PHARMACOKINETIC EVALUATION OF ICI 35868 IN MAN

Single induction doses with different rates of injection

H. K. ADAM, L. P. BRIGGS, M. BAHAR, E. J. DOUGLAS AND J. W. DUNDEE

Blood concentrations of ICI 35868 have been measured in patients following a single bolus dose of 2 mg kg⁻¹. Three different rates of injection of the anaesthetic agent (3–5 s, 20 s and 40 or 50 s) were examined. Pharmacokinetic indices, derived from blood concentrations of ICI 35868, were independent of the speed of injection. The blood profiles could be described by a two-compartment open model with a mean α-phase half-life of 2.5 min and a mean β-phase half-life of 54.5 min. The mean total body clearance was 3454 ml min⁻¹. Similar data were obtained from a 4-mg kg⁻¹ dose. The mean recovery time (4.4 min) and concentration of ICI 35868 at awakening (1.05 ng ml⁻¹) were also independent of the rate of injection. Using the derived pharmacokinetic model, predictions of drug concentrations have been made for repeated bolus doses, or infusions, of ICI 35868.

From a series of alkylphenols found to possess anaesthetic activity on i.v. administration, 2, 6-diisopropylphenol (ICI 35868) was selected as a potential drug for use in man (James and Glen, 1980; Glen, 1980). Studies in man have shown that it was an effective induction agent (Kay and Rolly, 1977; Rogers et al., 1980; Rutter et al., 1980; Kay and Stephenson, 1981) and that it was of value in the maintenance of anaesthesia by infusion (Prys-Roberts, Sear and Adam, 1981) or by repeated injections (Clarke, Briggs and Dundee, 1981; Kay and Adam, 1981; Major et al., 1981).

For the optimal use of an i.v. anaesthetic agent, detailed pharmacokinetic evaluation is essential (Ghoneim and Korttila, 1977). Although studies in animals (Adam, Glen and Hoyle, 1980) and preliminary work on ICI 35868 in man (Adam, Kay and Douglas, 1982) have been reported, a full pharmacokinetic evaluation of the drug has not been performed in man. This communication reports the results of a study designed to provide this information following a single dose administered i.v.

PATIENTS AND METHODS

The study was carried out in 24 fit unpremedicated women, (ASA grades 1 and 2) scheduled for minor gynaecological procedures and who had given informed consent to the study. All were between 18 and 65 years-of-age and weighed less than 85 kg (table I). Patients with a history of atopy, allergy or a possible previous exposure to cremophor-containing drugs within the previous 6 months, were excluded.

A 16-s.w.g. cannula, for blood sampling, was inserted to the non-dominant arm under local anaesthesia. This was flushed periodically with heparinized saline. The predetermined induction dose of ICI 35868 was injected to an antecubital vein in the other arm over the requisite time. Twenty-two of the subjects received an induction dose of ICI 35868 2 mg kg⁻¹. This dose was given at three different rates: over 3–5 s (n = 6), over 20 s (n = 10), or over 40–50 s (n = 6). Two patients received ICI 35868 4 mg kg⁻¹ over 20 or 30 s. None of the patients was premedicated.

<table>
<thead>
<tr>
<th>Dose</th>
<th>Rate of injection</th>
<th>n</th>
<th>Age (yr)</th>
<th>Weight (kg)</th>
<th>Height (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 mg kg⁻¹</td>
<td>over 3–5 s</td>
<td>6</td>
<td>26 ± 2.1</td>
<td>59 ± 5.0</td>
<td>160 ± 2.5</td>
</tr>
<tr>
<td>2 mg kg⁻¹</td>
<td>over 20 s</td>
<td>10</td>
<td>28 ± 2.5</td>
<td>60 ± 3.0</td>
<td>160 ± 1.6</td>
</tr>
<tr>
<td>2 mg kg⁻¹</td>
<td>over 40–50 s</td>
<td>6</td>
<td>35 ± 5.6</td>
<td>56 ± 3.2</td>
<td>160 ± 3.9</td>
</tr>
<tr>
<td>4 mg kg⁻¹</td>
<td>over 20 s</td>
<td>1</td>
<td>21</td>
<td>58</td>
<td>162</td>
</tr>
<tr>
<td>4 mg kg⁻¹</td>
<td>over 30 s</td>
<td>1</td>
<td>24</td>
<td>58</td>
<td>162</td>
</tr>
</tbody>
</table>
Two assessments of recovery were made following administration of ICI 35 868: (a) time to opening of eyes on request and (b) time to ability to give date of birth correctly.

