Adverse Events Associated With the Use of Intravenous Epinephrine in Emergency Department Patients Presenting With Severe Asthma

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Study objective: We determine the rate of adverse effects associated with the use of intravenous (IV) epinephrine by infusion for the treatment of severe asthma in the emergency department (ED).

Methods: This retrospective, structured, medical record review included adult patients who presented to the ED of Western Hospital between 1998 and 2003 and who were triaged as category 1, 2, or 3, had a discharge diagnosis of asthma, and were administered IV epinephrine in the ED. Patients were excluded if they were older than 55 years or if a diagnosis of asthma was not confirmed. The primary outcome measures were occurrence of cardiac arrhythmia or ischemia, local tissue ischemia, hypotension or hypertension, neurologic injury, or death related to epinephrine infusion.

Results: Two hundred twenty episodes of care met the inclusion criteria. Adverse events occurred in 67 episodes (30.5%; 95% confidence interval [CI] 24.5% to 37.1%); however, most were minor and self-limiting. There were no deaths. Major adverse events occurred in 3.6% of cases (8/220; 95% CI 1.7% to 7.3%), including 2 cases of supraventricular tachycardia, 1 case of chest pain with ECG changes, 1 case of incidental elevated troponin, and 4 cases of hypotension requiring intervention.

Conclusion: IV epinephrine is associated with a low rate of major and a moderate rate of minor adverse events in patients with severe asthma; however, a causal relationship has not been established. Further research investigating effectiveness, as well as safety, is warranted. [Ann Emerg Med. 2006;47:559-563.]

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SEE EDITORIAL, P. 564.

INTRODUCTION

Background

β-Agonists have long been the mainstay of acute asthma treatment. Until the commercial production of terbutaline and albuterol, subcutaneous epinephrine was commonly used. Now, inhaled albuterol is standard treatment in mild to moderate asthma,[1] with intravenous (IV) agents reserved for severe attacks.[2] Although IV albuterol is the most commonly used agent in Australia, some centers prefer epinephrine. The rationale for this is that in patients with severe asthma, α adrenoreceptor agonists provide vasoconstriction in addition to bronchodilation, thus reducing airway edema and improving gas flow.[1]

Despite this theoretical rationale, there is a paucity of evidence to support the use of IV epinephrine in acute asthma. Smith et al,[3] in a retrospective study of patients with severe asthma treated with IV epinephrine, reported no significant complications from its use. The accompanying editorial warned against the widespread use of IV epinephrine based on such a small group.[4] It is important to quantify the frequency of adverse events to make judgments about the potential risk:benefit ratio and to justify comparative studies.

This article aims to report the frequency of adverse events associated with the use of IV epinephrine by infusion for severe asthma in the study institution, where it is used in preference to IV albuterol.

MATERIALS AND METHODS

Study Design

This was a retrospective cohort study using explicit medical record review methodology.

Editor's Capsule Summary

What is already known on this topic
Although rarely used in the United States, intravenous (IV) catecholamines are commonly administered in Australia for acute severe asthma.

What question this study addressed
What type and frequency of adverse events are observed when IV epinephrine infusions are administered to severe asthmatic patients aged 18 to 55 years?

What this study adds to our knowledge
Of 220 occurrences in which IV epinephrine infusions were used to treat asthma, serious adverse events—myocardial ischemia in 2 patients, tachyarrhythmia in 2 patients, and hypotension in 4 patients—were uncommon and of unclear relationship to the epinephrine. The efficacy of epinephrine could not be evaluated by this retrospective study.

How this might change clinical practice
This large case series of IV epinephrine for severe asthma suggests that the likelihood of serious adverse events is low, and a wider role for such therapy may be appropriate.

Research we'd like to see
A randomized controlled trial is warranted, comparing inhaled albuterol versus IV epinephrine in severe asthma.

Setting

The study was performed at Western Hospital, a 250-bed community teaching hospital in Melbourne, Australia. The emergency department (ED) has an annual census of 32,000.

