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ORIGINAL ARTICLE

Centhaquin Effects in a Swine Model of Ventricular Fibrillation. Centhaquin and Cardiac Arrest

Konstantina Papalexopoulou, MSc [a,1], Athanasios Chalkias, PhD [a,b,1*], Paraskevi Pliatsika, MSc [a], Apostolos Papalois, PhD [c], Panagiotis Papapanagiotou, PhD [a], Georgios Papadopoulos, PhD [d], Eleni Arnaoutoglou, PhD [d], Anastasios Petrou, PhD [d], Anil Gulati, PhD [e], Theodoros Xanthos, PhD [f]

[a]National and Kapodistrian University of Athens, Medical School, MSc ''Cardiopulmonary Resuscitation'', Athens, Greece
[b]Hellenic Society of Cardiopulmonary Resuscitation, Athens, Greece
[c]ELPEN, Experimental-Research Centre, Athens, Greece
[d]University of Ioannina, Medical School, Department of Anesthesiology, Ioannina, Greece
[e]Chicago College of Pharmacy, Department of Pharmaceutical Sciences, Midwestern University, Downers Grove, Illinois
[f]European University Cyprus, Nicosia, Cyprus

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Background Centhaquin citrate is a novel agent being developed for use in the treatment of haemorrhagic shock. The aim of our study was to assess whether the administration of centhaquin would improve initial resuscitation success, 24-hour survival, and neurologic outcome compared with adrenaline alone in a porcine model of ventricular fibrillation.

Methods Ventricular fibrillation was induced in 20 healthy Landrace/Large White piglets. The animals were randomised to receive placebo plus adrenaline 0.02 mg/kg (n=10, Group C) and adrenaline 0.02 mg/kg plus centhaquin 0.015 mg/kg (n=10, Group S). All animals were resuscitated according to the 2010 European Resuscitation Council guidelines. Haemodynamic variables were measured before arrest, during arrest and resuscitation, and during the first two hours after return of spontaneous circulation. Survival and a neurologic alertness score were measured at 24 hours after return of spontaneous circulation.

Results A significant difference was observed in ROSC rate between the two groups, as 10 animals (100%) from Group S and 4 animals (40%) from Group C achieved ROSC (p=0.011). Systolic, diastolic, and mean aortic pressure and coronary perfusion pressure were significantly higher in Group S at the end of the second cycle of CPR. In our study, all subjects with ROSC survived for 24 hours, while we observed no statistically significant differences in neurologic examination (Group C 100±0, Group S 96±12.64; p=0.527).

Conclusion The addition of centhaquin to adrenaline improved ROSC rates in a swine model of VF cardiac arrest.

Keywords Ventricular fibrillation • Cardiopulmonary resuscitation • Centhaquin • Return of spontaneous circulation

*Corresponding author at: National and Kapodistrian University of Athens, Medical School, M.Sc. ''Cardiopulmonary Resuscitation'', 3 Ir. Politechniou Av., 18532, Piraeus, Greece. Tel.: +302104133992; fax: +302110121758, Email: thanoschalkias@yahoo.gr

[1] These authors equally contributed to the study.

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Introduction

Q4 Despite advancements in pharmacology of cardiopulmonary resuscitation (CPR), the outcome of patients remains dismal. Survival of cardiac arrest victims strongly depends on prompt CPR and increases if duration of CPR is kept to an absolute minimum. Although the latter demands high quality CPR with an emphasis on chest compressions, drugs may play a crucial role in restoring spontaneous circulation (ROSC).

Centhaquin citrate is a novel agent being developed for use in the treatment of haemorrhagic shock. Centhaquin has been reported to augment cardiac output, reduce systemic vascular resistance and increasing survival over Lactated Ringer's solution (R-L) alone in haemorrhagic models [1–3]. Of note, centhaquin's pharmacological effects favour its use in emergency and critical care patients. This agent appears to stimulate a-adrenergic receptors [4], while at the same time it exerts central sympatholytic activity that can reduce vasoconstriction [5], which may be crucial for the preservation of microvascular blood flow and tissue perfusion. The first phase of drug concentration decline is rapid, while at steady state (i.e. the second phase), centhaquin has a half-life of 3.24 min. During the third phase, presumed tissue release occurs and parameter value estimates are similar to those seen with other vasoactive agents, such as norepinephrine and dopamine [6].

