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Clinical paper

Naloxone in cardiac arrest with suspected opioid overdoses☆

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ABSTRACT

Introduction: Naloxone's use in cardiac arrest has been of recent interest, stimulated by conflicting results in both human case reports and animal studies demonstrating antiarrhythmic and positive ionotropic effects. We hypothesized that naloxone administration during cardiac arrest, in suspected opioid overdosed patients, is associated with a change in cardiac rhythm.
Methods: From a database of 32,544 advanced life support (ALS) emergency medical dispatches between January 2003 and December 2007, a retrospective chart review was completed of patients receiving naloxone in cardiac arrest. Forty-two patients in non-traumatic cardiac arrest were identified. Each patient received naloxone because of suspicion by a paramedic of acute opioid use.
Results: Fifteen of the 36 (42%) (95% confidence interval [CI]: 26–58) patients in cardiac arrest who received naloxone in the pre-hospital setting had an improvement in electrocardiogram (EKG) rhythm. Of the participants who responded to naloxone, 47% (95% CI: 21–72) (19% [95% CI: 7–32] of all study subjects) demonstrated EKG rhythm changes immediately following the administration of naloxone.
Discussion: Although we cannot support the routine use of naloxone during cardiac arrest, we recommend its administration with any suspicion of opioid use. Due to low rates of return of spontaneous circulation and survival during cardiac arrest, any potential intervention leading to rhythm improvement is a reasonable treatment modality.

1. Introduction

Naloxone has long had a presence in the armamentarium of emergency physicians caring for opioid poisoned patients.[1] Its use in cardiac arrest has been of recent interest, stimulated by conflicting results in both human case reports and animal studies demonstrating antiarrhythmic and positive inotropic effects.[1–6] Naloxone alone in high doses has been shown to increase cardiopulmonary resuscitation (CPR) rates following asphyxia induced cardiac arrest in rats.[7] Further animal data supports naloxone administration alone or in combination with epinephrine in simulated asphyxia induced cardiac arrest models.[5,6] Naloxone with and without epinephrine resulted in increased incidence of return of spontaneous circulation (ROSC) as well as shorter resuscitation times. Additionally, a recent case report and literature review presented a patient with pulseless electrical activity (PEA) who returned to spontaneous circulation after receiving naloxone, subsequently questioning the routine usage in cardiac arrest.[1]

The interest in the utilization of naloxone in the non-overdosed opioid cardiac arrest patient stems from many hypotheses, one being that endogenous opioids are felt to have a myocardial depressant effect with a lowering of systemic blood pressure. Alternatively, naloxone may stimulate catecholamine release and increase sympathetic nerve activity significantly elevating heart rate and blood pressure.[1] Importantly, the safety profile of naloxone has been demonstrated in opioid toxicity as well as other non-poisoning scenarios such as spinal cord injury, shock, and acute ischemic stroke.[8–22]

Naloxone has been demonstrated to reduce action potential upstroke in guinea pig, canine, rabbit, and sheep myocardium.[8,18,19] The inhibition of action potential upstroke is correlated with the inhibition of fast inward sodium currents. In addition, an effect on repolarizing potassium currents has been shown to suppress re-entrant rhythms by prolonging action potential duration and increasing the refractory period.[23] Therefore, naloxone's antiarrhythmic activity appears to be similar to both class I and III antiarrythmics.[23]

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Based on the known and hypothesized effects of naloxone, we sought to investigate naloxone's role in cardiac arrest in patients with suspected opioid overdose. This is the first human cohort studied to date. We hypothesized that naloxone administration during cardiac arrest, in suspected opioid overdosed patients, is associated with improvements in cardiac rhythm.

2. Methods

2.1. Design

This was a retrospective cohort study conducted by chart review, with analysis of subgroups. The study was approved by the institutional review board at our institution.

2.2. Setting

The study was conducted at our university-based Level I trauma center in an urban setting surrounded by multiple suburban regions. The emergency medical service (EMS) contains six advanced life support (ALS) units that treat approximately 6500 patients out of 30,000 dispatches per year, including basic life support units. In our setting, naloxone may only be administered by ALS providers.

This system contains 90 paramedics, 140 basic emergency medical technicians, one full time medical director, and two EMS fellows. The system provides 100% on-line medical direction via cellular phone with a board certified or board eligible emergency physician working clinically in the emergency department. The state has multiple standing order protocols whereby the paramedic can initiate treatment; however, naloxone in cardiac arrest must be given under physician medical control. ALS units comply with state protocols and contain two paramedics in ambulances or response units. EMS supervisors respond on all "critical calls" as defined by the medical communicator.

