What is the role of subcutaneous adrenaline in the management of acute asthma?

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The World Health Organization has produced guidelines for the management of common illnesses in hospitals with limited resources. This series reviews the scientific evidence behind WHO's recommendations. The WHO guidelines, and more reviews are available at:
http://www.who.int/child-adolescent-health/publications/CHILD_HEALTH/PB.htm

This review addresses the question: *What is the role of subcutaneous adrenaline in the management of acute asthma?*

The WHO Pocketbook of Hospital Care for Children recommends that in children with asthma admitted to hospital give oxygen and a rapid acting bronchodilator and a first dose of steroid promptly. If nebulised or spacer delivered salbutamol is unavailable then give a subcutaneous injection of epinephrine (adrenaline) .01 mg/kg of 1:100 solution up to a maximum of 0.3 ml and if there is no improvement after 20 minutes to repeat the dose once. (Pocketbook chapter 4.4.2, page 88).

INTRODUCTION

The mainstay of management of acute asthma in adults and children is the administration of beta-adrenergic agonists that produce bronchodilatation. Formerly, drugs having non-selective action viz adrenaline (epinephrine) were used. While initial studies proved that adrenaline was very useful in relieving bronchospasm, its non-selective action resulted in several cardiovascular and metabolic adverse effects. The emergence of selective beta-2 agonists reduced the problem of unacceptable side effects considerably, with more selective bronchodilating properties. Over the years, adrenaline (which was hitherto the most commonly used drug in the emergency room setting) lost its popularity giving way to drugs with more selective action.

The other major change in the management of acute asthma was the realization that the inhaled route is far more effective, acts more rapidly, has fewer systemic side effects and is generally more acceptable than injections. This heralded a decline in the use of injectable preparations of adrenaline and the emergence of inhaled beta-2 agonists (especially salbutamol) in the management of acute asthma episodes. However, experience over the past four decades suggests that adrenaline is still a very useful drug, particularly in resource poor settings.

This review attempts to identify the role of adrenaline in present day practice for the management of acute asthma. The following issues are addressed:

1. What is the role of subcutaneous adrenaline in the management of acute severe asthma?

2. What is the efficacy of subcutaneous adrenaline relative to inhaled salbutamol?

3. How much subcutaneous adrenaline can be safely given?

METHODOLOGY

The Haynes Clinical Queries was searched using "Find systematic reviews" and "Search by Clinical Study Category using the narrow option. The search terms were: adrenaline and asthma. Besides this, PubMed was searched using the terms asthma AND (adrenaline OR epinephrine) AND acute. All abstracts were read, if there was any doubt as to the relevance of the article, the complete article was sourced. The role of subcutaneous adrenaline was determined by identifying trials that randomized subjects to receive subcutaneous adrenaline versus placebo. The relative efficacy of subcutaneous adrenaline compared to inhaled salbutamol was determined from trials comparing the two drugs. The maximum safe dosage of subcutaneous adrenaline was determined by identifying trials that randomized subjects to receive various doses of adrenaline.

RESULTS

The search for systematic reviews yielded 8 reviews. Six abstracts were available; two were found relevant. One of the systematic reviews (1) assessed the role of adrenaline in elderly patients for conditions including asthma and anaphylaxis, in order to determine whether administration of subcutaneous epinephrine carries a risk of cardiovascular side effects that warrant relative contraindication to its administration in the prehospital setting. However, the review included only three case reports that did not find any significant risk in elderly patients. The other systematic review (2) was focused to develop evidence-based guidelines for the assessment and treatment of acute asthma in adults in the emergency setting. The role of subcutaneous adrenaline was recommended as an alternative to conventional therapy in unresponsive life-threatening cases; however the evidence for the same was cited as grade B.

The strategy "Search by Clinical Study Category" using the narrow option yielded 66 studies. Besides this, PubMed search for "asthma and adrenaline and acute" resulted in 165 citations, from which two additional trials were available. The search for "asthma and epinephrine and acute" yielded 173 citations; no additional trials of relevance were found.

