PHARMACOKINETICS IN LABORATORY ANIMALS OF ICI 35 868, A NEW I.V. ANAESTHETIC AGENT

H. K. ADAM, J. B. GLEN AND P. A. HOYLE

SUMMARY

Blood concentrations of ICI 35 868 have been determined in rat, pig, rabbit and cat after single i.v. injections. In all species the initial distribution volume was greater than blood volume and the overall distribution volume was large. Half-lives of the distribution phase were extremely short (1-6 min) and the terminal half-lives were also short (16-55 min). In all species examined a correlation existed between the systemic blood concentration of ICI 35 868 and duration of sleep, with concentrations in the range 1-4 ng ml\(^{-1}\) being effective in producing unconsciousness. No changes in pharmacokinetics or in the effective concentration occurred on repeated administration or after infusion.

There are several reports on the possibility of using i.v. anaesthetic agents for both induction and maintenance of anaesthesia (du Cailar, 1972; Breimer et al., 1975; Savege et al., 1975; Sear and Pryse-Roberts, 1979). Work aimed at the development of new i.v. agents has concentrated on compounds which are eliminated from the body rapidly.

A review of recently introduced i.v. agents pointed out the importance of understanding their pharmacokinetics (Ghoneim and Korttila, 1977). We describe the pharmacokinetics in laboratory animals of ICI 35 868, a new i.v. anaesthetic agent, and relate systemic blood concentrations of this agent with the pharmacological effects produced.

MATERIALS AND METHODS

ICI 35 868 was administered as a 2% formulation in 10% Cremophor in saline to all species. The compound was administered to rats (ICI Alderley Park Wistar-derived albino strain) via the tail vein and blood samples obtained by cardiac puncture; to pigs (young white Large White x Landrace) via an indwelling jugular vein cannula and samples obtained from an arterial cannula; to rabbits (Dutch) via an ear vein and samples obtained from an indwelling jugular vein cannula; and to cats (domestic) via the cephalic vein and samples obtained from an indwelling jugular cannula.

Animals were given single doses by i.v. injection over 30 s. Doses administered were as follows: rats and rabbits 7.5 and 15 mg kg\(^{-1}\), pigs 5 and 10 mg kg\(^{-1}\), cats 5 and 15 mg kg\(^{-1}\). Blood samples were obtained before dosing and at various times up to 2 h after administration. Samples were also obtained from rats (10 and 15 mg kg\(^{-1}\)) and pigs (5 and 7.5 mg kg\(^{-1}\)) which had received these doses once daily for 30 successive days. For infusion studies pigs received either a constant infusion at a rate of 24 mg kg\(^{-1}\) h\(^{-1}\) or an infusion rate adjusted to maintain a light level of surgical anaesthesia. In both cases infusion was begun immediately after an induction dose of 5 mg kg\(^{-1}\).

Analysis of ICI 35 868 content

To 1 ml of oxalated whole blood was added dipotassium hydrogen phosphate 0.1 mol litre\(^{-1}\), followed by cyclohexane/n-butanol (95 : 5 v/v) 4 ml. The mixture was shaken for 10 min and the phases separated by centrifugation. An aliquot of the organic phase was obtained by cardiac puncture; to pigs (young white Large White x Landrace) via an indwelling jugular vein cannula and samples obtained from an arterial cannula; to rabbits (Dutch) via an ear vein and samples obtained from an indwelling jugular vein cannula; and to cats (domestic) via the cephalic vein and samples obtained from an indwelling jugular cannula.

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To 1 ml of oxalated whole blood was added dipotassium hydrogen phosphate 0.1 mol litre\(^{-1}\), followed by cyclohexane/n-butanol (95 : 5 v/v) 4 ml. The mixture was shaken for 10 min and the phases separated by centrifugation. An aliquot of the organic phase was assayed in a spectrofluorimeter (Perkin-Elmer MFP2A) by examining the emission at 310 nm produced by an excitation wavelength of 265 nm. Unknowns were quantified by comparison of the peak heights obtained with those from a standard series prepared by adding known amounts of ICI 35 868 to control blood. The limit of detection of this procedure was ICI 35 868 0.2 µg ml\(^{-1}\) whole blood.

