INFLUENCE OF SAMPLE SITE ON BLOOD CONCENTRATIONS OF ICI 35 868


SUMMARY

Simultaneous blood samples from an artery, a peripheral vein and a central vein were analysed for ICI 35 868 concentrations following an induction dose of 2.0 mg kg\(^{-1}\) administered i.v. over 60 s, to five patients before cardiac surgery. Up to 60 s after the end of the administration of the drug there were wide differences in drug concentration between the sampling sites. Thus, any attempt to correlate effect with blood concentration over this early period would be problematic. From 60 s there were no significant differences in drug concentration between the three sites. Thus, as long as the mixing period is allowed for, peripheral venous sampling provides an acceptable alternative to arterial puncture in studies to correlate drug effect and concentration and for pharmacokinetic investigations.

Pharmacokinetic studies of drugs administered i.v. require multiple blood samples which, on occasions, may be taken in rapid succession. Samples are withdrawn usually from a peripheral vein (Van Homme, Ghoneim and Ambre, 1978; Morgan et al., 1981) no doubt because it is more convenient and less intrusive than central venous or arterial blood sampling, although both these routes have been used.

Bullingham and colleagues (1980) used samples of blood from the radial artery during a study of buprenorphine kinetics. Austin, Stapleton and Mather (1981) used a central venous line positioned in the subclavian vein for sampling during a continuous pethidine infusion. Matteo and colleagues (1980) in a study of tubocurarine kinetics used both arterial and central venous samples apparently indiscriminately, but did not stipulate the exact position of the central venous line.

The various pitfalls in conventional pharmacokinetic evaluation have been well outlined by Chiou (1979). He pointed out that it has been traditional to assume "instantaneous" mixing of an injected drug but suggested that this may not be true and that considerable errors in calculating parameters such as the initial volume of distribution might occur if unmixed drug was sampled.

Broadbent and Wood (1954) found a mean "lag time" of 14 s between the injection of dye i.v. and its appearance at a peripheral artery. Chiou (1979) postulated that this lag time would be increased if peripheral venous samples were taken or if the circulation was slowed by disease or drugs.

In view of the differences of opinion over the site of sampling we have conducted a study to compare the blood concentrations of ICI 35 868 (diisopropyl phenol) at three sites following an induction dose i.v.

PATIENTS AND METHODS

Patients about to undergo mitral or aortic valve replacement under cardiopulmonary bypass gave informed consent for the administration of ICI 35 868 and repeated blood sampling.

Patients were excluded if the valvular disease was gross, if heart failure was present clinically, or if there was evidence of coronary insufficiency. Atopic individuals and those who had received Cremophor in the previous 12 months were also excluded.

Following premedication with papaveretum and hyoscine, cannulae were placed, under local anaesthesia, in the femoral artery and the right internal jugular vein. Correct positioning of the internal jugular central venous catheter in the right atrium or superior vena cava was verified radiographically after operation. Two 14-gauge cannulae were inserted in forearm veins for the administration of the drug and, in the opposite antecubital fossa, for withdrawal of samples.

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The electrocardiogram was monitored continuously and arterial pressure measured between blood sampling. Control blood samples were taken and anaesthesia was induced via the forearm cannula with ICI 35 868 2.0 mg kg\(^{-1}\) administered over 60 s from a volumetric constant infusion pump.

Following the start of injection simultaneous blood samples were taken for the estimation of the concentration of ICI 35 868 from the arterial, peripheral venous and central venous catheters every 30 s for 4 min. Samples requiring more than 15 s for collection were discarded.

All samples were immediately placed in coded bottles containing oxalate anticoagulant and deep frozen for later analysis.

After 4 min, anaesthesia and surgery proceeded in the usual fashion.

**Analysis of the concentration of ICI 35 868**

The concentration of ICI 35 868 in haemolysed whole blood was assessed using the method of Adam and colleagues (1981). Samples were analysed blind and the code broken only after results had been reported to the clinician. Statistical analysis was performed by means of least squares regression.

**RESULTS**

Five patients were studied (three male). Their mean age was 50 yr (range 36–66) and mean weight 70.4 kg (SEM ± 3).

The concentrations of ICI 35 868 in two patients are shown in figure 1. Patient number 2 (fig. 1, left) was typical of all patients except patient number 5 (fig. 1, right) and illustrates that the central venous blood concentrations usually increased first, followed by the concentrations in arterial and peripheral venous blood.

During the infusion of the drug the central venous concentrations exceeded the arterial, in several instances by a factor of 2, and in three patients the central venous blood concentration was greater than 80 \(\mu g \, ml^{-1}\). The greatest arterial concentration in any of the patients was 50 \(\mu g \, ml^{-1}\) at 90 s in patient number 1. The peripheral venous concentrations predictably took longer to increase than either of the other two and it was some time after the completion of the infusion that the arterial concentrations were of similar magnitude to the central venous concentrations.