In three subjects ICI 35 868 was the sole agent used. In the remaining patients anaesthesia was reinduced with thiopentone and the definitive operation performed.

Blood samples were drawn before induction of anaesthesia and at approximately 0.5, 1, 1.5, 2, 3, 5, 10, 15, 30, 45, 60, 120 and 240 min after the administration of the drug, the exact time being recorded for each sample. Additional samples were taken, where appropriate, at the times of recovery. In four subjects, all receiving 2 mg kg\(^{-1}\) over 20 s, blood samples were only taken at recovery.

The samples were transferred to oxalate tubes and stored at \(-20\) °C until the haemolysed whole blood was analysed for ICI 35 868 by the method of Adam and colleagues (1980). Pharmacokinetic analysis was performed on each individual log blood concentration – time plot by the method of residuals (Gibaldi and Perrier, 1975) and the resulting variables corrected for duration of injection as outlined by Loo and Riegelman (1970).

Three anaesthetists were involved with each patient. The first was in clinical charge of the anaesthesia, while the second administered the drugs and recorded their effects. The third person was responsible for blood sampling at the correct times and for the subsequent handling of the samples.

**RESULTS**

Anaesthesia was satisfactory in all subjects except the two who received 4 mg kg\(^{-1}\). Both of these patients had a period of apnoea which lasted for more than 2 min, during which they were ventilated with oxygen. This was not accompanied by either tachycardia or a decrease in arterial pressure. These two patients had their operations carried out under a bolus dose of ICI 35 868 as the sole agent without any difficulty.

In two of the 20 sets of data relating blood concentrations with time no clearly defined \(a\)-phase could be established and these were not amenable to full pharmacokinetic analysis. In the remaining data sets the concentration profiles, from 1.5 min after administration, could be represented by a biexponential equation of the form:

\[
C_p = A_1 e^{-\alpha t} + B_1 e^{-\beta t}
\]

Figure 1 shows the mean data derived from the injection of 2 mg kg\(^{-1}\) over 3–5 s and illustrates the type of plot obtained.
After correcting for duration of injection, as described above, the data were treated as conforming to a two-compartment open linear model and the relevant variables calculated for each individual data set. The mean parameters from the three different injection speeds of ICI 35 868 2 mg kg\(^{-1}\) are presented in Table II. Since there was no significant difference between the results from the three different rates of injection, mean values for ICI 35 868 2 mg kg\(^{-1}\) were calculated (Table II).

Also included in Table II are the derived variables for two subjects who received ICI 35 868 4 mg kg\(^{-1}\) as the sole agent. Comparison of these values with the mean 2-mg kg\(^{-1}\) data show that, with the exception of the area under the curve which, as expected, is doubled, the pharmacokinetic indices are virtually the same at the two doses. Thus, the pharmacokinetic behaviour of ICI 35 868 in man is characterized by a relatively large initial apparent volume of distribution (36.8 litre) and an extremely rapid distribution phase (half-life 2.5 min) into a large apparent volume of distribution (271 litre). However, clearance from the body is rapid with a terminal half-life of 54.5 min and a total body clearance (3454 ml min\(^{-1}\)) which exceeds liver blood flow.

These indices were derived from a consideration of drug concentrations from 1.5 min after the end of the injection. In the period before 1.5 min the data showed wide variations between subjects. Figure 2 illustrates the early data points from the five subjects, included in the analyses, given 2 mg kg\(^{-1}\) over 20 s. All samples were thus taken after the end of the injection. It can be seen that, in four of six patients some initial venous concentrations were less than

![Graph](https://example.com/graph.png)

**FIG. 2.** Individual ICI 35 868 concentrations up to 5 min after 2 mg kg\(^{-1}\) over 20 s.

<table>
<thead>
<tr>
<th>TABLE II. Pharmacokinetic indices (± SEM as appropriate) of ICI 35 868 in man</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose 2 mg kg(^{-1})</td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td><strong>No. of subjects</strong></td>
</tr>
<tr>
<td>A(\text{I}^{\text{a}}) (µg ml(^{-1}))</td>
</tr>
<tr>
<td>α (min(^{-1}))</td>
</tr>
<tr>
<td>β (min(^{-1}))</td>
</tr>
<tr>
<td>β (µg ml(^{-1}))</td>
</tr>
<tr>
<td>V(\text{I}^{\text{a}}) (m³)</td>
</tr>
<tr>
<td>V(\text{I}^{\text{b}}) (litre)</td>
</tr>
<tr>
<td>V(\text{I}^{\text{c}}) (litre)</td>
</tr>
<tr>
<td>T(\text{I}^{\text{a}}) (min)</td>
</tr>
<tr>
<td>T(\text{I}^{\text{b}}) (min)</td>
</tr>
<tr>
<td>Total body clearance (ml min(^{-1}))</td>
</tr>
</tbody>
</table>

