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 inotropic 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.

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1. Introduction

Naloxone has long had a presence in the armamentarium of emergency physicians caring for opioid poisoned patients. 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. Naloxone alone in high doses has been shown to increase cardiopulmonary resuscitation (CPR) rates following asphyxia induced cardiac arrest in rats. Further animal data supports naloxone administration alone or in combination with epinephrine in simulated asphyxia induced cardiac arrest models. 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.

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. 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.

Naloxone has been demonstrated to reduce action potential upstroke in guinea pig, canine, rabbit, and sheep myocardium. 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. Therefore, naloxone’s antiarrhythmic activity appears to be similar to both class I and III antiarrhythmics.
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 by 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.

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.
Table 2
Immediate and delayed responders to naloxone therapy.

<table>
<thead>
<tr>
<th>Age and gender</th>
<th>Rhythm change over naloxone treatment interval (a)</th>
<th>Narrative of all pharmacologic and external defibrillations interventions (b)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>73 F Asystole → ventricular fibrillation (c) 4 min</td>
<td>Found in asystole. Over 22 min received epinephrine 3× and atropine 3× without effect. Subsequently administered naloxone 2 mg followed by epinephrine 1×.</td>
<td>Pronounced in ED</td>
<td></td>
</tr>
<tr>
<td>49 F PEA → sinus tachycardia 1 min</td>
<td>Found in asystole. Over 16 min received epinephrine 1× and atropine 1×. Rhythm changed to PEA (rate unknown). Naloxone 2 mg administered, rhythm changed to sinus tachycardia (118 bpm).</td>
<td>Survived to admission; died on HD #2</td>
<td></td>
</tr>
<tr>
<td>37 M Asystole → accelerated junctional rhythm (c) 1 min</td>
<td>Found in asystole. Received epinephrine 2× and atropine 2× over 8 min. Naloxone 2 mg administered followed immediately by epinephrine at which point EKG converted to accelerated junctional rhythm (60 bpm).</td>
<td>Pronounced in ED</td>
<td></td>
</tr>
<tr>
<td>24 M Asystole → PEA 4 min</td>
<td>Found in ventricular fibrillation. Defibrillated at 200 J and converted to asystole. Administered epinephrine and atropine without rhythm change. Naloxone 2 mg administered, rhythm changed to PEA (rate unknown).</td>
<td>Pronounced in ED</td>
<td></td>
</tr>
<tr>
<td>62 M PEA → ventricular fibrillation (c) 6 min</td>
<td>Found in PEA (rate 40 s). Over 6 min, received epinephrine 1× and atropine 1×. Remained in PEA (rate 90). Received naloxone 2 mg and epinephrine 1× and rhythm change to ventricular fibrillation.</td>
<td>Survived to admission; died HD #1</td>
<td></td>
</tr>
<tr>
<td>47 F Asystole → PEA (c) 3 min</td>
<td>Arrest witnessed by BLS with &lt;1 min anoxic time. Found in asystole. Received epinephrine 1×, atropine 1×. No changes. Received naloxone 2 mg, epinephrine 1× and atropine 1× and spontaneous non-sustained 20–30 s runs of idioventricular PEA (HR unknown) were noted.</td>
<td>Pronounced in pre-hospital setting</td>
<td></td>
</tr>
<tr>
<td>23 M Asystole → ventricular tachycardia (pulseless) (c) 7 min</td>