![Fig. 1](image1.png)

*Fig. 1. Blood concentrations of ICI 35 868 simultaneously sampled from an artery □—□, a central vein ○—○ and a peripheral vein ▲—▲. Left: from patient 2, was typical of all patients except patient 5 (right).*
of the infusion before the peripheral venous concentration approximated to the arterial and central venous concentrations. The results for all five patients are combined in figure 2. During, and immediately following, the infusion there was gross disparity in the blood concentrations both between patients, as demonstrated in figure 2 by the large standard errors of mean around each point, and between sample sites. One minute following discontinuation of the infusion, blood concentrations from all three sites were approaching each other and for the next 2 min the concentrations decreased progressively and there were no statistically significant differences between the three sites thereafter.

A comparison of arterial with central and peripheral venous blood concentrations using regression analyses is shown in table I. The correlation between sites is poor for up to 120 s from the start of

![Graph](image-url)

**Fig. 2.** Mean ICI 35 868 concentrations from all five patients: artery □—□, central vein ○—○, peripheral vein ▲—▲ (± SEM).

**Table I. Comparison of arterial with central and peripheral venous blood concentrations by regression analysis**

<table>
<thead>
<tr>
<th>Time (s)</th>
<th>90</th>
<th>120</th>
<th>150</th>
<th>180</th>
<th>210</th>
<th>240</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Arterial v.</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central venous</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slope</td>
<td>0.14</td>
<td>0.53</td>
<td>0.83</td>
<td>1.05</td>
<td>0.85</td>
<td>0.70</td>
</tr>
<tr>
<td>Correlation coefficient</td>
<td>0.34</td>
<td>0.56</td>
<td>0.97</td>
<td>0.98</td>
<td>0.92</td>
<td>0.88</td>
</tr>
<tr>
<td>Peripheral venous</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slope</td>
<td>-0.01</td>
<td>-0.14</td>
<td>0.83</td>
<td>1.05</td>
<td>0.70</td>
<td>0.83</td>
</tr>
<tr>
<td>Correlation coefficient</td>
<td>0.24</td>
<td>0.15</td>
<td>0.95</td>
<td>0.95</td>
<td>0.80</td>
<td>0.75</td>
</tr>
</tbody>
</table>
the injection, but both the correlation coefficient and the slope of the regression line approach unity from 150 s onwards.

DISCUSSION

The use of patients with cardiac disease in this study may be open to criticism. It is likely that patients with aortic or mitral valvular disease would have a slower than average circulation time, which would delay complete mixing and increase the "lag time" before the drug appeared in the peripheral venous samples. This would be further exacerbated by the large distribution volume present in such patients. In addition, a standard induction dose of 2.0 mg kg⁻¹ might well be more depressant to the diseased heart than to a healthy one, with a consequent decrease in cardiac output and further effects on mixing time and lag time. This effect was minimized but not abolished by the slow (60 s) induction. However, the selection of these patients was based purely on ethical considerations in that such patients represent one of the few groups who routinely have arterial, central and peripheral venous cannulae inserted. In addition, the nature of the study (a within-patient comparison of three sample sites) ensured that variation between patients was not of paramount importance. It is important, however, to exercise caution in extrapolating our data to the healthy patient.

The amount of drug in the blood reaching the target organ (in this case the brain) must be the most appropriate value in plotting drug concentration against effect. A femoral arterial sample is a good compromise in view of the undesirability of carotid puncture, and for the purpose of this discussion it has been assumed that the arterial values approach the ideal.

Broadbent and Wood (1954) demonstrated that there was a delay between the injection of a drug and its appearance in a peripheral artery and Chiu (1979) has suggested in a review of pharmacokinetic pitfalls that this lag time may be increased by sampling from a peripheral vein, or by decreases in blood flow as a result of drugs or disease. The lag time is well demonstrated in this study and is greatest with the peripheral venous samples. Lag time is least in samples from the central venous line and in one patient the peak blood concentration was found in the first sample taken at 30 s. These are not surprising findings.

The fact that the central venous blood concentrations increased quickly to a peak which was greater than that found in the arterial samples is explained simply on the basis that the central line was sampling drug which had not properly mixed. Another explanation of the arterial–central venous difference might be that circulating drug was taken up by the lung, whilst peripheral tissue uptake would result in further discrepancy between arterial and peripheral venous blood concentrations. In one patient however (fig. 1, right) the central venous concentrations did not increase quickly and did not exceed the arterial values. In fact they closely approximated the peripheral venous values. This patient's central venous cannula was correctly placed in the superior vena cava close to the right atrium and there was no obvious explanation for this difference. Whatever the explanation for the differences, our data clearly show that peripheral venous sampling is inappropriate during and immediately after i.v. administration of a drug because of the lag time. If it is assumed that arterial concentrations provide the best estimate of values at the site of action, then our data demonstrate that central venous samples are also inappropriate over the same time-scale in any attempt to correlate effect and concentration of an anaesthetic agent. Equally, it is clear that any pharmacokinetic evaluation of data after i.v. administration must take account of a lag time before complete mixing has occurred within the "central compartment". The relatively slow (60 s) infusion of ICI 35868 may have affected the data, but since a slow injection effectively means dilution into a larger volume of blood, mixing in the blood stream might have been more efficient.