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the peak value. In two patients there was a suggestion of an initial more rapid phase. This was typical of the data seen in subjects at the other speeds of injection.

In more than half of the patients (10 out of 18) at least one early drug concentration in blood, taken after the end of the injection, decreased below the projected α-phase. In all others an early more rapid phase was suggested by the profile. This latter phenomenon became more apparent as the speed of injection was decreased. In four patients it was possible to estimate a further exponential phase in the concentration profile. The half-life of this apparent phase ranged from 0.35 to 0.8 min. Further evaluation of this phase to produce a revised estimate of the apparent volume of distribution of the central compartment yielded values ranging from 2.4 to 17.9 litre.

Table III presents the mean recovery times and the corresponding mean ICI 35 868 concentrations at recovery in relation to the three rates of injection. None of the differences between the series was statistically significant (grouped t test). Thus, the mean values of 4.4 min to eyes open and 5.2 min to being able to give date of birth on request can be taken as representative of the recovery from the 2-mg kg⁻¹ dose of ICI 35 868, irrespective of the speed of injection. The corresponding drug concentrations were 1.05 and 0.91 µg ml⁻¹ respectively. The results from the two patients given 4 mg kg⁻¹ fitted this pattern, with sleep time being approximately double and concentrations on awaking being similar.

By applying standard linear pharmacokinetic principles to the indices derived from this study (for equations see Gibaldi and Perrier, 1975) it is possible to produce theoretical blood concentration profiles for maintenance regimens with this agent. Figure 3 illustrates the calculated profiles for a repeat bolus dose of 1.0 mg kg⁻¹ at a fixed repeat time (4 min) and the terminal portion of the concentration profile after seven repeat doses. Figure 4 illustrates the theoretical profile from a zero order infusion of ICI 35 868 (80 µg kg⁻¹ min⁻¹) with and without a loading dose of 2 mg kg⁻¹. Figure 4A represents a 2-h infusion period and figure 4B illustrates the

<table>
<thead>
<tr>
<th>Dose (mg kg⁻¹)</th>
<th>Over time (s)</th>
<th>n</th>
<th>Time (min)</th>
<th>Conc (µg ml⁻¹)</th>
<th>Time (min)</th>
<th>Conc (µg ml⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>3–5</td>
<td>6</td>
<td>3.8 ± 0.7</td>
<td>1.23 ± 0.24</td>
<td>4.7 ± 0.7</td>
<td>1.01 ± 0.12</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>10</td>
<td>4.6 ± 0.5</td>
<td>1.02 ± 0.12</td>
<td>5.3 ± 0.5</td>
<td>0.89 ± 0.33</td>
</tr>
<tr>
<td>2</td>
<td>40–50</td>
<td>6</td>
<td>4.9 ± 0.3</td>
<td>0.97 ± 0.15</td>
<td>5.6 ± 1.0</td>
<td>0.86 ± 0.15</td>
</tr>
<tr>
<td>2</td>
<td>Mean</td>
<td>22</td>
<td>4.4 ± 0.3</td>
<td>1.05 ± 0.09</td>
<td>5.2 ± 0.3</td>
<td>0.91 ± 0.7</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
<td>1</td>
<td>7.3</td>
<td>1.8</td>
<td>8.0</td>
<td>1.9</td>
</tr>
<tr>
<td>4</td>
<td>30</td>
<td>1</td>
<td>8.2</td>
<td>1.0</td>
<td>8.8</td>
<td>1.0</td>
</tr>
</tbody>
</table>

**TABLE III. ICI 35 868 concentrations and times (means + SEM) on opening eyes and correctly giving date of birth (times from start of injection)**
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FIG. 4. Theoretical ICI 35 868 concentrations resulting from a 2-h zero order infusion of 80 μg kg⁻¹ min⁻¹ (—) and (---) the same infusion plus a 2-mg kg⁻¹ induction dose at time zero; a allowing an identical infusion to achieve steady state and then stopping drug administration.

post-infusion profile after achieving a “steady state”.

