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The Effects Vasopressin and Epinephrine on Cardiac Arrest Following Desipramine Overdose in a Porcine Model

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Abstract

Background: Desipramine, a tricyclic antidepressant, is used for depression particularly related to post traumatic stress disorder. The use of the drug escalates the possibility of an overdose. The purpose of this study was to determine the survivability of swine that have a cardiac arrest from an overdose of desipramine. This was the first study to investigate the effects of vasopressin vs. epinephrine in the treatment of cardiac arrest following an overdose of desipramine.

Methods: This study was a prospective, between subjects, experiment design following a cardiac arrest from an overdose of desipramine. Pigs (n = 21) were randomly and equally assigned to 1 of 3 groups: cardiopulmonary resuscitation (CPR) only (n = 7); epinephrine + CPR (n = 7); or vasopressin + CPR (n = 7).

Results: A Fisher's Exact Test (FET) indicated that there was no significant difference between the CPR only and the epinephrine + CPR groups (p = 1.00); a significant difference between CPR only and the vasopressin + CPR groups (p = .001); and a significant difference between epinephrine + CPR only and vasopressin + CPR groups (p = .005).None of the pigs in the CPR only and one in the epinephrine + CPR survived; all of the pigs in the vasopressin + CPR group survived. The odds of survival in the vasopressin + CPR group was 225 times greater than CRP only (p = 0.008) and 65 time greater than epinephrine + CPR group (p = 0.015).

Conclusion: The results strongly suggest that vasopressin + CPR is much more effective than CPR only or epinephrine + CPR.

Keywords

Vasopressin; Epinephrine; Desipramine; Porcine model

Introduction

Cardiac arrest remains one of the leading causes of morbidity and mortality with more than 900 occurrences daily in the United States [1-3]. One of the causes of cardiac arrest is suicide from overdose of antidepressants. Depression is often treated with antidepressants, but the use of antidepressants increases the risk of overdose and subsequent cardiac arrest. Desipramine, a tricyclic antidepressant (TCA), is a noradrenergic uptake inhibitor. The drug is a commonly used antidepressant and is effective for such conditions as Post Traumatic Stress Disorder (PTSD). The incidence of PTSD and codependence of alcohol has increased tremendously in the last ten years particularly in Soldiers returning from Iraq and Afghanistan. PTSD accounted for 52% of the mental health diagnoses overall among the population seeking mental health care at the veterans administration hospitals. Eighty percent of individuals with PTSD suffer from another psychiatric disorder with alcohol abuse or dependence being the most commonly occurring [4]. Petrakis stresses that patients with PTSD and alcohol codependence are at an increased risk for suicide. In that study, the investigators found desipramine is the drug of choice for depression, PTSD, and alcoholism [4].

Based on limited evidence-based data, the American Heart Association (AHA) recommends 1 mg of epinephrine ***or*** 40 units of vasopressin be administered intravenous (IV) for patients in arrest [5-8]. There is limited research relative to the treatment of cardiac arrest from an overdose with desipramine. One nonrandomized controlled interventional trial of 92 rats studied the use of epinephrine, norepinephrine, or placebo and a 5-minute bolus infusion of sodium bicarbonate or another placebo drug after a 2 mg/kg/minute overdose of amitriptyline, another TCA. Researchers found that the optimal treatment was epinephrine plus sodium bicarbonate [9]. One case presentation described rapid improvement after vasopressin administration of a 56 year-old man who over dosed on amitriptyline. The individual was initially treated with sodium bicarbonate and norepinephrine for a wide complex junctional rhythm and hypotension with minimal improvement. Vasopressin was started on the individual at 0.04 units per minute, and within the next three hours, his blood pressure improved [10]. There are no prospective studies that have investigated the use of vasopressin for any TCA overdose. Currently, advanced cardiac life support (ACLS) guidelines for patients in arrest are for the optional administration of vasopressin 40 units instead of the first or second dose of epinephrine 1mg with pulseless ventricular tachycardia [8]. No studies exist comparing vasopressin to epinephrine for treatment of desipramine overdose. The purpose of this study was to determine the survivability of swine that have a cardiac arrest from an overdose of desipramine. Specifically, the research question that guided the study was as follows: Is there a significant difference in survival between the groups: cardiopulmonary resuscitation (CPR) only; epinephrine + CPR; or vasopressin + CPR in swine in arrest from desipramine?

Methods

This study was a prospective, between subjects, experimental design using the porcine model. Twenty-one Yorkshire male swine weighing approximately 70 kg were randomly assigned (n = 7 per group) to one of three groups: CPR; epinephrine + CPR; or vasopressin + CPR. The rationale for using males only was to avoid any hormonal effects. This particular weight range was used because it is representative of an average sized adult.