RESULTS

All animal species showed similar pharmacokinetic profiles. Figure 1, which shows the profile obtained in the rat after a single i.v. dose of ICI 35 868 15 mg kg\(^{-1}\), is typical. There was a very rapid initial distribution phase, followed by a slower
any degree of confidence. However, it was apparent that, apart from the cat, no major change in pharmacokinetics occurred in any species between the two doses. In all cases $T_{1/2}$ was extremely short with a range of 1.1-5.8 min. The terminal elimination half-life ranged from 16 min in the rabbit to 55 min in the cat. The apparent volumes of distribution of the central compartment ($V$) ranged from 33% in the rabbit to 90% in the cat. Overall distribution volumes were larger, ranging from 133% in the cat to 275% in the pig.

No major change in the pharmacokinetics in rat or pig occurred after daily dosing for 30 consecutive days.

In all species a measure of duration of sleep after dosing was made and the systemic concentration of ICI 35 868 at the end of this period was determined (table II). In each species the concentration was independent of dose or numbers of doses and was characteristic of that species. With the exception of the rabbit, which seems less sensitive, the concentration range required to achieve sleep in laboratory animals was 1-4 μg ml$^{-1}$.

The concentrations of ICI 35 868 found in a pig in which sleep had been maintained for 2 h by continuous infusion of ICI 35 868 24 mg kg$^{-1}$ h$^{-1}$ are presented in figure 2 (●). Also included in this figure are the results obtained in this species after a single i.v. injection (fig. 2, □). The terminal half-lives were similar. Head lift in the animal in the infusion study occurred at a concentration of about ICI 35 868 3 μg ml$^{-1}$. In a similar infusion study a lighter level of anaesthesia was maintained by infusion rates between 8.2 and 16.7 mg kg$^{-1}$ h$^{-1}$. In this animal, anaesthesia was maintained at concentrations in the range 3-5 μg ml$^{-1}$ and head lift occurred 6 min after stopping the infusion when the systemic concentration was less than 2 μg ml$^{-1}$.

**DISCUSSION**

Our studies show that a correlation exists between systemic blood concentrations of ICI 35 868 and the

<table>
<thead>
<tr>
<th>Species</th>
<th>Concentration (μg ml$^{-1}$)</th>
<th>Number of studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rabbit</td>
<td>7.2</td>
<td>4</td>
</tr>
<tr>
<td>Cat</td>
<td>4.3</td>
<td>4</td>
</tr>
<tr>
<td>Rat</td>
<td>2.8</td>
<td>5</td>
</tr>
<tr>
<td>Pig</td>
<td>1.1</td>
<td>3</td>
</tr>
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</table>

**TABLE II. Mean waking concentrations of ICI 35 868 in laboratory animals**

**TABLE I. Pharmacokinetic parameters of ICI 35 868 in laboratory animals. Results are mean ± SEM of each parameter from individual animals, except in the rat, where they are derived from groups of animals at each time point (see figure 1). $V_{\text{a}}$ calculated from the area under the curve according to Gibaldi, Nagashima and Levy (1969)**

<table>
<thead>
<tr>
<th>Species</th>
<th>$V$ (μg ml$^{-1}$)</th>
<th>$V_{\text{a}}$ (μg ml$^{-1}$)</th>
<th>$T_{1/2}^\alpha$ (min)</th>
<th>$T_{1/2}^\beta$ (min)</th>
<th>No. animals studied</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat</td>
<td>43±14</td>
<td>250±20</td>
<td>1.1</td>
<td>19</td>
<td>30</td>
</tr>
<tr>
<td>Pig</td>
<td>155±33</td>
<td>1.9±0.3</td>
<td>16</td>
<td>55±3</td>
<td>30</td>
</tr>
<tr>
<td>Rabbit</td>
<td>133±19</td>
<td>5.8±0.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cat</td>
<td>90±16</td>
<td>155±33</td>
<td>1.9±0.3</td>
<td>16</td>
<td>30</td>
</tr>
</tbody>
</table>

**FIG. 1. Blood concentrations of ICI 35 868 in rats (three at each time point ±SEM) after a single i.v. dose of ICI 35 868 15 mg kg$^{-1}$.**
PHARMACOKINETICS OF ICI 35 868 IN ANIMALS

Fig. 2. Concentrations of ICI 35 868 in pig blood after 2 h infusion at 24 mg kg\(^{-1}\) (time zero = end of infusion) (●); and after a single i.v. dose of 10 mg kg\(^{-1}\) (○).

