Pharmacokinetic Differences Between Peripheral and Central Drug Administration During Cardiopulmonary Resuscitation

UZI TALIT, MD, SHIMON BRAUN, MD, HILLEL HALKIN, MD,* BORIS SHARGORODSKY, MD, SHLOMO LANIADO, MD, FACC
Tel-Aviv, Israel

Advanced resuscitation techniques are dependent on drug therapy to increase survival. Because drugs must reach their site of action instantaneously, the choice of appropriate route of administration may be critical. To study the pharmacokinetics of drug administration by peripheral and central venous routes during resuscitation, nine mongrel dogs were studied. Arterial blood pressure and electrocardiograms were monitored continuously. Cardiac output was evaluated before resuscitation to determine control levels. After thoracotomy and fibrillation of the heart, cardiac massage was started with a frequency of compression maintained at 60/min.

Bolus injections of two different radioisotopes were given simultaneously through a peripheral and a central vein. Isotope activity was sampled through a catheter in the right femoral artery at 5 second intervals for 90 seconds and at 30 second intervals for 210 seconds. The major differences between the two routes of administration were that central injection produced a 270% higher peak concentration ($p < 0.001$) and significantly shorter lag times to the first appearance of tracer (16 ± 7 versus 38 ± 13 seconds, $p < 0.05$) and times to peak concentration (13 ± 5 versus 27 ± 12 seconds, $p < 0.01$). In contrast, there were no significant differences in area under the time-counts curve, mean residence time, total body clearance and steady state volume of distribution. The central compartment volume of distribution was significantly smaller after central than after peripheral injection (26.1 ± 56 versus 76.3 ± 16.5 ml, $p < 0.01$). The therapeutic implications of these findings must be investigated for individual drugs used during cardiopulmonary resuscitation to determine the most appropriate route and dosage for each agent.

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Methods

Animal preparation. Nine mongrel dogs weighing 9 to 15 kg were included in this study. After the dogs were anesthetized with phenobarbital sodium (30 mg/kg body weight intravenously) and intubated with a cuffed endotracheal tube, catheters were placed in the right femoral artery, for recording of blood pressure, in the left femoral artery for withdrawal of blood samples and in the right brachial...
vein and superior vena cava for injection of tracers. An electromagnetic flow probe was placed around the ascending aorta just above its root, and instantaneous aortic blood flow was recorded by a square wave electromagnetic flow meter (model 501, Carolina Medical Electronics). The frequency response of the flow meter was selected at 30 Hz with a time lag of less than 3 ms. The velocity curve recorded by the probe was a true reflection of actual flow, because the circumference of the aorta was constant and the probe fit tightly around the aorta. The arterial pressure and electrocardiogram were monitored continuously and recorded on a multichannel recorder.

**Induction of fibrillation and cardiopulmonary resuscitation.** Ventricular fibrillation was produced by a 100 W-s direct-current shock. After 30 seconds, cardiac massage was started with a frequency of compression maintained at 60/min. One person performed compression for the duration of the experiment in each dog, to keep an even cardiac output.

**Figure 1.** Simulated (A) and observed (B) arterial blood concentration of the tracer after central venous administration (data projected as mean ± SEM). CPM = counts per minute.

Drug administration. After blood pressure during resuscitation had stabilized (25 to 30 seconds), a bolus injection of 2 ml of iodine-125 ($50 \times 10^6$ counts/min) was injected into the right brachial vein; simultaneously, a bolus injection of 2 ml of chromium-51 ($50 \times 10^6$ counts/min) was injected into the superior vena cava. Both isotopes were compounds of sodium, $\text{Na}^{131}\text{I}$ and $\text{Na}_2^{51}\text{CrO}_4$ (Amersham) and both injections lasted approximately 3 seconds.

Blood samples were obtained through the catheter in the right femoral artery at 5 second intervals for 90 seconds after the bolus injections and at 30 second intervals for an additional 210 seconds after injection. Activity in each sample was counted in a well scintillation counter.

