vigorous control of pHa is the attempt to prevent acidosis induced by tissue anoxia. In order to do this, humidified 50–100% oxygen is recommended[35]

(it takes 6–12 hr of 100% O_2 to damage the lungs). At JMC every effort is made to maintain a PaO_2 between 80 and 100 mmHg, and O_2 delivery is initiated almost immediately.

Hydration

While the likelihood of dehydration in ill children is great for many reasons,[19] the fluid deficit should be replaced with care. Both hypovolemia, a reported complication of status asthmaticus,[51] and a significant increase in pulmonary blood volume[52] and pulmonary edema must be avoided.[53] Patients should be encouraged to ingest fluids at home to minimize dehydration. The occurrence of markedly negative mean pleural pressures in severe asthma raises questions about fluid intake. An increase in microvascular hydrostatic pressure with a decrease in plasma colloid osmotic pressure favors pulmonary edema.[53] Moreover, peribronchial cuffs of edema can lead to airway narrowing with increases in airway resistance and a tendency to premature airway closure.[54] Prolonged wheezing and pulmonary congestion occasionally follow status asthmaticus. Fluid restriction and spontaneous and/or induced diuresis have been followed by improvement in such patients.

Elevated plasma concentrations of antidiuretic hormone (ADH) have been reported in all of seven acutely and severely ill asthmatics, aged 6–52 years.[55] In each the ADH fell upon recovery. Therefore, care must be taken to avoid water intoxication during status asthmaticus. Patients must be observed carefully for a change in mental state, even though the chest symptoms have been alleviated. Although anoxia, hypercarbia, and theophylline toxicity must be ruled out, the occurrence of hyponatremia with a low serum osmolarity, a high urine osmolarity, and an elevated urinary sodium level would confirm the diagnosis. One cause of the elevated ADH could be β-adrenergic stimulation, because increases in ADH have followed administration of 0.03–0.06 μg/kg/min of isoproterenol by infusion. The effect was blocked by the β blocker propranolol.[56]

Intravenous Adrenergic Agents

Because of the complications of controlled ventilation in apparently medically irreversible status asthmaticus, the Children's Hospital of Philadelphia group (CHPhil) introduced the use of intravenous isoproterenol infusion.[57,58] Another large series has been reported from Denver.[59] The reader is referred to these three references for techniques and comprehensive discussions, because the decision to utilize this technique must not be taken lightly and should be made only by experienced personnel in an ICU where continuous cardiac monitoring and controlled ventilation are possible. Ten percent of the 20 CHPhil patients required subsequent controlled ventilation. Seven of 27 (21%) of the Denver patients were nonresponders and were successfully managed by mechanical ventilation. Interestingly, only 19% required mechanical ventilation before the introduction of intravenous isoproterenol in Denver.

It has been pointed out that a "cardinal advantage" of this technique is the short half-life of its cardiovascular effect (approximately 1 min) and elevated

blood levels (approximately 4 min) in contrast to those of theophylline.[58] Yet, all three of these reports detailed experiences before titering of theophylline dosage with serum concentrations was common.

Although there is little doubt that this procedure should be used in children before controlled ventilation, it is not without its own set of complications. Ventricular tachycardia (more than 200 beats/min) was immediately reversed upon discontinuation.[58] The Denver study described nodal tachycardia which reverted spontaneously in ½ min to sinus tachycardia; and another patient developed acute mobilization of copious secretions during the infusion. Weaning may present a problem, because of rebound bronchospasm. Myocardial ischemia in a 14-year-old[60] and fatal myocardial toxicity in an 18-year-old[61] have followed the use of intravenous isoproterenol.

Intravenous isoproterenol can cause a significant change in theophylline kinetics. An increase in theophylline clearance reverses when the isoproterenol is discontinued.[62] These changes do not correlate with pHa changes.

Alternatives to isoproterenol have been suggested in periodic reports. Ten children with unresponsive advanced status asthmaticus received multiple injections of 0.01–0.04 mg/kg of terbutaline at 15- to 30-min intervals. The mean cumulative dose was 3.1 mg given in a mean of six doses over a mean duration of 7 hr. No cardiac arrhythmias occurred. One patient required controlled ventilation.[63] Acute myocardial infarction was reported to have followed the administration of intravenous salbutamol in a 58-year-old patient, and others have cautioned about the use of isoproterenol in adults for this reason.[59,64]

The protocol used at the CHPgh and JMC differ from those used in the reports cited in this section. The most significant difference is the approach to *vigorous pHa control* with $NaHCO_3$. At JMC controlled ventilation was used once, because a rapid turn of events prevented an adequate trial of $NaHCO_3$ and isoproterenol. This was the only time in my 16-years of using this protocol that its vigorous enforcement failed. This record could not have been accomplished without a dedicated staff, initially at the CHPgh and later at JMC and CHH.

Controlled Ventilation

The use of controlled ventilation with muscle paralysis in the treatment of children with status asthmaticus was first employed in the United States in 1964.[65,26] Since then several comprehensive reviews have appeared.[27,66,67] Readers likely to use this procedure should review the references, since techniques have been described elsewhere. Fortunately, most pediatric house staffs become proficient in the use of ventilators during their neonatal rotations. Essential to the successful outcome of any procedure is a written protocol. Generally speaking, it is more important for the implementor to do what he or she does best, rather than to set down inflexible guidelines.

Established indications are the presence of three of the following:[57]

1. Severe inspiratory retractions
2. Absence of inspiratory breath sounds
3. Generalized muscular weakness

4. Decreased level of consciousness and response to pain
5. Cyanosis in 40% ambient oxygen
6. A $PaCO_2$ of 65 mmHg or higher.

Yet, in the absence of obvious clinical deterioration, most of these patients respond to intensive medical therapy within 12 hr,[27] A rise in the $PaCO_2$ of 10 mmHg/hr over two consecutive hours is an ominous sign.

Most practitioners sedate, oxygenate, proceed with nasotracheal intubation, paralyze, aspirate, connect to a volume-cycled ventilator, and set the ventilator for moderate hyperventilation, with the addition of a slight expiratory resistance to help prevent airway collapse[26] and with an initial tidal volume of 10 ml/kg body weight.

Continuation of the sedation for amnesia, paralysis to facilitate ventilation, and asthmatic medications is essential. Controlled ventilation in two children, not previously treated with intravenous isoproterenol, had no effect on theophylline clearance.[62] Continuous observation by an experienced physician is mandatory. Complications have been extensively reported.[59,68]

If controlled ventilation is unsuccessful in adequately ventilating the patient, there are three alternatives. The most promising is the use of halothane.[69] It successfully reversed status asthmaticus in an 11-month-old who was unresponsive to terbutaline, aminophylline, isoproterenol infusion, controlled ventilation with meperidine and pancuronium, and increasing doses of isoproterenol to a heart rate of 210 beats/min and blood pressure of 180/80 while on the ventilator. Halothane, 1% with 99% oxygen, was started by inhalation and in 10 min better aeration, increased chest movement, and increased wheezing (a good sign in this case) occurred. After 75 min of halothane, the patient had improved dramatically. The authors speculate that possibly the intubation could have been prevented if halothane had been used first. Halothane is known to be an excellent bronchodilator.

Bronchopulmonary lavage has been used successfully in adults with status asthmaticus,[70] but it is a most difficult procedure.

Finally, extracorporeal membrane oxygenation might be considered.[71]

Conclusion

The essence of pediatrics is prevention. It is easier to prevent the need for each advance in treatment than it is to use that modality. It all begins by preventing status asthmaticus.[50]

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