Selection of Participants

Patients were identified from the ED database. Medical records of all patients between the ages of 18 and 55 years inclusive, with an ED diagnosis of asthma between July 28, 1998, and November 29, 2003, and Australasian Triage Scale of 1, 2, or 3 were examined to determine whether IV epinephrine was administered as an infusion in the ED. The study institution has a written protocol for epinephrine infusion for asthma through peripheral IV cannulae starting at 0.25 to 1 μg/min and titrated to effect, with the usual dose rate being 2 to 3 μg/min. Patients were excluded if the ED record or inpatient notes failed to confirm the diagnosis of asthma or they did not receive IV epinephrine as part of their treatment. The age range was chosen to minimize overlap with chronic obstructive pulmonary disease. The triage categories were chosen to screen out mild asthma. Australasian Triage Scale categories reflect urgency of care, with Australasian Triage Scale 1 requiring immediate attention, Australasian Triage Scale 2 within 10 minutes, and Australasian Triage Scale 3 within 30 minutes. The date range was chosen with the aim of obtaining a sample of the order of 200.

Data Collection and Processing

Data were collected onto a specifically designed, piloted data collection sheet. Source documents were medical and nursing notes, drug orders, and the nursing observation chart (on which vital signs and the like are recorded). Data included demographic data, clinical information about severity (according to National Asthma Council[2] guidelines), treatment provided, and complications. An adverse event mentioned on any of these was regarded as a true positive. The main abstractor (M.P.) was not blinded to the aim of the study. If an item was not recorded, it was assumed to be absent.

Outcome Measures

The primary outcome measure was the occurrence of any defined adverse events. Serious adverse events were defined as death, nonsinus tachyarrhythmia, hyper- or hypotension with adverse outcome or requiring treatment, objective (ECG or biomarker) evidence of myocardial ischemia, nontransient neurologic sequelae, or an extensive area of local tissue necrosis. Minor adverse events included sinus tachycardia, hyper- or hypotension without adverse outcome and not requiring treatment, clinical suspicion of myocardial ischemia without objective evidence, transient neurologic sequelae, or a small area of local tissue necrosis.

Cardiac arrhythmia was defined as the development of new arrhythmia within 60 minutes of the initial dose of epinephrine or while the patient was receiving an epinephrine infusion. Sinus tachycardia was included only if the rate reached 10% higher than the presenting pulse rate. Cardiac ischemia was defined as chest pain thought by treating clinicians to be ischemic, ECG changes suggestive of ischemia, or cardiac biomarker increase within 24 hours of epinephrine administration. Hypotension was defined as a decrease in systolic blood pressure of 10% or more, resulting in systolic blood pressure less than 90 mm Hg, or a decrease in systolic blood pressure of 10% or more in a patient with preexisting systolic blood pressure less than 90 mm Hg within 30 minutes of use of IV epinephrine. Hypertension was defined as an increase in systolic blood pressure of 10% or more, resulting in systolic blood pressure greater than 160 mm Hg or an increase in systolic blood pressure of 10% or more in a patient with preexisting systolic blood pressure greater than 160 mm Hg within 30 minutes of use of IV epinephrine. Neurologic injury was defined as new neurologic injury believed to be due to cerebral ischemia or hemorrhage within 24 hours of epinephrine infusion being completed. Death was death during the index admission. Local tissue injury was defined as ischemic injury to skin or extremities believed to be due to extravasation of epinephrine.

Primary Data Analysis

Data were analyzed using descriptive statistics. Agreement and interrater reliability of data collection were assessed by a convenience sample of 10% of the included subjects. The items tested were epinephrine use, presence of complications, chest pain, cardiac ischemia, and local tissue ischemia.

Approval for the study was obtained from the institutional research ethics committee.

RESULTS

One thousand three hundred fifty-four patients met the screening diagnostic, age, and triage category criteria. Of these patients, 185 records (13.7%) were not locatable or there was no record of the visit in the patient's medical record. Of the remainder, 949 records met 1 or more exclusion criteria (the majority did not receive IV epinephrine), leaving 220 cases for analysis.