**Data analysis.** Time intervals to the first appearance of tracer at the sampling site (lag time) and from that point to the peak counts per minute value (time to peak) were determined directly from the plasma counts per minute versus time curves. Pharmacokinetic analysis of these curves was performed in two ways: 1) The data were fitted to a two compartment open-body model assuming a constant rate infusion input (subsequent to the lag time) of duration equaling time to peak, and a constant rate of elimination from the central compartment (6). Fitting was implemented on an HP-85 microcomputer using an iterative nonlinear regression program (7) and yielded estimates of the central compartment volume of distribution and intercompartmental rate constants. 2) Model-independent noncompartmental determinations (8,9) were made of the steady state volume of distribution, total body clearance and mean residence time of the tracer, as well as the area under the time-counts curve.

Times, volume and clearance values for the two routes of administration were compared by paired $t$ tests. Data are presented as mean ± SD.

**Results**

**Hemodynamics.** Control cardiac output averaged 3.7 ± 1.4 liters/min. The cardiac output during resuscitation was 0.67 ± 0.07 liters/min (range 0.6 to 0.7) or 18% of control cardiac output. The systolic blood pressure averaged 85 ± 17 mm Hg before induction of ventricular fibrillation and 32 ± 10 mm Hg during resuscitation. None of the nine dogs regained a spontaneous electrocardiographic complex or pulsatile blood pressure during the experiment. Data from the peripheral injection in Dog 1 were not included in the pharmacokinetic analyses because of difficulty during the injection.

**Pharmacokinetics.** The central and the peripheral venous injections produced concentration-time curves that differed during the first 100 seconds (Fig. 1 and 2). Central injection produced a significantly higher peak concentration ($620 \pm 21 \times 10^3$ versus $226 \pm 84 \times 10^3$ counts/min, $p < 0.001$) and significantly shorter lag time ($16 \pm 7$ versus...
38 ± 13 seconds, p < 0.05) and time to peak (13 ± 5 versus 27 ± 12 seconds, p < 0.01). In contrast, values for area under the time-counts curve, mean residence time, total body clearance and steady state volume of distribution (VDss) did not differ significantly with the two routes of administration (Table 1). The central compartment volume of distribution (Vc) was significantly smaller after central injection (26.1 ± 5.6 versus 76.3 ± 16.5 ml, p < 0.01) with a proportionately elevated VDss/Vc ratio (4.4 ± 2.0 versus 1.60 ± 0.33, p < 0.01).

The mean residence time for tracers was 64.6 ± 20.5 seconds in the systemic circulation (56.5 ± 18.1 seconds for the central injection and 74.6 ± 21 seconds for the peripheral injection, p = NS); clearance for both injection routes occurred at a rate of 154 ± 41 ml/min. Given the total blood flow rate of 0.68 ± 0.75 liters/min during the experiment, this clearance value represents 22.6% of total blood flow.

Discussion

The criteria now used for drug administration during resuscitation have evolved empirically and are not based on sound scientific data (2,5,6,10). The findings of our study indicate that the central venous and peripheral venous routes of drug administration during cardiopulmonary resuscitation result in pharmacokinetic differences.

Central versus peripheral venous injection. The most prominent difference between the central venous and the peripheral venous injections was the difference between the peak levels of tracer. The tracer enters the circulation on the venous side in both injections; the difference in peak levels can be attributed to the greater amount of tracer mixing that takes place after peripheral venous injection than after central venous injection. After central venous injection, the tracer mixes only with the blood present in the vena cava, the right side of the heart and the pulmonary artery circulation before reaching the sampling site. After peripheral venous injection, the tracer mixes with blood in the superior vena cava coming from the head and foreleg. Therefore, the peripheral injected bolus is considerably more dilute when it reaches the level of the sampling point and the tracer concentration is correspondingly lower. In choosing the kinetic model employed, we assigned our lag-time value to this venous-pulmonary sequestration phase, which clamped the initial bolus injection and converted it into a brief constant rate infusion, as seen by the arterial sampling site. The time to peak value estimates the duration of this

<table>
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<th>Table 1. Kinetic Variables After Central Venous and Peripheral Venous Injection of Tracers During Cardiopulmonary Resuscitation in Dogs</th>
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<td><strong>Lag time (seconds)</strong></td>
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* p < 0.001; † p < 0.01; ‡ p < 0.05. Vc = estimated volume of distribution, central compartment; VDss = estimated steady state volume of distribution.
rapid infusion. These points underlie the differences found between the two injection routes (Fig. 3).