Correlating the anaesthetic effect with the systemic blood concentration assumes that the latter is in dynamic equilibrium with the site of action. Although the initial apparent volume of distribution may include brain, and the whole body autoradiographic studies cited above showed that brain concentrations of volatile material, which was considered to be unchanged drug, decreased very rapidly, some questions must remain as to whether venous blood concentrations reflect concentrations in the "bio-phase". This is especially true for ICI 35 868 with which the initial distribution phase is rapid and in some species, such as rabbit, awakening occurred during the \(\alpha\)-phase. Infusion studies should allow a closer approximation of dynamic equilibrium between site of action and systemic concentrations. After infusion of ICI 35 868 to the pig the systemic concentrations at awakening were similar to those observed after acute administration, indicating that the values given in table II are proportional to biophase concentrations.

Several implications follow from these pharmacokinetic findings. First, the rate of administration of ICI 35 868 must be sufficiently rapid to compensate for the rapid redistribution from the brain to other parts of the body. Second, if recovery occurs during the \(\alpha\)-phase, it will be extremely rapid. Finally, even if distributional equilibrium is achieved before recovery occurs, this will still be rapid because of the short terminal half-life.

If the agent is given by infusion, tissue equilibration will be approached. The effect of this is seen in figure 2 (●) where, in comparison with the single dose (fig. 2, ○), the \(\alpha\)-phase was effectively shortened. This is because transfer of the drug between the central compartment and the tissues occurred throughout the infusion, resulting in a lower flux of the agent from the central compartment being required to establish tissue equilibration at termination of the infusion.

This examination of ICI 35 868 in animals has shown that it has a pharmacokinetic profile similar to Althesin (Child et al., 1972) and etomidate (Ambre et al., 1977), but markedly different from that of thiopentone (Brodie et al., 1950).

Although the newer agents discussed above have the desired pharmacokinetic properties required for short-term maintenance anaesthesia, excitatory phenomena have been noted with methohexitone and etomidate (Whitwam, 1978). ICI 35 868 possesses suitable pharmacokinetic properties and produces fewer excitatory effects than Althesin or methohexitone.
(Glen, 1980) in laboratory animals. Work is in progress to study its pharmacokinetics in man.

ACKNOWLEDGEMENTS
The authors gratefully acknowledge the valuable technical assistance given by Mr M. B. Cosgrove, Mrs S. C. Hunter and Mr D. Jones and staff.

REFERENCES

DIE PHARMAKOKINESE VON ICI 35 868, EINEM NEUEN INTRAVENÖSEN NARKOSEMITTEL BEI LABORATORIUMSTIEREN

ZUSAMMENFASSUNG

FARMACOCINETICAS EN ANIMALES DE LABORATORIO, DEL ICI 35 868 QUE ES UN NUEVO AGENTE ANESTESICO INTRAVENOSO

SUMARIO
Se han determinado concentraciones de ICI 35 868 en la sangre de ratas, cerdos, conejos y gatos, después de una única inyección intravenosa. El volumen inicial de la distribución fue, para todas las especies, superior al volumen de sangre, y el volumen de la distribución global fue cuantioso. Las media-vidas de la fase de distribución fueron extremadamente cortos (1-6 min) y la media-vida terminal fue también de corta duración (16-55 min). En todas las especies que se examinaron existió una correlación entre la concentración sistémica de ICI 35 868 en la sangre y la duración del sueño, siendo efectivas concentraciones comprendidas dentro de la gama 1-4 µg ml⁻¹ para producir estados inconscientes. No se produjeron cambios en las farmacocinéticas ni en la concentración efectiva, bajo la administración sucesiva ni después de una infusión.

MAPHARACOCINETIQUE SUR DES ANIMAUX DE LABORATOIRE DE ICI 35 868—NOUVEL AGENT ANESTHESIANT INTRAVENEUX

RESUME
Les concentrations d’ICI 35 868 dans le sang ont été déterminées sur des rats, cochons, lapins et chats après des injections intraveineuses uniques. Sur toutes ces espèces, le volume de répartition initial a été plus fort que le volume sanguin total et le volume de répartition d’ensemble a été important. Les demi-vides de la phase de répartition ont été extrêmement courtes (1-6 min) et les demi-vides terminales ont également été courtes (16-55 min). Sur toutes les espèces examinées, il y a eu une corrélation entre la concentration d’ICI 35 868 dans le sang systémique et la durée du sommeil, les concentrations dans la plage de 1-4 µg ml⁻¹ étant efficaces pour provoquer la perte de conscience. Il n’y a eu aucun changement dans la pharmacocinétique ou dans la concentration effective après une administration répétée ou après une infusion.

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