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Short paper

Pharmacokinetics of epinephrine during cardiac arrest: A pilot study

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Abstract

Aim of the study: Epinephrine has been recommended for several decades for the treatment of cardiac arrest. However, although this potent medicament has a documented impact on the return of spontaneous circulation, it does not improve long-term survival. Decreased cerebral blood flow, one of the side effects of epinephrine, indicates that the use of this drug is a two-edged sword. Despite clinical recommendations, no study has investigated epinephrine pharmacokinetics in a setting of cardiac arrest. Therefore, in a pilot setting, we measured the plasma concentrations of epinephrine following a single administration.

Methods: Nine patients with cardiac arrest were included in our study. A single dose of 1 mg epinephrine was administered into a peripheral vein. Simultaneously, blood samples were withdrawn every minute from the jugular vein to determine the plasma concentration. A mixed effects model was used to estimate the $T_{1/2}$ following the peak concentration.

Results: One patient did not achieve a peak concentration during observation and was hence excluded. The remaining eight patients had 26 measurements suitable for modelling. In a stable model, the decline is estimated to be −0.259 [95 % CI (-0.361, −0.157) ($p < 0.001$)]. This implies a half-time for epinephrine of 2.6 (1.9, 4.4) minutes.

Conclusion: Our study indicates that elimination of epinephrine during cardiac arrest is prolonged and that repeated doses of epinephrine may lead to increased plasma levels. Further and larger studies are warranted to determine the optimal plasma concentration during resuscitation.

Clinical trial registration: NCT03036202.

Institutional protocol number: 2016-00189.

Keywords: Cardiac arrest, Pharmacokinetic, Half-time, Epinephrine, Adrenaline

Introduction

In the recent ERC guidelines for advanced treatment of cardiac arrest, the use of epinephrine is still advocated during resuscitation.[1] Epinephrine is a short-acting vasoconstrictor that acts on both alpha-adrenoreceptors and beta-adrenoreceptors, which in experimental settings increases the blood flow to the heart and cerebral cortex.[2,3] This action may increase the incidence of return of spontaneous circulation (ROSC),[4–6] although clinical studies have failed to document increased survival to discharge in patients who receive epinephrine during resuscitation.[4,6] The prehospital administration of epinephrine in cases of nontraumatic cardiac arrest in humans, although showing an improved ROSC ratio and short-term survival, also indicates a lack of benefit or even harm in terms of long-term survival or functional recovery.[6–11] Why this initial increase in ROSC does not trans-

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late into long-term survival is probably multifactorial, i.e., involving myocardial oxygen consumption[12] and a dysfunctional, postarrest heart.[13]

The recommended dose of epinephrine in adults is 1 mg iv, administered every 3–5 minutes or every second cycle (4 minutes) and is hence given in close correlation to a shock.[1] This dose is extrapolated from animal studies where 20 μg/kg appeared to be rational.[14] If ROSC occurs and a recent administration of epinephrine has been given, the heart is initially influenced by high levels of epinephrine, which may be harmful. This is the main reason why the Norwegian Resuscitation Council (NRC) advocates three-minute cycles, where epinephrine may be administered one minute after a shock, if ROSC has not occurred.[15] Theoretically, the plasma levels of epinephrine may decrease the following two minutes until the next shock. Despite current recommendations, no human studies have documented epinephrine pharmacokinetics during human resuscitation or whether repeated doses of epinephrine accumulate in the patients. This gap of knowledge is acknowledged in the recent guidelines, urging for further studies.[1] To elucidate these issues, we conducted a pilot study to explore the pharmacokinetics of epinephrine following a single dose in patients treated for cardiac arrest in the prehospital setting.

Methods

Ethics

The study was approved by the Regional Committees for Medical Research Ethics (REK-Nord 2016/189) and the Norwegian Medicines Agency. Deferred consent was obtained, and the patients' families had the opportunity to withdraw the patient data from analysis. One patient regained consciousness and was able to receive information and sign a written consent form. The trial was registered on ClinicalTrials.gov (NCT03036202).

Study population and environment

The study was performed in a prehospital setting with a physician-staffed helicopter emergency medical service (HEMS), as previously described.[16] Adult patients (18–85 years) with witnessed nontraumatic OHCA with a probable cardiac origin were included. Patients with epinephrine administered by emergency medical services before arrival of HEMS, terminal illness, residential status at a nursing home, obvious signs of death such as rigor mortis or hypothermia were excluded. Treatment was provided according to international guidelines with national adjustments.[15] Relevant data according to the Utstein-template for out-of-hospital cardiac arrest were recorded.[17] In addition, the patient's weight and height were estimated by the attending physician.