Considering that a-adrenergic stimulation increases coronary perfusion pressure (CPP), as well as that the preservation of microvascular perfusion during CPR may decrease the occurrence of post-resuscitation syndrome, the use of centhaquin during CPR seems very attractive. The aim of our study was to assess whether the administration of centhaquin would improve initial resuscitation success, 24-hour survival, and neurologic outcome compared with adrenaline alone in a porcine model of ventricular fibrillation.

Materials and Methods

The protocol was approved by the Directorate of Veterinary Services of Prefecture of Athens, Attica, Greece, according to Greek legislation regarding ethical and experimental procedures (license No 7096/05-11-2014). Twenty healthy female Landrace/Large-White piglets aged 10–12 weeks with average weight 20±1 kg, all purchased from the same breeder (Validakis, Koropi, Greece) were the study subjects.

One week prior to the experiment, the animals were transported to the research facility (Experimental-Research Center Elpen, European Ref Number EL 09 BIO 03) and were acclimatised to laboratory conditions, as previously described [6]. The day before the experimentation the animals were fasted but had free access to water. All animals received anaesthetic and surgical procedures in compliance with the Guide for the Care and Use of Laboratory Animals. Centhaquin citrate (Lot # PMZ-2010/2012/09A) was synthesised at Pharmazz India Private Limited, Greater Noida, India (courtesy Dr. Manish Lavhale).

The experimental protocol has been previously described [7]. In brief, initial sedation in each animal was achieved by intramuscular injection of ketamine hydrochloride (Merial, Lyon, France) 10 mg/kg, midazolam (Roche, Athens, Greece) 0.5 mg/kg and atropine sulfate (Demo, Athens, Greece) 0.05 mg/kg. Propofol (Diprivan 1% w/v, AstraZeneca, Luton, United Kingdom) 2 mg/kg and fentanyl (Janssen Pharmaceutica, Beerse, Belgium) 2 μg/kg were also delivered as an intravenous bolus via the lateral auricular vein to induce anaesthesia.

Whilst spontaneously breathing, but anaesthetised, the animals were intubated with a size 6.0-mm cuffed endotracheal tube which was secured on the lower jaw. Correct placement of the tracheal tube was ascertained by auscultation of both lungs while ventilated with a self-inflating bag. The animals were then immobilised in the supine position on the operating table. Additional propofol 1 mg/kg, cis-atracurium (Nimbex 2 mg/ml GlaxoSmithKline, Athens, Greece) 0.15 mg/kg and fentanyl 0.01 mg/kg were administered intravenously to ascertain synchrony with the ventilator, followed by a propofol infusion of 150 μg/kg/min to maintain adequate anaesthetic depth. Ventilation was delivered using a volume control ventilator (Siare Alpha-Delta Lung Ventilator; Siares.r.l Hospital supplies, Bologna, Italy) with a tidal volume of 15 ml/kg and fractional inspired oxygen (FiO_2) of 0.21. End-tidal CO_2 ($ETCO_2$) (Tonocap TC-200-22-01; Engstrom Division, Instrumentarium Corp, Helsinki, Finland) was continuously monitored and the respiratory frequency was adjusted to maintain $ETCO_2$ 35-40 mmHg. Pulse oximetry (SpO_2) was monitored throughout the experiment. Electrocardiographic monitoring was continuously used, using leads I, II, III, aVR, aVL, and aVF, which were connected to a monitor (Mennen Medical, Envoy; Papapostolou, Athens, Greece). The monitor electronically calculated the heart rate. Arterial blood gases were measured on a blood-gas analyser (IRMA SL Blood Analysis System, part 436301; Diametrics Medical Inc, Roseville, MN, 55113, pH, pO_2, pCO_2).

For measurement of the aortic pressure, an arterial catheter (model6523, USCI CR, Bart; Papapostolou) was inserted and forwarded into the descending aorta after surgical preparation of the right internal carotid artery. Systolic (SAoP) and diastolic aortic pressures (DAoP) were recorded, whereas mean aortic pressure (MAoP) was determined by the electronic integration of the aortic blood pressure waveform. Coronary perfusion pressure (CPP) was electronically calculated as the difference between minimal DAoP and the simultaneously measured right atrial diastolic pressure. The right internal jugular vein was also cannulated with a catheter to measure central venous pressure (CVP). The second internal jugular vein was also surgically prepared. All catheters were calibrated before use and their correct position was verified by the presence of the typical pressure waveform. Cardiac output (CO) was measured as the product of time-velocity integral of Doppler transaortic flow, the diameter of the aortic valve, and heart rate, as previously described [8].

Baseline data were collected after allowing each animal to stabilise for a 30-minute period. Before the experimental procedure, the piglets were randomly assigned to two different groups of 10 subjects each, according to the agents

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