It may be relevant to mention at the outset that a precise definition of asthma in children is often difficult, not only because many young children with wheezing do not have asthma and vice versa, but also because measuring variable airflow limitation and airway inflammation is technically difficult in them. In young children, recurrent wheezing, especially with a history of personal or family atopy is often considered as asthma and improvement with therapy may be taken as supportive evidence for diagnosis. Beyond six years of age, it may be possible to apply more conventional definitions with measurement of objective parameters. Therefore studies that have included children with wheezing without further specifying its nature cannot be confidently interpreted for the role of sc adrenaline in asthma.

The overall quality of studies assessing subcutaneous adrenaline in asthmatic children is poor; there are very few studies comparing sc adrenaline with other drugs and none of them has a placebo arm. This makes it difficult to assess both the effect size and the response rate of sc adrenaline. In addition a number of studies excluded subjects with severe disease. The only double blind trial that compared sc adrenaline with a placebo (saline) in was conducted in wheezing infants less than 24 months of age, but not even half the enrolled subjects had recurrent episodes likely to be asthma. The study showed that the respiratory status measured by a novel respiratory assessment score, improved more in infants who received adrenaline rather than placebo. However, there was no objective indicator of improvement in airflow or in oxygenation that could support the clinical observations. The response in older infants (older than 12 months), more likely to have recurrent episodes was significantly better than in younger infants, indirectly suggesting a useful role of sc adrenaline in asthma (3).

There were five studies comparing the effect of subcutaneous adrenaline versus inhaled salbutamol (4-8) . One study compared intramuscular adrenaline with nebulized salbutamol (9). Four studies examined the effects of subcutaneous adrenaline versus inhaled metaproterenol (10-13), six compared subcutaneous adrenaline with subcutaneous terbutaline (14-19), four studied the effect of subcutaneous adrenaline versus inhaled terbutaline (20-23), two studies were conducted on subcutaneous adrenaline versus inhaled fenoterol (24, 25) and three examined the role of subcutaneous adrenaline versus aminophylline (26-28), in addition to one of the previously mentioned studies (5) that included aminophylline in one of the arms. One study compared the effect of subcutaneous adrenaline versus aerosolised adrenaline (29). There were two studies that used various dosages of subcutaneous adrenaline in a randomized fashion to test the safe upper limit of dosage.

Of the five studies comparing subcutaneous adrenaline with inhaled salbutamol, four studies included only children (4, 6-8) while one included adolescents and adult patients (5). The outcome variables were different in the studies and included respiratory rate (5-7), clinical scores (6-8), oxygen saturation (7), peak expiratory flow rate (4-6), patient's subjective assessment scale (5) and spirometry measurements (7).

All the five studies demonstrated that the outcome measures were similar in subjects who received sc adrenaline and inhaled salbutamol. Table 1 summarizes the salient points of each study. One of the studies (6) showed that the addition of long-acting adrenaline to inhaled salbutamol did not have any additional beneficial effect, although the clinical effect was comparable with either drug. Another (7) study reported better oxygen saturation in the group that was administered adrenaline. The studies reported greater incidence of side effects among those who received adrenaline, although none was designed to study this aspect specifically.