DISCUSSION

Preliminary studies on blood concentrations suggested that the pharmacokinetics of ICI 35 868 in man would be similar to those in animals. The present study has confirmed this. In addition, it has further extended to 4 mg kg⁻¹ the dose range over which the pharmacokinetics have been demonstrated to be linear. The data from the patients in whom ICI 35 868 was used as sole agent were in general agreement with the majority of patients who received additional hypnotic agents, showing that the presence of these did not significantly affect the concentration profile of the drug. Thus, the pharmacokinetics of ICI 35 868 in man may be described by an open two-compartment model with an extremely rapid distribution phase (half-life 2.5 min) and a rapid terminal elimination phase (half-life 54.5 min). The picture fits that expected of a lipophilic drug, with a large apparent volume of distribution for the central compartment (50% body weight). The total body clearance (3454 ml min⁻¹, referenced to whole blood) exceeds liver blood flow and suggests elimination pathways other than hepatic metabolism. The pharmacokinetic evaluation discussed above was based on consideration of ICI 35 868 concentrations obtained more than 1.5 min after the end of injection. Data obtained before this were not amenable to consistent analysis. In the few patients in whom an early more rapid phase could be evaluated the “distribution” half-lives were less than 1 min and the “apparent volume of distribution” of the central compartment ranged from 3.4 to 26% body weight. These figures are probably artefactual and the scatter of the data at times less than 1.5 min may result from mixing within the blood. Standard pharmacokinetic analysis requires “instantaneous mixing” in the central compartment. The disadvantages of this approach, and examples where a finite mixing time is required, have recently been reviewed by Chiou (1979). The data from this study provide a further example which clearly shows a mixing phase within the central compartment.

Once a mixing time had been allowed for, the data could be described by a biexponential equation. However, the inter-subject variation in the variables for the distribution phase (coefficients of variation of A₀ 75% and α 39%) were considerably larger than those of the terminal phase (B₀ 25% and β: 12%). It is probable that the wide variability was caused partially by the speed of the distribution phase, with a small change in α leading to a large change in A₀ and partly by our inability to define clearly the mixing time in each individual subject. This latter factor is important as it has been shown that there can be a relationship between the time of the first sample and the derived volume of distribution (Chiou, 1980). However, it is clear that the apparent volume of distribution of the central compartment exceeds blood volume. It has been suggested that, in animals, the central compartment includes the brain (Rhodes and Longshaw, 1977). Since a good correlation existed in the present study between hypnotic effect and peripheral blood concentration, a similar argument can be made for man. However, it must be borne in mind that this correlation was found at recovery, that is at about 4 min after administration which was considerably later than the “mixing period” discussed above. If the mixing time is a true phenomenon, it is unlikely that drug concentrations at very early times after injection of ICI 35 868 will be of much value in predicting, or for correlating with, hypnotic effect.

However, a consistent correlation has been seen, both in this study and others, between systemic blood concentration and maintenance, or disappearance, of hypnotic effect. Prys-Roberts, Sear and...
Adam (1981) showed that hypnosis was maintained, in the presence of nitrous oxide, by a blood ICI 35 868 concentration of 1.54 μg ml⁻¹. Adam, Kay and Douglas (1982) showed that recovery from single doses of ICI 35 868 1, 2 or 3 mg kg⁻¹ occurred at a mean concentration of 1.04 μg ml⁻¹, and that hypnosis was maintained on repeated injection by concentrations in the range 1–1.5 μg ml⁻¹.

These figures are in good agreement with the values from the present study.

The theoretical blood concentrations generated from the pharmacokinetic model derived from the present single dose study are also of relevance to the previously observed clinical effects. It has been reported that recovery from maintenance, produced by repeated injections (Kay and Rolly, 1977; Major et al., 1981), or by infusion (Prys-Roberts, Bear and Adam, 1981) was extremely rapid, as had been suggested by animal studies. Figures 3 and 4 in this report show that the systemic concentrations of the drug decline to less than 1 μg ml⁻¹ within 10 min after a seventh dose, or after cessation of infusion, even from steady state.

Thus hypnotic concentrations can be maintained by either procedure without loss of the rapid recovery which is characteristic of this agent. In addition, figure 4A shows that a hypnotic concentration can be exceeded over the entire course of an infusion regimen with a loading dose corresponding to the clinically useful induction dose. This suggests that, as a result of the short α-phase, a loading bolus dose should be an integral part of the technique for continuous infusion of ICI 35 868. This is in agreement with the clinical observations of Wright and colleagues (1982).