The protocol was approved by the Institutional Animal Care and Use Committee and the animals received care in compliance with the Animal Welfare Act, the Guide for the Use of Laboratory Animals. The pigs were allowed to acclimate to the research facility for a period

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of four days. Swine were allocated to each group as assigned by a computer random number generator. Sedation was administered with intramuscular injection of Telazol (4-8mg/kg). Once sedated, personnel transported the pigs to the preparation room where they were intubated. Anesthesia was provided by isoflurane. Pigs were not allowed to eat after midnight but were allowed to drink water as desired. An ear vein was then cannulated, and infusion was started with lactated ringers at 10 mL/kg/hour for the remainder of the procedure. The left carotid artery was cannulated to allow for pressure monitoring.

After the application of the monitors, we stabilized the pigs for 10 minutes. The toxic dose of desipramine was then administered via the jugular catheter and was followed by 20 mL normal saline flush. In a review of the literature, we found that no studies have investigated the toxic IV dose of desipramine. However, there have been documented case studies of the toxic oral dose of desipramine from patients arriving at the Emergency Room. There was a wide variation of doses of desipramine that was lethal [11]. Therefore, in the model development phase of this project, we injected each swine with a dose of IV desipramine until a non-perfusing rhythm occurred. We postulated that because we were avoiding the first pass effect of the liver as with oral medication, the lethal dose would be much less. We found that the mean toxic dose of desipramine was 8mg/kg for each group. We injected the desipramine and observed for a non-perfusing arrhythmia as defined as ventricular fibrillation, ventricular tachycardia, or standstill, a stopwatch was started. Anesthesia was stopped, and after 30 seconds of a continuous non-perfusing arrhythmia, we initiated CPR with a mechanical device, the "Thumper" (Michigan Instruments, Inc.). The Thumper was used to automatically compress the sternum at a predetermined depth of 1 1/2 inches at a rate of 100 beats per minute as per guidelines of the AHA [8]. The Thumper was used to ensure that the rate and depth of compression were consistent over time and reproducible from animal to animal. Use of this device also prevented any variability of delivered compressions. Compressions were continued with ventilations with 100% oxygen at a ratio of 30:2 (compressions to ventilations). CPR was continued for 2 minutes at which time the IV resuscitation medication, (either epinephrine or vasopressin), was then administered and followed up with a 20 mL normal saline flush according the group designation. For the epinephrine group, 1 mg was administered by IV every 2 minutes or until there was a sustainable rhythm; for the vasopressin group, 40 units were administered for a one-time dose after 2 minutes of CPR was initiated. The procedures were the same for the CPR group except no medications were administered. Every 2 minutes thereafter compressions were stopped, and the cardiac rhythm was evaluated. When the pigs in all groups were found to have either ventricular fibrillation or ventricular tachycardia, they were defibrillated beginning with 200J and subsequently increased to 360J.

Idris states that in 42 laboratory studies on cardiac arrest, 29 widely discrepant definitions of return of spontaneous circulation were used. He recommends that there should be consistency in definition and that the operational definition should be maintenance of a systolic aortic blood pressure of at least 60 mm Hg for at least 10 minutes [12]. Therefore, if the treatment resulted in a sustainable rhythm while maintaining a systolic blood pressure ≥ 60mmHg for 10 minutes, we documented the treatment as successful. The pigs were monitored for a total of 40 minutes if successful; otherwise the treatment was discontinued after 30 minutes. If the treatment did not result in a systolic blood pressure ≥ 60mmHg for 10 minutes, CPR was discontinued and documented as unsuccessful.

The investigators used G-Power 3.0.10 [13] to determine the sample sizes needed in the experiment. Using data from our pilot study, we calculated an effect size of 0.6. We used an alpha of 0.05 for all data analyses. Using an alpha of 0.05, power of .80, and a large effect size, 0.6, the number needed was determined to be 7 per group. A multivariate analyses of variance (MANOVA) was used to determine if the groups were equally distributed with regard to pre-intervention (weight, temperature, vital signs) data. Intervention data were analyzed using a Fisher's Exact test and odds-ratio. Percentages of survival vs. non survival were calculated. We used SPSS version 18 (SPSS Inc., Chicago, IL, USA) for the MANOVA and for the Fisher's Exact test and MedCal [14] to calculate the odds/ratio.

Results

Twenty one swine were used in this study, 7 per group. A MANOVA indicated that there were no significant difference in the pretest data specifically vital signs, weights, or core body temperatures ($p > 0.05$) indicating that groups were equivalent on these parameters. None of the swine in the CPR group (0%); all of the swine in the vasopressin + CPR group (100%); and 1 in the epinephrine + CPR group (14.2%) survived. All of the swine in the CPR group (100%); none of the swine in the vasopressin + CPR group (0%); and 6 in the epinephrine + CPR (85.7%) died. We used a Fisher's Exact test to determine if there were statistically significant differences between the groups. There was no significant difference between the CPR only and the epinephrine + CPR groups ($p = 1.00$), but there was a significant difference between CPR only and the vasopressin + CPR groups ($p = .001$); and a significant difference between epinephrine + CPR and vasopressin + CPR groups ($p = .005$) (Table 1, Figure 1).