<td>Found in asystole. Received epinephrine 2× and atropine 2× over 16 min. Remaining in asystole. Received naloxone 2 mg, dextrose 50% 25 g, epinephrine, atropine, and sodium bicarbonate 50 mEq over 7 min. Converted to pulseless ventricular tachycardia.</td>
<td>Pronounced in ED</td>
<td></td>
</tr>
<tr>
<td>36 F Asystole → sinus tachycardia 2 min</td>
<td>Found in asystole. Received epinephrine 2× and atropine 2× over 13 min. Remained in asystole. Received naloxone 2 mg. Converted to sinus tachycardia (130 bpm) within 2 min.</td>
<td>Survived to admission; survived to discharge HD#11</td>
<td></td>
</tr>
<tr>
<td>72 F Asystole → PEA 2 min</td>
<td>Arrest witnessed by ALS 2–3 min after arrival with &lt;1 min anoxic time. Fluctuated between PEA, asystole, and ventricular fibrillation. Received epinephrine 8×, atropine 3×, sodium bicarbonate 50 mEq 2×, and calcium chloride 1 g over 32 min. Defibrillated at 360 J 2×. Stayed in asystole. Received naloxone 2 mg. Converted back to PEA (rate unknown).</td>
<td>Pronounced in ED</td>
<td></td>
</tr>
<tr>
<td>66 M PEA → ventricular tachycardia (pulseless) (c) 10 min</td>
<td>Found in PEA (rate 35). Received epinephrine 2× and atropine 1× over 10 min. Remained in PEA. Received naloxone 2 mg, epinephrine, and sodium bicarbonate 50 mEq over 6 min. Converted to pulseless ventricular tachycardia (rate 150).</td>
<td>Pronounced in ED</td>
<td></td>
</tr>
<tr>
<td>22 M Asystole → PEA 2 min</td>
<td>Found in asystole. Received epinephrine 2×, atropine 2×, and naloxone 2 mg over 7 min. Remained in asystole. Received 2nd dose of naloxone 2 mg. Converted to PEA (rate unknown).</td>
<td>Survived to admission; further outcome unknown</td>
<td></td>
</tr>
<tr>
<td>24 F PEA → asystole 5 min</td>
<td>Found in PEA (rate unknown). Four minutes after ALS arrival, patient received epinephrine and converted to asystole. Over 9-min interval patient received epinephrine 2× and atropine 2× and rhythm converted to PEA (rate 70). Patient received naloxone 1 mg and rhythm converted back to asystole.</td>
<td>Pronounced in ED</td>
<td></td>
</tr>
<tr>
<td>45 M PEA → asystole (c) 2 min</td>
<td>Found in PEA (rate 10–20). Over 2 min interval, patient received epinephrine 1× and atropine 1×. Remained in PEA. Patient administered naloxone 2 mg, epinephrine 1× and atropine 1×. Converted to asystole.</td>
<td>Pronounced in ED</td>
<td></td>
</tr>
<tr>
<td>45 M Ventricular fibrillation → PEA 2 min</td>
<td>Found in PEA (rate 110) and received epinephrine 1×. Converted to ventricular fibrillation. Patient received naloxone 2 mg and converted back to PEA (rate 60).</td>
<td>Pronounced in pre-hospital setting</td>
<td></td>
</tr>
<tr>
<td>43 F PEA → asystole (c) 8 min</td>
<td>Found in asystole. Over 22 min received epinephrine 3×, atropine 2× and thiamine 100 mg. Converted to PEA. Over 3 min patient received epinephrine 1× and dextrose 50% 75 g without rhythm change. Patient received naloxone 10 mg, epinephrine 2×, and bicarbonate 50 mEq and converted back to asystole.</td>
<td>Unknown outcome</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ALS, advanced life support; BLS, basic life support; ED, emergency department; EKG, electrocardiogram; HD, hospital day; PEA, pulseless electrical activity.

\(a\) The interval between naloxone administration and the first recorded change in EKG rhythm.

\(b\) All pharmacologic and external defibrillations administered starting at the time of ALS arrival and ending at the time of the first recorded EKG change following a naloxone dose. Unless otherwise specified: anoxic times unknown, all medications administered intravenously, epinephrine dose 1 mg of 1:10,000 concentration, and atropine dose 1 mg.

\(c\) Delayed response.
Table 3
Number of patients receiving additional therapy.