Observation

After high-quality chest compressions and airway management were established, cannulation of the external/internal jugular vein was performed, through which all blood samples were withdrawn. In addition, a peripheral vein in one arm was used for the administration of epinephrine. During resuscitation, the first blood sample (6 ml) was withdrawn to determine the base level. Epinephrine (1 mg) was then administered in the peripheral vein, followed by a bolus of 20 ml normal saline (0.9 mg/ml). Infusion was then stopped completely. Sampling was performed from a 3-way connection near the IV-cannula, and two ml samples were removed as waste to ensure fresh samples from the jugular vein. Every minute following the administration of epinephrine, samples were drawn into pre-cooled containers until the end of registration (five minutes). If cardiac arrest persisted after five minutes, epinephrine was further administered according to guidelines. Blood samples were kept cool on ice and processed at the biochemistry laboratory at Haukeland University Hospital immediately afterwards, where plasma was extracted from the samples and frozen at −80 °C. Samples were later analysed at Dept. Medical Diagnostics, Karolinska University Hospital, Stockholm (Sweden), where plasma concentrations of epinephrine were determined using high-performance liquid chromatography (HPLC) with electrochemical detection. The reproducibility of plasma-adrenalin, as depicted by CV%, is 4.63 %.

Statistics

For the statistical analysis, the values until the peak concentration were excluded. According to standard calculations in pharmaceutical elimination, the natural logarithm of the actual concentrations was used to estimate $T_{1/2}$. A mixed effects model was estimated, with the log-transformed concentration as the dependent variable by the time from peak, with a random intercept and slope. The nlme package in R (The R Foundation for statistical Computing, Vienna, Austria) was used for estimation.

Results

There were 9 included patients between June 2017 and May 2018, of whom one survived to discharge. The median age was 71 (55–80) years, and all patients received bystander CPR within the first minute. The median time from the collapse until the anaesthesiologist was present and the start of the study was 25 (2–39) minutes. Prehospital data and the accompanying concentrations of epinephrine are presented in Table 1.

Nine patients with six measurements each provided a potential of 54 measurements, of which there were 26 measurements after the peak for 8 patients. One patient (Table 1) had increasing concentrations during the observation period and hence was excluded from the calculations.

For most of our patients, the peak concentration was achieved one minute following the administration of epinephrine (Fig. 1). In this stable model, the decline was estimated to be −0.259 95 % CI (-0.361, −0.157) ($p < 0.001$). This implied a half-time for epinephrine of 2.6 (1.9, 4.4) minutes.

Discussion

The most interesting result in this study is the elevated concentrations of epinephrine after 5 minutes. According to recent guidelines, epinephrine should be administered every 3–5 minutes.[1] This may lead to increased concentrations of epinephrine over time. Previous studies showed the association of epinephrine and increased survival in the hospital; however, it did not improve long-term survival.[6–11] Whether these observations are related to long-lasting resuscitation or repeated doses of epinephrine remains unknown. Despite the documented side effects associated with the use of epinephrine,[18,19] evidentiary gaps still exist, as ROSC is the best way to start a good recovery. Our results suggest that repeated doses of epinephrine i. v. over time may result in increasing concentrations of epinephrine

Table 1 – CA-EMS = time from cardiac arrest until EMS present on scene, CA-intervention = time from cardiac arrest until administration of epinephrine, $ETCO_2$ (kPa) measured every minute following administration, RR = respiratory rate (min^{-1}), CR = compression rate (min^{-1}).

	Patient	1	2	3	4	5	6	7	8	9
Clinical Parameters	Age (years)	55	69	80	61	71	72	71	74	72
	Initial Rhythm	VF	AS	AS	PEA	VF	VF	VF	AS	VF
	Bystander CPR	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	CA-EMS (min)	22	8	29	0	9	7	5	14	11
	CA-intervention (min)	30	24	31	2	22	21	25	39	25
	Weight (kg)	70	74	80	70	70	79	74	80	100
	Dose mg/kg	0.0143	0.0135	0.0125	0.0143	0.0143	0.0127	0.0135	0.0125	0.010
Concentration epinephrine (nmol/l)	0 min.	-	36	-	149	12	157	1	-	-
	1 min.	-	3956	10,715	138	2478	1237	9545	-	462
	2 min.	4	6057	7182	123	1642	1051	4107	1252	575
	3 min.	1178	-	5548	108	-	759	2913	538	353
	4 min.	230	7795	4056	118	857	527	2634	-	216
	5 min.	-	8642	3001	111	662	353	2433	328	148
$ETCO_2$/ RR/CR	0 min.	2.4/10/100	3.0/12/100	1.2/10/100	3.0/10/100	1.3/8/117	2.6/10/119	3.2/10/100	4.2/8/101	4.5/10/100
	1 min.	2.3/10/100	2.6/12/100	1.1/10/100	3.2/11/110	1.8/9/130	2.4/10/110	1.6/10/100	4.1/10/100	5.0/10/100
	2 min.	2.5/10/100	2.9/12/100	0.9/10/100	3.0/12/100	1.9/8/120	2.1/10/100	2.1/10/100	4.3/8/110	4.8/10/100
	3 min.	3.4/10/100	2.9/12/100	0.8/10/100	3.4/10/100	1.9/10/111	2.6/10/108	1.8/10/100	4.1/12/100	4.7/10/100
	4 min.	3.2/10/100	1.8/12/100	0.8/10/100	3.5/11/101	1.9/8/115	2.7/10/111	2.4/10/100	3.7/8/105	5.1/10/100
	5 min.	3.2/10/100	1.6/12/100	0.7/10/100	3.2/10/100	2.0/11/118	2.8/10/110	2.2/10/100	4.4/9/100	5.3/10/100