Of the included cases, 21% (46 cases) were Australasian Triage Scale category 1, 59% (129) were Australasian Triage Scale category 2, and 20% (45) were Australasian Triage Scale category 3. The average age was 36 years (range 18 to 55 years), and 60% (132) were women.

The average epinephrine infusion rate was 1.5 μg/min (range 0.5 to 13.3 μg/min). Total dose ranged from 15 to 99,551 μg (6 cases missing data). Duration of infusion ranged from 10 minutes to 11.4 days, with a median of 19.5 hours (6 cases missing data).

There was isolated asthma in 98.6% of cases. The remaining 3 cases had confounders or comorbidities (1 pneumonia, 1 onset post-IV ceftriaxone, 1 onset post aspirin) but were included because treating clinicians considered that asthma was a significant component of the illness.

Eighty-eight adverse events occurred in 67 episodes of use, giving an adverse event rate per episode of 30.5% (95% CI 24.5% to 37.1%). Uncomplicated sinus tachycardia and hypertension accounted for the majority of the episodes (23/88 and 30/88, respectively).

Serious adverse events occurred in 3.6% (95% CI 1.7% to 7.3%) of episodes (Table 1). There were no deaths. Three of the 4 cases of hypotension requiring treatment occurred related to sedation for endotracheal intubation. The other patient received a 200-mL normal saline solution fluid bolus. The 2 episodes of supraventricular tachycardia were without adverse sequelae and occurred at infusion rates between 1.5 and 2.5 μg/min. Neither patient with chest pain had ECG or biomarker changes, and both had uneventful courses. One reported "typical" pain and was further investigated with a thallium scan within 24 hours, with a result that was normal. The other patient reported atypical pain that was not further investigated. The highest infusion rate in both cases was 2 μg/min.

Epinephrine was ceased because of an adverse event in 10 cases (4.6%). Five of these events were due to extravasation of the drug or blanching around an IV site (4 of these in 1 patient), 2 were due to sinus tachycardia, 1 was due to hypertension, 1 was due to a brief unresponsive episode that may have been a seizure, and 1 was due to compensated metabolic acidosis in a patient who also had persistent sinus tachycardia and an episode of hypotension requiring a 200-mL fluid bolus.

Table 1. Serious adverse events.

Adverse Event Category	Number	% (95% CI)
Death	0	0 (0–0.17)
Nonsinus tachycardia arrhythmia (both SVT)	2	0.9 (0.3–3.33)
Hypertension with adverse event	0	0 (0–0.17)
Hypotension with adverse outcome or requiring treatment	4	2 (0.7–4.9)
Objective evidence of myocardial ischemia	2	0.9 (0.3–3.3)
Nontransient neurologic sequelae	0	0 (0–0.17)
Area of local tissue necrosis	0	0 (0–0.17)

Table 2. Other adverse events.

Adverse Event Category	Number	% (95% CI)
Sinus tachycardia	23	10.5 (7.1–15.2)
Hypertension	30	13.6 (9.7–18.8)
Hypotension not requiring intervention	5	2.3 (1.0–5.2)
Chest pain without ECG or marker changes	2	0.9 (0.3–3.3)
Neurologic injury	0	0 (0–1.7)
Local tissue ischemia	11	5 (2.8–8.7)

Other adverse events are summarized in Table 2. Of note, with the 30 episodes of hypertension, no clinically significant consequence was found. There were 2 cases of chest pain (1 "typical" and 1 "atypical") without ECG or cardiac marker changes. There were no episodes that met the study criteria for neurologic injury. Local tissue ischemia occurred in 11 episodes and 7 patients (5 times in the same patient). All were mild (local tissue pallor or mottling) and resolved without the occurrence of tissue necrosis.