REFERENCES


EVALUATION PHARMACOCINETIQUE DE L’ICI 35 868 CHEZ L’HOMME

*Doses d’induction uniques avec différentes vitesses d’injection*

**RESUME**

Les concentrations sanguines d’ICI 35 868 ont été mesurées chez des patients après une dose d’injection unique de 2 mg kg⁻¹. Trois vitesses différentes d’injection de l’agent anesthésique (3–5 s; 20 s; et 40 ou 50 s) ont été considérées. Les paramètres pharmacocinétiques, dérivés des concentrations sanguines d’ICI 35 868, étaient indépendants de la vitesse d’injection. Les profils sanguins pourraient être décrits par un modèle ouvert à deux compartiments avec une demi-vie moyenne en phase alpha de 2.5 min, et une demi-vie moyenne en phase beta de 54.5 min. La clairance corporelle totale moyenne était de 3454 ml min⁻¹. Des données semblables ont été recueillies avec une posologie de 4 mg kg⁻¹. La durée moyenne de réveil (4,4 min) et la concentration d’ICI 35 868 au réveil (1,05 μg ml⁻¹) étaient également indépendantes de la vitesse d’injection. En utilisant un modèle pharmacocinétique dérivé, des prévisions de concentrations plasmatiques ont été faites pour des doses flash répétées ou pour des perfusions d’ICI 35 868.
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ZUSAMMENFASSUNG

Bei Patienten wurden die Blutkonzentrationen von ICI 35868 nach einer einzelnen Bolusgabe von 2 mg kg\(^{-1}\) gemessen. Drei verschiedene Injektionsgeschwindigkeiten des Narkosemittels wurden geprüft: 3-5 s, 20 s und 40-50 s. Die pharmakokinetischen Indices, die aus den Blutkonzentrationen von ICI 35868 berechnet wurden, waren unabhängig von der Injektionsgeschwindigkeit. Die Blutprofile ließen sich mit einem offenen Zwei-Kompartiment-Modell beschreiben mit einer mittleren \(\alpha\)-Phasen-Halbwertszeit von 2,5 min und einer mittleren \(\beta\)-Phasen-Halbwertszeit von 54,5 min. Die mittlere totale Clearance betrug 3454 ml min\(^{-1}\). Ähnliche Werte wurden nach einer Dosis von 4 mg kg\(^{-1}\) errechnet. Die durchschnittliche Aufwachzeit (4,4 min) und die Konzentration von ICI 35868 beim Aufwachen (1,05 \(\mu\)g ml\(^{-1}\)) war ebenfalls unabhängig von der Injektionsgeschwindigkeit. Aus dem hergeleiteten pharmakokinetischen Modell wurden Konzentrationen von ICI 35868 nach wiederholter Bolusgabe und Infusionen errechnet.

EVALUACIÓN FARMACOCÍNÉTICA DEL ICI 35868 EN EL HOMBRE: DOSIS ÚNICA DE INDUCCIÓN CON RITMOS DE INYECCIÓN DISTINTOS

Se llevaron a cabo mediciones de las concentraciones de ICI 35868 en la sangre de pacientes que habían recibido una dosis única de bolo de 2 mg kg\(^{-1}\). Se examinaron tres ritmos diferentes de inyección del agente anestésico (3-5 s, 20 s, y 40-50 s). Los índices farmacocinéticos derivados de las concentraciones de ICI 35868 en la sangre eran independientes de la velocidad de inyección. Los perfiles sanguíneos podían describirse mediante un modelo abierto de dos compartimientos con una media-vida promedio de la fase-\(\alpha\) de 2,5 min y una media-vida promedia de la fase-\(\beta\) de 54,5 min. La eliminación total promedio del cuerpo tomó 3454 ml min\(^{-1}\). Se obtuvieron datos similares con una dosis de 4 mg kg\(^{-1}\). El tiempo de recuperación promedio (4,4 min) y la concentración de ICI 35868 al momento del despertar (1,05 \(\mu\)g ml\(^{-1}\)) eran también independientes del ritmo de inyección. Al usar el modelo farmacocinético derivado, se han hecho predicciones de las concentraciones de sustancias en dosis repetidas de bolo o de infusiones de ICI 35868.