The single study (9) that compared intramuscular adrenaline versus nebulized salbutamol reported better efficacy with salbutamol measured in terms of greater improvement in peak expiratory flow and lower hospitalization rate. Data on optimum dose with regard to efficacy and safety is very limited. Two studies comparing various doses of subcutaneous adrenaline in acute asthma were conducted in adults (30, 31) and used three doses viz. 0.1 mg, 0.3 mg, or 0.5 mg. In one study (30), comparable bronchondilation measured by peak expiratory flow rate 10, 20, and 40 minutes after injection occurred with all three dosages of epinephrine without significant increase in adverse effects. In the other (31), bronchodilation, measured by peak expiratory flow rate was significantly greater with the 0.5 mg dose than with the 0.1mg dose (at 10 and 20 minutes) and the 0.3 mg dose (at 20 minutes). Arterial blood gas analysis, heart rate and blood pressure were not significantly different for the three groups, suggesting that up to 0.5 mg can be safely administered in adults. Studies in children have usually used a dose of 0.01mg/kg; this dosage has been used across various age groups (and hence weight) of subjects. No complications were reported suggesting that the dose is safe; however the maximum safe dose cannot be inferred from these studies. Recommendations for adrenaline in other clinical settings such as anaphylaxis suggest using a dose of 0.01mg/kg/dose (32) intramuscularly or subcutaneously (American Academy of Allergy, Asthma and Immunology). The Australasian Society of Clinical Immunology and Allergy (33) recommends intramuscular doses of 0.15mg for children 10 to 20 kg in weight and 0.3mg in those over 20 kg. Obviously it is not clear whether the same doses can be extrapolated for use in children with asthma.

There are no quality data on recommendations regarding indications for repeat doses of subcutaneous adrenaline in asthma. The observation that peak action of the drug occurs 30-60 minutes after administration (30) suggests the need for caution in repetitive administration during this period.

DISCUSSION

Despite the waning popularity of subcutaneous adrenaline in favour of inhaled beta-2 agonists (especially salbutamol), available data suggests that the bronchodilator effect is comparable with both drugs. This equivalence of effect is demonstrated across a variety of clinical outcome measures including subjective assessment of patients as well as objective measurements, suggesting that the findings are reliable. However, salbutamol is superior to adrenaline in at least two respects, viz the lower frequency of side effects (tremors and tachycardia) and the ease of administration by the inhaled route. It would be obviously unethical to devise randomized trials comparing subcutaneous adrenaline versus inhaled salbutamol or placebo for management of acute asthma in modern practice. The usual dosage of sc adrenaline in children is 0.01 mg/kg and there is no evidence to recommend indications for additional doses. There is limited data that suggests that dosage up to 0.5 mg subcutaneous adrenaline can be safely administered in adults, although the maximum safe dose in children is not known.

SUMMARY

Subcutaneous adrenaline in the dose 0.01 mg/g can be safely given in acute asthma in children; it is at least as efficacious as inhaled salbutamol but the side effects are greater. The safe upper limit of dosage in adults is 0.5 mg; however the corresponding dose in children is not clearly established.

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Table 1: Characteristics of included studies

Study	Subjects	No. of subjects	Intervention	Main outcome measures	Main results	Remarks	Ref
Sharma A et al	Children 6-14 years	50	Sc epinephrine versus nebulized salbutamol	Increase in PEFR (%)	Mean increase in PEFR (%) similar in both groups epinephrine 27.7 + 0.7 vs salbutamol 28.8 + 0.06, p >0.05		4
Anantharaman V.	Children and adults 15-40 years	71	Sc adrenaline, nebulised salbutamol and intravenous aminophylline	Respiratory rate, Peak Expiratory Flow Rate (PEFR) and Patient's Subjective Assessment Scale (PSAS)	PEFR and PSAS were similar in subjects who received adrenaline and salbutamol; both were better than those who received aminopylline		5
Kornberg AE et al	Children 3-12 years	43	Sc adrenaline (long-acting) plus albuterol versus only albuterol*	Clinical score, peak expiratory flow rate and respiratory rate.	All three comparable in both groups		6
Becker AB et al	Children	40	Sc adrenaline versus nebulized salbutamol	Clinical score, respiratory rate, PaO2, PaCO2, FVC, FEV1, FEV1/FVC, and FEF25-75%.	All clinical and spirometry parameters comparable in both groups. PaO2 remained unchanged after salbutamol but increased significantly after epinephrine.		7
Ferres Mataro J et al	Children	100	Sc epinephrine versus inhaled salbutamol (4 puffs and 7 puffs delivered by metered dose inhaler)	Clinical score at 0, 30 and 60 minutes	No statistical differences were observed between the three groups	Salbutamol was delivered by metered dose inhaler	8