

EVIDENCE BASED PRACTICE

Article 990310

**Out-of-hospital administration of corticosteroids to patients with acute asthma:
A case study and literature review**

David Long, Jason Bendall, Andrew Bower

Ambulance Service of New South Wales, Australia

Abstract

Objectives

Asthma is an important health problem in Australia with more than 2.2. million Australians currently diagnosed with Asthma. Asthma is associated with significant mortality and frequent use of emergency medical services. The objectives of this paper were to: a) present a case study of a near-fatal episode of severe acute asthma in which the patient was administered corticosteroids by an Ambulance Service of New South Wales Extended Care Paramedic; b) review the epidemiology and pathophysiology of acute asthma as well as current pharmacotherapy in asthma management; and c) conduct a literature search and critical appraisal of existing evidence supporting the out-of-hospital administration of corticosteroids for acute asthma by paramedics.

Methods

The purpose of the literature search was to identify comparative studies of adult patients with “acute” asthma treated by paramedics with corticosteroids prior to arrival at the emergency department (ED) to evaluate whether this intervention is associated with improved outcomes. A literature search of databases included the Cochrane Database of Systematic Reviews (Cochrane Reviews Issue 4 2008), Cochrane Central Register of Controlled Trials (Clinical Trials), Medline (1950- November 2008), EMBASE and CINAHL. A pre-hospital filter was applied to increase the sensitivity of the searches as appropriate. MeSH headings included exp/asthma, exp/hydrocortisone, exp/prednisone, exp/prednisolone and exp/glucocorticoids. Searched text words included asthma, hydrocortisone, prednisone and prednisolone. Titles and abstracts of interest were inspected to identify relevant articles with the full text of selected articles retrieved. Identified papers were independently appraised by two reviewers.

Results

Only two original studies were identified. The first was a retrospective comparative study of adult patients with moderate to severe asthma who received 125 mg methylprednisolone prior to transport to hospital or after arrival in the ED. The second study was a retrospective chart review to determine whether the out-of-hospital administration of systemic steroids to asthmatic patients had any effect on hospital admission rates.

Conclusion

Corticosteroids have been widely used in the hospital setting for many years in the treatment of acute asthma and there is good evidence to support their early administration in an ED

setting. Out-of-hospital studies provide only weak evidence of benefit. There is insufficient evidence of adequate quality to determine if corticosteroids should be routinely used by paramedics. A prospective randomised controlled trial is needed to determine the true value of early corticosteroid administration in the ambulance setting.

Keywords: ambulance; asthma; corticosteroid; emergency medical technician; out-of-hospital; paramedic

Introduction

Corticosteroids have been used in hospital for the treatment of asthma since the 1950s¹ and their benefits are now widely accepted.² Indeed, as the primary pathophysiologic mechanism of asthma is airway inflammation, corticosteroids are seen as the drug of choice.³⁻⁴ Moreover, some authors have suggested the early administration of corticosteroids reduces the need for hospital admissions and improves outcomes.⁵ In a recent systematic review, the use of corticosteroids within 1 hour of presentation to an emergency department (ED) was associated with a significant reduction in the need for hospital admission for patients with acute asthma.⁶ It is the extrapolation of these studies, based primarily in EDs, that provides the theoretical basis for benefits of out-of-hospital administration of corticosteroids.

Corticosteroids (also known as adrenocorticoids) are a naturally occurring hormone secreted from the adrenal cortex. A sub-class of corticosteroids includes glucocorticoids which have a number of general metabolic, immunosuppressant and anti-inflammatory effects.⁷ In broad terms, the anti-inflammatory effects are achieved by inhibiting the production of a number of mediators including prostaglandins, thromboxanes and leukotrienes.

Six of the eight major ambulance services in Australia currently administer corticosteroids for patients with asthma. The Ambulance Service of NSW (ASNSW) currently authorises only a relatively small number of qualified paramedics to administer corticosteroids (prednisolone or hydrocortisone) for moderate and severe asthma as part of an Extended Care Paramedic (ECP) proof-of-concept program.