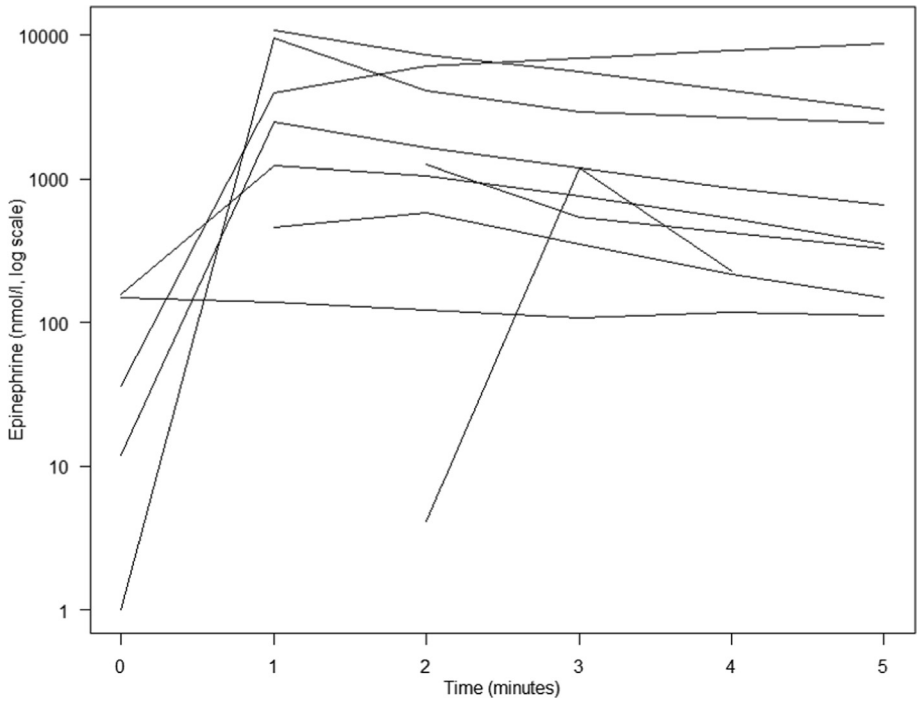

Fig. 1 – Concentrations of epinephrine (semilogaritmic plot).

in plasma. The optimal plasma concentration during resuscitation has not been determined, and we have observed a variety of concentrations among patients over time despite equal high-quality compressions. This uncertainty haunts clinicians, as the concentration of epinephrine within actual patients remains unknown during resuscitation. Ironically, resuscitation with epinephrine is double-blinded. We do not know the patient's concentration, and we do not know the optimal level. Our result with a modelled half-time for epinephrine of 2.6 (1.9, 4.4) minutes is based on measurements from those patients who had a documented peak. According to Table 1, one patient had continuously increasing levels during the observation period and hence was excluded from the model. As such, the half-time for our patients may have been longer, as we stopped the observation before a peak value was observed in one patient.

Another result of this study is the documented ability to perform pharmacokinetic studies in a prehospital setting. In retrospect, it appears more efficient to undertake similar studies in a hospitalized population, preferably in patients with established central venous access.

It appears that intermittent injections of epinephrine fail to achieve steady levels of epinephrine. An initial bolus of epinephrine followed by a continuous infusion may reduce the variations observed. In emergency services capable of handling such equipment, this may represent a future treatment. Our data suggest that elevated levels of epinephrine may be expected in prolonged resuscitation and that giving reduced doses or using increased intervals may be a reasonable alternative to maintain a steady state. To our knowledge, this is the first human study to document the levels of epinephrine during resuscitation following a single dose administration; however, further studies are required to challenge our results.

Limitations

This study has several challenging aspects. The number of included patients appears small. However, our EMS was not limited in their administration of epinephrine. The patients included in this study were those who had not been given epinephrine previously in the resuscitation. Workload of the physician came into consideration, as complete blood samples were not obtained from all patients. A well-staffed hospital setting appears more rational for similar studies.

Conclusions

Our study indicates that elimination of epinephrine during cardiac arrest is prolonged and that repeated doses of epinephrine may lead to increased plasma levels. Further and larger studies are warranted to determine the optimal plasma concentration during resuscitation.

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Role of the funding source

The RAKOS had no influence of the topic, study design nor interpretation of the data.

CRediT authorship contribution statement

Bård E. Heradstveit: Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Geir-Arne Sunde.:** Writing – review & editing, Methodology, Conceptualization. **Helge Asbjørnsen:** Writing – review & editing, Methodology, Formal analysis. **Rune Aalvik:** Writing – review & editing, Validation, Methodology, Investigation, Formal analysis. **Tore Wentzel-Larsen:** Writing – review & editing, Software, Formal analysis, Data curation. **Jon-Kenneth Heltne:** .

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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