Interrater reliability was assessed with percentage of agreement and κ statistic. The results were epinephrine use (100%, $\kappa=1.00$), presence of 1 or more complications (77%, $\kappa=0.50$), chest pain (95%, $\kappa=0.78$), cardiac ischemia (100%, $\kappa=1.00$), and local tissue ischemia (100%, $\kappa=1.00$).

LIMITATIONS

The major limitation of this study rests in its design, a retrospective medical record review, with all the well-known weaknesses of this methodology. There is no comparison group, so nothing can be said about the risk of IV epinephrine compared to any other intervention for severe asthma. No data were collected to examine the effectiveness of IV epinephrine. The interrater reliability was low for some of the variables examined, possibly because of the study design, requiring searching of several source documents.

The study design precluded controlling for potential confounders. Some of the adverse events were probably related

to concurrent therapy (eg, sedation for intubation), disease severity, or comorbidities (ie, ischemic heart disease). Thus, we are likely to have overestimated the adverse events truly caused by IV epinephrine.

DISCUSSION

This study found that, although minor adverse events are common with IV epinephrine used for asthma, serious adverse events are rare (on the order of 4%) and did not appear to be related to infusion rate. The latter is, however, likely to be an overestimate because almost half of these cases were of hypotension related to sedation for endotracheal intubation, well recognized as being associated with episodes of hypotension.

There are few other data about adverse events related to use of IV epinephrine in severe asthma. Smith et al[3] reported a series of 23 ICU patients, examining death, new arrhythmia other than sinus tachycardia, cardiac ischemia, focal neurologic lesions believed to be caused by cerebral ischemia, and development of hypotension or hypertension (with the same definitions as this study). They found results similar to those of this study, with 9 cases of sinus tachycardia and 4 cases of hypertension all without clinical consequence. They also found 4 patients who had chest tightness that worsened on or after IV epinephrine and in whom the drug was stopped. None of these patients had ECG or biochemical evidence of ischemia. The obvious drawback of their study was its small study population. Also, epinephrine was largely administered as boluses rather than as infusions. As was pointed out in the accompanying editorial, the 95% confidence interval for the occurrence of serious morbidity and mortality in such a small population was up to 11%.[4] Another small uncontrolled case series reported by Tirot et al[5] (in French) found that it was "well tolerated," but a detailed analysis of adverse events was not undertaken.

There is some rationale to the use of IV epinephrine in preference to albuterol in severe asthma. Although bronchoconstriction is the major pathology in asthma, airway edema also contributes. There is some evidence that α adrenoreceptor agonists reduce airway resistance in patients with severe asthma.[1] Epinephrine, with an α-agonist effect, as well as its bronchodilating β-agonist effect,[6] may address both elements of the pathology.

A discussion about the adverse effects of IV epinephrine in severe asthma in isolation is of limited value. The alternative treatment, albuterol, is not without adverse effects. It is recognized to produce sinus tachycardia, decreases in serum potassium concentration, and increases in serum glucose concentration.[7,8] The incidence of these and other possible adverse effects is hard to quantify. Santana et al[9] report an incidence of "tachycardia" of 29.4% in the albuterol group in a study of 50 pediatric ICU patients randomized to IV albuterol, IV magnesium, or placebo in addition to normal therapy. We contacted the manufacturer, requesting adverse effect details relating to IV albuterol for comparison, but were unable to obtain these.

It is also important to remember that the clinical utility of a drug is a balance between its therapeutic effect and the risk of harm in comparison to alternative agents. This study cannot comment on the therapeutic effectiveness of IV epinephrine, but the low rate of serious adverse events provides a basis to recommend further research. Clarification of the place of IV epinephrine in asthma management would require large, prospective, controlled studies comparing it to the current "standard" (IV albuterol). As the role of IV therapy has not been proven, a non-IV arm would also be of interest.

In Retrospect

It may have been preferable to collect data prospectively, but this was difficult because of low patient numbers and lack of specific funding.

In summary, IV epinephrine is associated with a low rate of major and a moderate rate of minor adverse events in patients with severe asthma; however, a causal relationship has not been established. Further research investigating effectiveness, as well as safety, is warranted.

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