This paper presents a case study of a 'life threatening' episode of acute asthma. The patient received intravenous (i.v.) hydrocortisone from an ECP and survived to discharge without any significant morbidity. Although this isolated case does not provide any evidence on the efficacy of out-of-hospital administration of corticosteroids, it does provide an opportunity to explore whether corticosteroids played any significant role in the outcome of this patient.

This case raised the following clinical question: "In patients with severe asthma requiring an ambulance, does out-of-hospital administration (versus ED administration) of corticosteroids, improve outcomes?" This paper will:

- a) review the epidemiology and pathophysiology of asthma;
- b) critically appraise the literature relating to out-of-hospital corticosteroid administration in adults; and
- c) discuss contemporary pharmacologic therapy in adult asthma management.

Case presentation

Late in the evening, a 42 year old female living in a metropolitan area of Sydney contacted the Ambulance Service of New South Wales via the emergency number "000" complaining of severe breathing difficulties. Consequently, two ambulance resources were assigned to the incident including a transport ambulance and an ECP vehicle.

First on scene was a basic life support ambulance crewed by two qualified paramedics. A primary survey was conducted revealing shallow and ineffective ventilation. The chest was hyper-inflated and accessory muscle use was clearly evident. Despite only being able to speak a few words at a time, the patient communicated that she had no symptomatic relief from her reliever [a short acting beta-agonist (SABA)]. Her history also included sudden exacerbations and prior intubations requiring intensive care unit (ICU) admission.

The second resource was a single Intensive Care qualified ECP. The patient was administered nebulised salbutamol (5 mg) with ipratropium bromide (500 mcg) and intramuscular (i.m.) adrenaline (500 mcg). Intravenous access was established en-route to hospital and the patient was administered i.v. hydrocortisone (200 mg).

The patient was transported to the nearest ED and was triaged as Australasian Triage Score category 2 and was promptly allocated to a resuscitation bed. Approximately 20 minutes later, the patient deteriorated and suffered a respiratory arrest. She was successfully intubated and was retrieved to a tertiary ICU. The patient was intubated overnight but was extubated the following day.

Epidemiology

There are over 2.2 million Australians who are presently diagnosed with asthma.⁸ Compared with the rest of the world, the prevalence of asthma is relatively high with 14-16% of children and 10–12% of adults being diagnosed with the disease.⁸

In 2004, 311 people died from asthma in Australia with the highest risk in the elderly and those living in lower socio-economic areas.⁸ Indigenous Australians are also at a higher risk⁸ as are rural communities who suffer higher mortality rates, hospital admissions and readmissions.⁹ One study reported that 40% of adults in Australia who present to an ED due to an asthma attack will represent for emergent care within one year.¹⁰

The Ambulance Service of NSW is the largest single ambulance provider in Australia providing out-of-hospital care to a population estimated at 6.82 million people in 2006.¹¹ The Service is essentially a two-tiered response system. All graduate (Diploma) paramedics can administer nebulised bronchodilators (salbutamol and ipratropium bromide) and i.m. adrenaline. Intensive Care Paramedics can also administer i.v. adrenaline if asthma is “severe or extreme” with a decreased level of consciousness or minimal air movement.

The Service responded to a total of 633,212 emergency responses during 2006/07.¹² Of these, approximately 6% (38,550) were for a main condition/complaint of “asthma and airflow limitation”¹². During this period, parenteral adrenaline was administered on 51 occasions for “asthma/airflow limitation” and 35 patients were intubated for “asthma/airflow limitation”.¹²

It should be noted that “airflow limitation” and “asthma” are not separated by either the main condition or the protocol fields. Consequently, these cases may represent a mix of asthma and chronic airway limitation as the primary pathophysiology. Accordingly, the data was stratified for patients aged 40 or less to increase the likelihood of the primary pathology being asthma. For patients aged 40 or less, the annual presentations was almost 7000 cases with 6 recording the administration of adrenaline and 10 being intubated.