The peripheral injection results in a longer lag time and time to peak as well as a larger central compartment volume of distribution as a result of the additional venous blood admixture for the peripheral venous injection route. This venous mixing also explains the considerable difference in peak concentration produced by the two injection routes. Nevertheless, the similar values produced by the two routes for the area under the time-counts curve, mean residence time and steady state volume of distribution emphasize the overall similarity of drug dose and disposition for both routes of administration.

Comparison with previous studies. In studies (4) on two different groups of dogs during open chest resuscitation, peak lidocaine levels were higher after the central than after the peripheral venous injection, but contrary to our results, no significant differences were found in times to effective and peak lidocaine concentration. However, no direct comparisons in the same dog were made in that study, and because of sampling at 20 second interval, the peak levels might be missed. Our experimental design enabled us to make direct comparisons and to generate a blood concentration-time curve of high temporal resolution, which is of significant importance in analyzing pharmacokinetics of a drug during the relatively short period of cardiopulmonary resuscitation.

A study by Kuhn et al. (3) performed during closed chest resuscitation in two groups of three patients showed a peak level of dye in femoral artery samples at 30 seconds after central venous injection. However, after peripheral venous injection, no peak was established in the 5 minute study period. Cardiac output was not measured in that study and because cardiac output during closed chest resuscitation may vary widely (11), this might be a significant limitation in interpreting results in such a small number of patients. Our experimental design enabled us to make a direct comparison between the central and peripheral routes under constant hemodynamic conditions. However, the discrepancies between our study and that of Kuhn et al. may be attributable to differences in blood flow patterns between open chest canine resuscitation and closed chest human resuscitation.

Methodologic considerations. It has been shown (11) that cardiac output during closed chest resuscitation in humans probably varies between 5 and 30% of normal. Because one of our objectives was to establish an experimental design giving a constant cardiac output during resuscitation, we chose the open chest method. We adjusted our rate of compression to consistently produce a cardiac output of 18% of the value before induction of ventricular fibrillation.

Although the characteristics of blood flow may differ slightly between open and closed chest resuscitation, we believe that our experimental design is valid for studying pharmacokinetics of drugs during markedly decreased cardiac output. Studies by Voorhees et al. (12) raised the question about the relation between arterial flow above and below the diaphragm during resuscitation. This question is relevant to our data because our sampling site was the femoral artery. However, recent data of Bellamy et al. (13) demonstrated comparable radiomicrosphere mixing in the ascending and abdominal aorta during cardiopulmonary resuscitation in pigs, suggesting that femoral sampling is adequate for pharmacokinetic evaluation. Moreover, our own data indicate that adequate flow was maintained below the diaphragm during our experimental procedure. This is demonstrated by the tracer clearance value of 154 ml/min, which is equal to 23% of cardiac output obtained. In view of the prevailing of renal and hepatic blood flow during resuscitation, the clearance mechanism is highly dependent on/and approximates blood flow (15). The value obtained indicates that nearly a quarter of the cardiac output was reaching the peripheral arterial circulation.

Clinical implications. Because the kinetics of tracers do not necessarily represent the kinetics of drug molecules, whose distribution and elimination characteristics may be quite different, immediate therapeutic implications must be interpreted with caution.

The most significant finding of our study is that central and peripheral venous administration routes result in definite differences in peak tracer concentration, lag time and time to peak concentration during cardiopulmonary resuscitation. The clinical significance of this finding depends on whether the therapeutic and toxic effects of the administered drug are related to peak blood levels or to the subsequent steady
If the peak level is critical for therapeutic effect, central administration would be preferable because higher levels can be achieved more efficiently by this route. In contrast, if the plateau level is important, little difference in outcome is likely to result from the two routes of administration. In fact, if the peak concentration is responsible for toxicity but has no therapeutic benefit, peripheral injection may be advantageous. Because the optimal approach will differ among drugs, a general recommendation cannot be made. However, it is important to recognize that the outcome of resuscitation efforts may be affected adversely if a significant period of highly toxic drug levels occurs after central venous administration during cardiopulmonary resuscitation. Further investigation is needed to compare the pharmacokinetics of central venous and peripheral venous routes with various drugs used during cardiorespiratory resuscitation.

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References