2.3. Selection of subjects

Participants were identified from a database of ALS responses between January 1, 2003 and December 31, 2007. Patients who had received naloxone in cardiac arrest were selected as participants. This query also retrieved records of subjects who received naloxone when they had a pulse, either before or after being in cardiac arrest. These subjects were excluded so only patients who were in cardiac arrest at the time naloxone administration were included.

2.4. Interventions

Patients in cardiac arrest were initially treated by paramedics in accordance with advanced cardiac life support (ACLS) guidelines. As paramedics are not permitted to give naloxone in this circumstance, all administrations were authorized by a physician via online telemetry orders. Subsequently, there were no standard dosages and patients received naloxone at varying steps in the ACLS algorithms. Naloxone was never the first pharmacologic intervention.

2.5. Methods of measurement

On standard patient care reports (PCR), paramedics recorded patients' vital signs before and after each medication administration. Pertinent vital signs recorded included heart rhythm, as interpreted by the paramedics providing patient care. All patient electrocardiogram (EKG) rhythms were verified by two prehospital paramedics and the emergency physician upon arrival at the hospital. PCRs were also reviewed after the call by the paramedic clinical coordinator and physician medical director during the quality assurance/quality improvement process. Naloxone doses and routes of administration were also recorded on the PCRs. Additional information obtained included time of cardiac arrest, duration of cardiac arrest, and time of pronouncement.

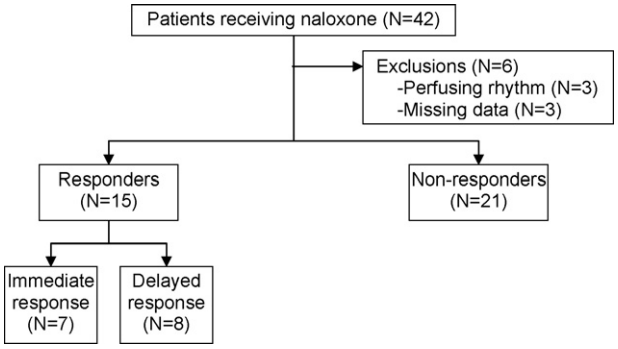

Fig. 1. Study design.

2.6. Data collection and processing

Data was collected by an investigator trained in Microsoft Access, the Emergency Department Information Management (EDIM), and Sunrise Clinical Manager (SCM) databases. From an Access database of EMS responses, a query was performed to retrieve all patients who were in cardiac arrest and received naloxone from January 1, 2003 to December 31, 2007. The original paper PCRs were obtained for each patient. The investigator recorded date, patient age and sex, time of cardiac arrest, duration of anoxia, duration of cardiac arrest, naloxone dosage, destination hospital, emergency department disposition, and time of pronouncement (if applicable). Additionally, the investigator recorded all of the patients' cardiac rhythms as well as pharmacologic interventions documented on the PCRs. Three of the authors reviewed all charts and had 100% agreements on all documented data. After enrolling qualified subjects, records of patients transported to our hospital were cross-referenced with emergency department records in EDIM to obtain information on outcomes. Furthermore, for patients that survived to admission, records were cross-referenced in SCM to determine hospital course and disposition. All data was entered into a standardized abstraction form. Endpoints were reconfirmed twice for each patient by re-inspection of PCRs by the same abstractor. The investigators met monthly to discuss progress.

2.7. Outcome measures

For each participant, cardiac rhythms were compared immediately before and after naloxone administration. The original rhythm was defined as the heart rhythm documented immediately prior to naloxone administration. Participants were then classified based on whether there was a change in EKG rhythm from baseline (respon-

Table 1
Baseline characteristics of patients by confirmation of EKG rhythm change.

	Responders ($N=15$)	Non-responders ($N=21$)
Age, years (SD)	44 (17)	40 (14)
Gender, % male (no.)	53 (8)	81 (17)
Naloxone dose, mg (SD)	2.6 (2.1)	2.0 (0.5)
Initial rhythm, % (no.)		
Asystole	53 (8)	71 (15)
PEA	40 (6)	29 (6)
Ventricular fibrillation	7 (1)	0 (0)

Abbreviations: EKG, electrocardiogram; PEA, pulseless electrical activity.