This data suggest that the incidence of life threatening episodes of “asthma” (requiring adrenaline or intubation) is approximately 10-15 per 10,000 patients with a main condition

complaint of “asthma/airflow limitation”. We hypothesise that these patients may benefit the most from corticosteroids if introduced service wide. These figures are conservative as they are likely to exclude patients with moderate asthma for which adrenaline and intubation were not indicated.

Pathophysiology

Asthma is a chronic inflammatory and bronchospastic disorder of the medium and small airways that results in recurrent episodes of wheezing, breathlessness, tightness and cough.¹⁴ It can be triggered by a number of stimuli in atopic individuals including exercise, emotional upsets, airborne pollutants, allergens and other environmental factors.¹⁵ The mechanism of asthma can be divided into acute-phase and late-phase responses.

The acute-phase is characterised by the immediate bronchoconstriction, vasodilation, airway oedema and mucous secretions within minutes of exposure to an inhaled allergen or irritant. This is caused by the release of chemical mediators including histamine, leukotrienes and prostaglandins from IgE-coated mast and epithelial cells. These mediators are also responsible for the initiation of a cascade of inflammation by drawing eosinophils, T-lymphocytes and neutrophils into the airways.¹⁵

The late-phase response develops some 4 to 8 hours after exposure to the initiating trigger.¹⁴ This is characterised by additional inflammatory cell recruitment and activation that produces epithelial injury, oedema, reduced clearance of respiratory tract secretions and increased airway responsiveness.¹⁴ It is this appreciation of the central role of inflammation in asthma that has deep implications for diagnosis, management and potential prevention of the disease.¹⁵

The initial assessment of severity of acute asthma in adults as used by ECP in NSW is adapted from the National Asthma Council guidelines⁸ and is shown in Table 1.

Table 1:

National Asthma Council Initial assessment of acute asthma severity in adults

Findings	Mild	Moderate	Severe
Talks in	Sentences	Phrases	Words
Physical exhaustion	No	No	Yes Paradoxical chest wall movement may be present
Pulsus paradoxus	Not palpable	May be palpable	Palpable [^]
Pulse rate	< 100/min	100-120/min	More than 120/min*
Wheeze intensity	Variable	Moderate/loud	Often quiet
Central cyanosis	Absent	Maybe be present	Likely to be present
PEF (% predicted)	> 75% (or best if known)	50 - 75% (or best if known)	< 50% or <100 L/min [#]
Oximetry on presentation			Less than 90%** Cyanosis may be present

* Bradycardia may be seen when respiratory arrest is imminent.

[^] Paradoxical pulse is more reliable in severe obstruction. Its presence (especially if > 12 mmHg) can identify patients who need admission. Absence in those with severe exacerbations suggests respiratory muscle fatigue.

[#] Patient may be incapable of performing test.

** Measurement of oxygen saturation is required: many patients look well clinically and may not appear cyanosed despite desaturation.

Out-of-hospital literature review

The Cochrane Database of Systematic Reviews (Cochrane Reviews Issue 4 2008) and the Cochrane Central Register of Controlled Trials (Clinical Trials) were searched for relevant overviews and clinical trials respectively. A comprehensive literature search was conducted using MEDLINE (1950-November Week 3 2008). The search was conducted using a range of population and intervention MeSH terms and text word terms. MeSH headings included exp/asthma, exp/hydrocortisone, exp/prednisone, exp/prednisolone and exp/glucocorticoids. Searched text words included asthma, hydrocortisone, prednisone and prednisolone.