<table>
<thead>
<tr>
<th></th>
<th>Immediate responders (N = 7)</th>
<th>Delayed responders (N = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Atropine</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Dextrose 50%</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Sodium bicarbonate</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Calcium chloride</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

ders) or no change (non-responders). Changes in original rhythm noted immediately following naloxone administration, but before additional pharmacologic interventions, were defined as immediate changes. Delayed changes were defined as cardiac rhythm changes occurring after additional medications were administered but within a 10-min interval following initial naloxone dose. The primary outcome measure was change in cardiac activity from baseline based upon EKG rhythm. Secondary outcome measures examined included return of spontaneous circulation (ROSC), survival to hospital admission, and survival to hospital discharge.

2.8. Primary data analysis

For all patients receiving naloxone during cardiac arrest over the five-year period, the percentage that had any rhythm change following naloxone administration was calculated. Additionally, the percent of participants with changes immediately after receiving naloxone was determined. Finally, the percentage of patients who had a return of spontaneous circulation was obtained.

The participants who were classified as responders were followed through their hospital course. From this information, rates of survival to admission and survival to discharge were computed.

3. Results

3.1. Characteristics of study subjects

From a database of 32,544 advanced life support (ALS) emergency medical calls, 42 patients in non-traumatic cardiac arrest at the time of ALS dispatch received naloxone because of suspicion by a paramedic of acute opioid use. Six patients were excluded from the study, three for having palpable pulses at the time of naloxone administration, and three due to missing data on PCRs. The data points missing were route of administration, dose, or record of EKG rhythm. Of the excluded patients with missing data, one demonstrated a rhythm change following naloxone administration. Thirty-six patients remained for enrollment in the study (Fig. 1).

3.2. Main results

From January 1, 2003 to December 31, 2007, 15 of the 36 (42%) (95% confidence interval [CI]: 26–58) patients in cardiac arrest who received naloxone in the pre-hospital setting had a change in EKG rhythm. Table 1 demonstrates the baseline characteristics of patients with rhythm change (responders: N = 15) and without (non-responders: N = 21). Prior to naloxone administration, each of the 15 responders received other standard protocol interventions as deemed necessary by ALS personnel and described in Table 2. A summary of these interventions is shown in Table 3.

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 (Table 4). During treatment by paramedics, 20% (95% CI: 0–40) of all responders converted from cardiac arrest to a perfusing rhythm.

3.3. Supplemental analysis

A total of four responding patients survived to hospital admission. This includes a patient who regained a perfusing rhythm while in the emergency department. Two of the patients who regained perfusion subsequently died during their hospital course and one patient survived to be discharged from the hospital 11 days after admission. The fourth patient's outcome could not be obtained because of being transported to another hospital. Of note, the single patient who survived to discharge tested positive for opiates in a routine urine toxicology screen performed in the hospital emergency department. All 21 non-responders were pronounced in the pre-hospital setting or in the emergency department.

4. Discussion

Our retrospective chart review demonstrated a possible association between naloxone administration during cardiac arrest and cardiac rhythm changes. Forty-two percent of patients who received naloxone while in cardiac arrest demonstrated some change in their cardiac rhythm. Notably, 19% of all recipients demonstrated changes in cardiac rhythm immediately following naloxone but prior to additional ALS interventions. In addition, 20% of responders (8% of all subjects) had a post-intervention rhythm sustainable with life. However, due to our lack of control group we cannot claim to have established a causal relationship.

Causality must also be determined by a suggested mechanism of naloxone in cardiac arrest, yet this remains elusive. Opioid drug binding is not limited to one receptor type. In addition endogenous opioids exhibit substantial crossover among the different mu, kappa, and delta opioid receptor types, therefore making the mechanism difficult to pinpoint. Opioid induced cardiovascular toxicity manifests as arteriolar and venous dilatation through the release of histamine. Although cardiovascular toxicity results in part from degranulation of histamine containing vesicles, the majority of opioid pharmacologic actions are through the mu, kappa, delta, and nociceptin receptors. For example, respiratory depression is implicated via stimulation of μ2 receptors that diminish sensitivity to hypercapnea and hypoxia.