In a recent study Christensen, Andreasen and Jansen (1982) found little difference in arterial and peripheral venous blood concentrations of thiopentone taken simultaneously within 1 min of unconsciousness in healthy young males. However, in elderly males (50–80 yr) they noted that the mean peripheral venous thiopentone concentration was similar to the younger group, but the simultaneous arterial concentrations were much greater.

In our patients central venous, arterial and peripheral venous concentrations did not approach each other till 60 s after the completion of the infusion. In healthy young patients without cardiovascular disease this interval might be expected to be less, since the circulation would be more rapid. Thus our results are not inconsistent with those of Christensen and colleagues. Possibly the most important finding of this investigation is that, provided at least 1 min has elapsed since the end of drug
administration, all three sample sites provide similar results
and the correlation between arterial and venous blood concentrations is extremely good. We cannot extrapolate from our short-term study to longer studies lasting hours or days, since other factors such as poor peripheral perfusion, changes in limb temperature and altered acid–base status might alter the relationship between arterial and venous concentrations.

REFERENCES

INFLUENCE DU LIEU DE PRELEVEMENT SUR LES CONCENTRATIONS SANGUINES D'ICI 35 868

RESUME
Les concentrations d'ICI 35 868 dans des échantillons simultanés de sang artériel, veineux, périphérique et veineux central ont été mesurées après une dose d'induction de 2 mg kg⁻¹ administrée i.v. en 60 s à cinq patients devant subir un acte de chirurgie cardiaque. Jusqu'à 60 s après la fin de l'administration du produit, il existait de grandes différences de concentration sanguine selon le lieu de prélèvement. Ainsi, toute tentative de corrélation entre l'effet et la concentration sanguine dans cette période précoce semblerait hasardeuse. Toutefois, à partir de 60 s, il n'y avait pas de différences significatives de concentration de l'agent entre les trois lieux de prélèvement. Ainsi, à condition d'attendre la fin de la période d'équilibration, un prélèvement veineux périphérique constituait une alternative acceptable au prélèvement artériel dans les études visant à corrélérer l'effet de l'agent et sa concentration ainsi que dans les études pharmacocinétiques.

EINFLUSS DER HERKUNFT VON BLUTPROBEN AUF DIE BLUTSPIEGEL VON ICI 35868

ZUSAMMENFASSUNG
Fünf Patienten erhielten vor Herzoperationen Einleitungsdosen von ICI 35 868 2.0 mg kg⁻¹ über 60 s; simultane Blutproben von arteriellen, peripheren und zentralen Venenblut wurden auf Plasmaspiegel untersucht. Bis zu 60 s nach Ende der Verabreichung gab es große Unterschiede in der Konzentration des Präparats in den verschiedenen Blutproben. Jeder Versuch, in dieser frühen Periode die Wirkung mit der Blutkonzentration zu korrelieren, wäre also problematisch. Nach 60 s gab es keine signifikanten Unterschiede im Spiegel der drei Proben. Wird die Periode der Vermischung berücksichtigt, bieten venöse Blutproben eine akzeptable Alternative zur Arterienpunktion bei Studien, die die Wirksamkeit des Medikaments mit dem Plasmaspiegel korrelieren, und bei pharmacokinetischen Forschungsarbeiten.

INFLUENCIA DEL LUGAR DE MUESTREO EN LAS CONCENTRACIONES DE ICI 35 868 EN LA SANGRE

SUMARIO
Se llevaron a cabo análisis de muestras simultáneas de sangre provenientes de una arteria, de una vena periférica y de una vena central respecto de las concentraciones de ICI 35 868 después de una dosis de inducción de 2,0 mg kg⁻¹ administrada i.v. durante 60 s a cinco pacientes antes de cirugía cardíaca. Hasta unos 60 s después del fin de la administración de la substancia, existían grandes diferencias en las concentraciones de la droga entre los sitios de muestreo. Por lo tanto, toda tentativa tendiente a correlacionar el efecto con las concentraciones en la sangre durante este tiempo era problemática. A partir de los 60 s, no hubo diferencias significativas en la concentración de la substancia entre los tres sitios. Entonces, siempre y cuando se prevea un periodo de mezcla, el muestreo venoso periférico constituye una alternativa aceptable a la punción arterial en los estudios tendientes a correlacionar el efecto y la concentración de una substancia y para las investigaciones farmacocinéticas.