A pre-hospital search filter¹⁷ was applied to refine the search for relevance to the clinical question. Our search identified 171 articles. Close inspection of titles and abstracts revealed 4 articles¹⁹⁻²² that specifically addressed the out-of-hospital / emergency medical services settings. Searches of EMBASE and CINAHL databases did not reveal any further articles. Full text of these articles was obtained for closer inspection. Of these four articles, only two were comparative studies.¹⁹⁻²⁰

These two comparative studies were critically appraised by two reviewers (DL, JB). This low number was not unexpected due to the dearth of out-of-hospital research. This deficiency is well known and authors have called for more research in the field of out-of-hospital asthma exacerbations.¹⁸ A summary of these two articles is included in Table 2.

Table 2:

Summary of out-of-hospital studies comparing out-of-hospital administration of corticosteroids to either in-hospital administration or standard care

Author	Population	Study Type	Intervention	Outcomes	Results
Stead & Whiteside, 1999 ¹⁹	Adult patients with "acute asthma" (defined by diagnostic codes) in New York City from July 1996-June 1997 transported to ED by paramedics.	Retrospective chart review Historical control group	Methylprednisolone administered out-of-hospital (n=11) versus patients treated with asthma in the preceding year (n=81) and no out-of-hospital steroids were administered	Hospital admission rates and emergency department length of stay	Reduced admission rates (0% versus 4%). No differences in emergency department length of stay
Knapp & Wood, 2003 ²⁰	Adults (18-50) with moderate to severe asthma administered i.v. methylprednisolone by Tidewater EMS from May 2000-April 2001	Retrospective chart review Historical control group	Methylprednisolone Out-of-hospital (n=31) vs in-hospital steroid administration (n=33)	Hospital admission	Increased likelihood of admission with hospital administration versus out-of-hospital administration (33% vs 13%)

The study by Stead & Whiteside (1999)¹⁹ was the earliest published comparative study of out-of-hospital steroids. In this retrospective chart review, the authors aimed to determine whether the out-of-hospital administration of systemic steroids to asthmatic patients had any effect on hospital admission rates in New York City. The study group were adult patients with asthma treated after the introduction of i.v. methyl prednisolone. These patients were compared to patients with asthma treated in the preceding year. In the treatment group, only 11 of 138 patients were given steroids out-of-hospital. Of these, one also received in-hospital oral steroids and three received adrenaline. These 11 patients were compared to 81 patients who were treated for asthma in the previous year. The admission rate in year 1 (no steroid available) and year 2 (steroid available) were both 4% (3/81 versus 6/138 respectively). The admission rate of the sub-set of year 2 that received out-of-hospital steroids was 0% (0/11). It was argued that this represented benefit of early steroids.

In this study, the severity of asthma was not described and steroids were only one of five options for medical command physicians accounting for only 11/138 patients receiving steroids. The most significant weakness was the power of the study. The authors remarked that 105 patients would have been required in the steroid group (versus 11) to make the differences observed significant.

Knapp & Wood (2003)²⁰ conducted a retrospective comparative study of patients aged 18 to 50 in an urban setting of Virginia, United States. Patients with moderate to severe asthma received either 125 mg methylprednisolone (Solu-Medrol) i.v. prior to transport to hospital or after arrival in the ED. The mean time to administration of methylprednisolone out-of-hospital was 15 min (95% confidence interval 7 to 22 min) compared to 40 min (95% confidence interval 23 to 57 min) in the ED group. Patients in this study were more than 2.5 times as likely to be admitted if the administration of steroids was delayed until presentation at the ED ($p=0.025$ one tail, Fisher's exact test).

The authors concluded that adult patients who received i.v. methylprednisolone in the out-of-hospital setting had significantly fewer hospital admissions. Limitations of this study include low numbers and thus low statistical power. Our calculations indicated the relative risk of admission with delayed steroids to be 2.58 (95% confidence interval 0.92-7.26) when compared to out-of-hospital administration. Other limitations included a non-randomised design, the use of a retrospective control group, inadequate definitions of asthma severity, non-standardised treatments between groups and subjective determination of study outcome (admission) that was ultimately based on a physician's judgment rather than any *a priori* criteria.