An odds-ratio was also used to analyze the data and indicated that the vasopressin + CPR had a 225 times greater odds of survival compared to CPR only group ($p = 0.008$) and 65 times greater odds of survival compared to the epinephrine + CRR group ($p = 0.015$). The

Table 1: Comparison of the Groups in Swine in Arrest from Desipramine.

Groups	Survived	Died	Fishers Exact Test results
CPR alone	0 (0%)	7 (100%)	CPR only vs. the epinephrine + CPR groups (p = 1.00)
Epinephrine + CPR	1 (14.2%)	6(85.7%)	CPR only and the vasopressin + CPR groups (p = .001)*
Vasopressin + CPR	7 (100%)	0 (0%)	Epinephrine + CPR vs. vasopressin + CPR groups (p =.005)*

*significant < 0.05

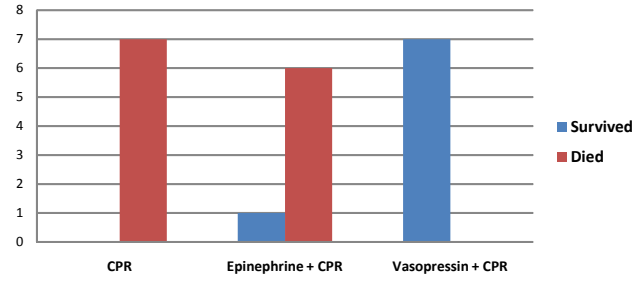

Figure 1: Summary of Survivability by Group.

odds indicated that the survival for the epinephrine + CPR group was 3.64 times greater than CPR only but not significant (p = 0.72).

Discussion

The results of our study indicate that in the presence of desipramine overdose, vasopressin + CPR is more effective for treatment of cardiac arrest than epinephrine + CPR or CPR alone. ACLS guidelines recommend epinephrine 1mg every 2 minutes for patients in arrest Alternatively, vasopressin 40 units may be used instead of the first or second dose of epinephrine [8]. Vasopressin has been shown to be effective in the treatment of cardiac arrest in swine and human models [15]. Although epinephrine and vasopressin both have vasoconstrictive properties, their mechanisms of action vary. Epinephrine acts on alpha-1 adrenergic receptors in vascular smooth muscle [16,17]. Vasopressin causes vasoconstriction by activating the V1 receptor on vascular smooth muscle [18].

TCAs have been shown to have alpha-1 adrenergic antagonism [19,20]. Previous studies have shown that in the presence of alpha-1 antagonism/inhibition, epinephrine is not effective in treating hypotension and/or cardiac arrest. The ineffectiveness of epinephrine in treating patients with cardiac arrest secondary to TCA overdose in this study may in part be because of alpha-1 adrenergic antagonism of TCAs.

Another possible explanation for the ineffectiveness of epinephrine in desipramine overdose may in part be because metabolic acidosis in cardiac arrest patients, which impairs functionality of alpha-adrenergic receptors, potentially causing diminished effectiveness of epinephrine [16]. Tricyclic antidepressant overdose morbidity is primarily associated with cardiac arrhythmias and hypotension that become increasingly refractory to treatment as acidosis worsens [21]. In the presence of metabolic acidosis secondary to cardiac arrest, vasopressin may have greater vasoconstriction effects and thus greater perfusion than epinephrine because its action on the V1 receptor as opposed to the alpha 1 adrenergic.

Further investigation into the effects of epinephrine and vasopressin in cardiac arrest secondary TCA overdose should be implemented. Examining the effectiveness of vasopressin versus epinephrine in the presence of direct alpha antagonism may be beneficial in determining why in some cardiac arrest situations vasopressin seems to be clearly beneficial over epinephrine.

Limitations of the Study

There are several limitations of this study which are as follows: 1.The sample size was small. 2. The results may not be generalizable to humans; however, the cardiovascular system is similar to humans. 3. The dose to produce a non-perfusing arrhythmia was inconsistent ranging from 7-10 mg/kg, but there was no difference in the mean doses between the three groups: each group had a mean of 8 mg/kg. Two subjects in the vasopressin + CPR required 10 mg/kg to achieve a non-perfusing arrhythmia.

Conclusion

The results indicate that 100% of the pigs were successfully treated with vasopressin + CPR. Of the 21 pigs that went into cardiac arrest with desipramine, all of the vasopressin + CPR pigs survived compared to 1 in the epinephrine + CPR group and none in the CPR only group. Current ACLS guidelines recommend treatment with epinephrine, but state vasopressin can be used for the first or second dose.

Based on these findings, we recommend that our study be replicated with a larger sample size and that prospective randomized trials be implemented using human subjects. More research needs to be compiled on cardiac arrest in humans following overdose on TCAs and desipramine. Using the same model as this study, researchers need to investigate overdoses from other TCAs.

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