The receptor properties that would obviously be most disadvantageous during cardiac arrest are respiratory depression and sedation. The mu receptor exhibits the strongest properties in this regard and is the receptor of most interest in cardiac arrest patients. In the proper doses, naloxone exhibits antagonistic effects at all receptors for endogenous and exogenous opioids. The actions of opioid agonists at the mast cell level that cause histamine degranulation are independent of the opioid receptors. As such, they are not blocked by naloxone. The hypotensive effects of histamine are deleterious to the patient in cardiac arrest.

Alternatively, naloxone may alter cardiac function through involvement with catecholamines and the autonomic nervous system. Naloxone has been shown to stimulate catecholamine release and increase sympathetic nerve activity. This may be a mech-
anism for elevating heart rate and blood pressure as well as raising in vivo levels of catecholamines to act synergistically with those administered medically.

Several limitations of our study exist. First, standard ACLS medications were administered to our patients prior to naloxone; true causality between naloxone and its rhythmogenic effects is difficult to establish. However, even minimal improvements in cardiac arrest outcomes may be of meaningful importance. Without a prospective study and patient randomization, there exists the possibility that the results may be due to other interventions, or by chance. The possibility of a prospective randomized study in this population remains difficult as a result of strict pre-hospital consent protocols in our state. Second, time of initial cardiac arrest to naloxone administration could not be determined because most of the patients were found by ALS providers after unknown anoxic times. This interval is a confounding variable, which could not be analyzed in the study. Similarly, we cannot assume that our population mimics the asphyxia induced cardiac arrest model. Though opioid intoxication and subsequent respiratory depression can lead to cardiac arrest, it is not appropriate to assume based upon paramedic suspicion alone that our population was entirely composed of opioid intoxications. Thus, our results could be biased in either direction. Additionally, it was impossible to compare the responders to non-responders in terms of naloxone’s adverse effects. Non-responders may have had worsened outcomes as a result of naloxone administration and because so many patients presented in asystole, it is impossible to make judgment about this group. Lastly, we are left with the questions of what should be the endpoint in evaluating the use of naloxone in cardiac arrest and what is the proper dose to observe that effect. We defined responders as those who had cardiac rhythm changes and patients were administered far lower doses than those used in animal models. A transient improvement in rhythm that still results in death does not constitute any real improvement. However, some post-naloxone rhythms may be more likely to lead to a perfusing rhythm, respond to antiarrhythmic medications, or convert to perfusing rhythm following defibrillation. Instead, our results simply represent a potential for improvement that may lead to a clinically significant change in a human model.

5. Conclusion

The utility of naloxone in suspected opioid arrests remains controversial. Based upon our data, we cannot firmly support its use during cardiac arrest involving any suspicion of opioid use. However, with current low rates of survival and low return of spontaneous circulation during cardiac arrest, any potential improvement in rhythm makes this a reasonable modality. With limited success of any medication in cardiac arrest, intervention with naloxone is a reasonable adjunctive treatment that poses little risk with potential benefit.

Conflict of interest statement

Only Dr Mark A Merlin has a potential conflict of interest to disclose. He receives a $125,000 grant (#7015) from the American Heart Association. This grant is studying the written Advanced Cardiac Life Support (ACLS) exam with skills performance at 0-, 3- and 6-month intervals. The grant is not related to this submitted manuscript. Frank Dos Santos is currently an active duty commander in the US Navy Medical Corps and the views of this article do not necessarily represent the view of the Department of Defense or its components. No financial and personal relationships with other people or organizations that could inappropriately influence (bias) the work exist. Specifically, Scott Alter, Mathew Saybolt, Diane Calello, Kevin Rynn, Daniel Nelson and Frank Dos Santos have no conflict of interest.

References