Current pharmacologic management

The primary focus of drug therapy in acute asthma is to achieve best lung function.⁸ Short-acting β_2 agonists (SABA) are widely regarded as first choice of treatment in managing acute asthma.^{6,8,23} Other accepted complimentary agents include ipratropium bromide, aminophylline, magnesium sulphate and adrenaline.

The National Asthma Council (NAC) is the peak body for asthma in Australia and has published their evidence-based and peer-reviewed guidelines in the 2006 edition of the *Asthma Management Handbook*.⁸ The NAC recommends oral or parenteral corticosteroids to be given to both adult and paediatric patients for moderate and severe acute asthma and should also be considered in mild cases. The related sections are detailed in Table 3.

Table 3:

National Asthma Council recommendations for the initial management of acute asthma in adults⁸

Treatment	Mild episode	Moderate episode	Severe episode
Oral corticosteroids eg. prednisolone	Yes (consider)	Yes 0.5-1.0 mg/kg initially	Yes 0.5-1.0 mg/kg initially
Intravenous steroids eg. hydrocortisone (or equivalent)	Not necessary	[^] Hydrocortisone 250mg (or equivalent)	[*] Hydrocortisone 250mg 6 hourly for 24 hours then review

[^] Use IV corticosteroids in moderate acute asthma if oral route not convenient

^{*} Either oral or IV corticosteroids can be given initially. Follow with oral course.

The National Heart, Lung and Blood Institute (NHLBI) through the Expert Panel of the National Asthma Education and Prevention Program (NAEPP) in the United States have published similar findings.¹⁶ The NAEPP is of comparable standing to the National Asthma Council in that they are both charged with the responsibility of enhancing the quality of life of patients with asthma at a federal level. The Expert Panel claims Level “A” evidence (meta-analysis of randomised controlled trials) for the inclusion of systemic corticosteroids “in the urgent care setting or ED” to decrease airway inflammation in moderate or severe exacerbations or for patients who fail to respond promptly and completely to SABA.

This early administration of corticosteroids is supported by a systematic review and meta-analysis of 12 studies.⁶ This overview showed that early use of corticosteroids in the ED (within 1 hour) significantly reduced admission rates (pooled OR: 0.50 95% confidence interval: 0.31-0.81). Furthermore there was evidence that this was more pronounced for patients not receiving corticosteroids and patients with more severe asthma.⁶

Although there largely appears to be a general consensus in the literature regarding the outcome benefits of systemic corticosteroids, there are still areas of controversy such as dose and route of administration.¹⁻² The decision is (in large part) based on the severity classification and the ability of the patient to take oral medication. Some authors have argued however, there is no significant difference between oral and i.v. routes of administration in either effectiveness or onset of action.^{1,18}

To illustrate in an agency context, ECPs in NSW administer corticosteroids both orally and parenterally with the oral (50 mg) prednisolone preferred in adult patients with moderate asthma and i.m./i.v. hydrocortisone (200 mg) preferred in patients with severe asthma. In contrast, Ambulance Victoria administers hydrocortisone (250 mg) i.v. to adults in cases of severe respiratory distress or if no response to 10 minutes of nebulised salbutamol occurs.²⁴

Table 4 provides a glance of the current usage of corticosteroids (CCS) for adults with acute asthma in Australia’s major ambulance services.

Table 4:

Current role of corticosteroids in the management of adult patients with asthma in Australia's major ambulance services*

Ambulance Service Jurisdiction	Steroids used for asthma	Use of steroid planned	Steroid	Dose	Route of administration	Years in use
A.C.T Ambulance Service	YES		Hydrocortisone	200 mg	IV or IM	Approx 6
Ambulance Service of NSW	NO	YES				
Ambulance Service of NSW (ECP program)	YES		Prednisolone Hydrocortisone	50 mg 200 mg	Oral IV or IM	1
Ambulance Victoria	YES		Hydrocortisone	250 mg	IV	> 10
Queensland Ambulance Service	YES		Hydrocortisone	200 mg - 250 mg	IV or IM	> 10
South Australia Ambulance Service	YES		Hydrocortisone	250 mg	IV	< 1
St John Ambulance (WA)	NO	NO				
St John Ambulance (NT)	YES		Hydrocortisone	250 mg	IV	< 1
Tasmania Ambulance	YES		Dexamethasone	8 mg	IV or IM	4

* Although the distinction has been made between Extended Care Paramedics (ECP) and other paramedics in the Ambulance Service of New South Wales, this has not been the case with other agencies. The authors acknowledge there are variances between Basic Life Support and Advanced Life Support/Intensive Care Paramedic and other specialists such as remote area clinicians in their authority to administer corticosteroids. For reasons of simplicity, these were not included in the table

Discussion

Whilst there are only two studies of out-of-hospital administration of corticosteroids for adults with asthma, both have suggested benefits. It is important to note that the study quality of one¹⁹ is poor and the inferences are probably hypothesis generating at best. The second,²⁰ whilst better in quality, provides weak evidence of an effect. Randomised controlled trials and subsequent meta-analysis does however provide strong evidence of benefit, at least in an ED setting. In addition to the two out-of-hospital comparative studies¹⁹⁻²⁰ there were two further studies that are worth brief consideration.²¹⁻²²

The third was a retrospective cross-sectional survey that examined the out-of-hospital treatment of patients referred to hospital with acute asthma in Edinburgh, Scotland.²¹ This study involved 150 patients who were divided into one of three groups:

- a) those that were part of a specialist asthma service,
- b) those under continuing supervision at a hospital respiratory outpatient clinic and

c) those managed in the community. The authors concluded the administration of bronchodilators and glucocorticoids are underutilised prior to hospital presentation.

The fourth was also a cross-sectional study conducted in a post-emergency asthma clinic in Liverpool, Sydney.²² The aim of the study was to describe decisions made by doctors and patients regarding out-of-hospital asthma management that ultimately resulted in a hospital presentation. Amongst their findings, the authors suggest that there is a failure of out-of-hospital management to implement current recommendations or actions in the treatment of exacerbations of asthma. Although the study did not specifically deal with ambulance attendances, it did concede that commencing oral steroids was probably the key action in avoiding an exacerbation.

There is high level evidence of benefits from early administration of corticosteroids in the ED. Despite the level of evidence from out-of-hospital studies, they support the potential benefits of out-of-hospital administration of corticosteroids prior to arrival in the ED in order to prevent possible delays. For the patient in the case study, early administration may well have contributed to her survival.

Based on the available evidence, the use of corticosteroids in most ambulance jurisdictions is a likely consequence of the application of largely in-hospital evidence to the out-of-hospital setting. Further out-of-hospital research is needed which ideally would be a well designed and appropriately powered prospective randomised controlled trial that assesses both asthma severity and meaningful outcomes. It is important to provide evidence (or not) of improved outcomes with early (out-of-hospital) administration compared with delayed (ED) administration. The Ambulance Service of NSW is planning to conduct a trial to answer this important clinical question (A/Prof PM Middleton, Senior Medical Adviser, ASNSW *pers com*).

Conclusion

The challenge for all ambulance jurisdictions is to deliver a service that is effective, appropriate, accountable and defensible by incorporating the best available evidence to guide patient treatment. At present there is insufficient evidence to determine if corticosteroids should be routinely used by paramedics. High quality evidence is required to address this gap in out-of-hospital practice knowledge. A prospective, randomised, controlled trial is required. The authors support the need for such a trial. In light of current clinical practice guidelines and benefits of in-hospital administration of corticosteroids for moderate and severe asthma, it seems unlikely that there would be harm associated with early administration by paramedics.

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Acknowledgements

Associate Professor Paul Middleton, Senior Medical Advisor. Ambulance Service of NSW. Western Cluster Library staff (Nepean). Sydney West Area Health Service. NSW Health.

This Article was peer reviewed for the Journal of Emergency Primary Health Care Vol.6, Issue 3, 2008