PRELIMINARY EXPERIENCE WITH ICI 35 868 AS AN I.V. INDUCTION AGENT: COMPARISON WITH ALTHESIN

K. M. ROGERS, K. M. S. DEWAR, T. D. MCCUBBIN AND A. A. SPENCE

SUMMARY

In a small open dose-finding study the i.v. dose of ICI 35 868 required to induce anaesthesia in healthy adults was 2 mg kg\(^{-1}\). Comparison of this dose with Althesin 0.05 ml kg\(^{-1}\) for i.v. induction, both injected over 30 s suggests that they have similar effects on heart rate, arterial pressure and breathing. The mean times to loss of eyelash reflex were 57 ± SD 10.1 s (ICI 35 868) and 46 ± SD 3.9 s (Althesin). The new drug was associated with pain and discomfort on injection in seven of 10 patients, but with less involuntary movement than occurred with Althesin.

ICI 35 868 (2 : 6-diisopropylphenol) is a new i.v. anaesthetic drug which has shown promising results in animal studies (Glen, 1980) and in preliminary clinical trials in Belgium (Kay and Rolly, 1977). In 1979 the Committee on Safety of Medicines gave permission for pilot studies of the drug in the U.K. The authors received permission to conduct a double-blind comparison of ICI 35 868 with Althesin as induction agents, on condition that not more than 20 patients received the new drug. The suggested dose of ICI 35 868 1 mg kg\(^{-1}\) i.v. (Kay and Rolly, 1977) failed to induce anaesthesia and consequently half of the allocated administrations were deployed in a short dose-finding study from which it was concluded that the appropriate dose was 2 mg kg\(^{-1}\). We report here the results of the open dose-finding study and of the double-blind comparison in 20 patients.

PATIENTS AND METHODS

A total of 30 patients in good general health, aged 17-50 yr and within 10% of the expected body weight gave written permission for the study. None was receiving concurrent drug therapy (including oral contraceptives) and none had a previous history of atopy or allergy. Since the present formulation of ICI 35 868 includes Cremophor EL 16% (w/v) as a solubilizing agent we ensured that no patient had received a previous Cremophor-containing anaesthetic, or indeed any anaesthetic in the past 10 years if the component drugs were unknown. The surgical procedures were all of a simple nature such as the ligation of varicose veins, herniorrhaphy or haemorrhoidectomy.

The anaesthetic procedure was standardized. Premedication was with diazepam 0.15 mg kg\(^{-1}\) given orally 60-90 min before induction. The induction agent was given over 30 s into a vein in the back of the hand via a 21-gauge indwelling (butterfly type) needle. At the end of the injection 5 ml of isotonic saline was injected rapidly to clear the dead-space of the needle. If, after 2 min from the start of injection, anaesthesia, judged by abolition of the eyelash reflex, had not been induced (this occurred only with the smaller doses of ICI 35 868) Althesin was injected until the agreed end-point was reached. Two minutes after the start of injection (or immediately following induction of anaesthesia in the patients who required the second injection) a face-mask was applied and anaesthesia was continued with appropriate concentrations of halothane in 70% nitrous oxide in oxygen.

Drug doses

In the initial dose-finding study in 10 patients, ICI 35 868 was given in the following doses: 1 mg kg\(^{-1}\) (three patients), 1.5 mg kg\(^{-1}\) (four), 2 mg kg\(^{-1}\) (two) and 2.5 mg kg\(^{-1}\) (one). For the comparative study the dose of ICI 35 868 was 2 mg kg\(^{-1}\) and of Althesin 0.05 ml kg\(^{-1}\); at this dose the volume of the Althesin injection would have been half that of the ICI 35 868 preparation and so the Althesin was diluted in an equal volume of isotonic saline to facilitate the double-blind technique. For each patient studied there were two anaesthetist observers and a third anaesthetist who prepared the injections.
Measurement and observations in the double-blind study

Induction time: from the start of injection to the abolition of the eyelash reflex.

Symptoms: pain or discomfort on injection, and other clinical observations such as involuntary movements.

Heart rate: recorded from three conventionally placed chest leads.

Breathing pattern: respiratory frequency and tidal spirogram were obtained using an inductance plethysmograph (Hanning, Smith and Ledingham, 1978). The heart rate, respiratory frequency and spirogram were recorded on a multi-channel Linzeis chart recorder.

Arterial pressure measured with an oscillotonometer was recorded immediately before induction, at 50, 110 and 180 s following the start of injection and at approximately 5-min intervals thereafter.

One and two minutes from the start of injection the response to the application of a sterile towel clip to the medial aspect of the thigh was noted.

Blood sampling. On the day before and on the day after surgery, venous blood was sampled for biochemical and haematological estimations.

Before induction of anaesthesia a 14-gauge cannula was inserted to a vein in the antecubital fossa of the arm opposite to that which was used for drug injection. From some patients who were known, after operation, to have received ICI 35 868, voided urine was collected for a 24-h period in dry sterile bottles. The blood and urine were analysed for the content of the induction drugs or metabolites. The data from this aspect of the study, part of a larger collection, will be presented in a later publication.

Postoperative evaluation. The patient’s opinion of both induction and recovery from anaesthesia was sought immediately after wakening and at 24 h after operation. The vein used for the induction injection was examined for signs of tissue damage immediately after injection and after 24 h; each patient was questioned by telephone about the condition of the hand after 3 weeks.

Biochemical and haematological assessment. Biochemical estimations included serum electrolytes, glucose, bilirubin, protein and enzyme indications of liver cell integrity. The haematological survey consisted of haemoglobin, differential white cell count and platelet numbers.

RESULTS

Dose-finding study

On the basis of 10 injections of ICI 35 868 with doses ranging from 1 mg kg\(^{-1}\) to 2.5 mg kg\(^{-1}\) we concluded that the dose required for induction of anaesthesia in the manner described was approximately 2 mg kg\(^{-1}\) (table I).

<table>
<thead>
<tr>
<th>Dose (mg kg(^{-1}))</th>
<th>Awake</th>
<th>Asleep</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>2*</td>
<td>1</td>
</tr>
<tr>
<td>1.5</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>2.0</td>
<td>2*</td>
<td>1</td>
</tr>
<tr>
<td>2.5</td>
<td>1</td>
<td>-</td>
</tr>
</tbody>
</table>

† Sleep induced in all 10 patients receiving ICI 35 868 in the double-blind study (see text).

Double-blind study

The mean induction times were 46 ± SD 3.9 s for Althesin and 57 ± SD 10.1 s for ICI 35 868. Applying Student’s \(t\) test this small difference was statistically significant \((P<0.05)\).

The cardiovascular responses to the two drugs were remarkably similar. The average reduction in arterial pressure in both groups was approximately 6% at 50 and 110 s after injection compared with the pre-injection baseline (table II).

<table>
<thead>
<tr>
<th></th>
<th>Althesin</th>
<th>ICI 35 868</th>
</tr>
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<tbody>
<tr>
<td>% Reduction in resting arterial pressure</td>
<td>7.7±5.8</td>
<td>4.9±3.2</td>
</tr>
<tr>
<td>% Increase in resting heart rate</td>
<td>11.8±7.1</td>
<td>6.8±7.5</td>
</tr>
</tbody>
</table>

At the same times following injection there was a mean increase in heart rate of 11% following Althesin compared with only 4% following ICI 35 868.

Althesin induced a period of apnoea, mean 24 ± SD 4.6 s. Following ICI 35 868 the corresponding values were 38 ± 14.0 s (Student’s \(t\) test: \(P<0.05\)).

Seven of 10 patients receiving ICI 35 868 complained of some form of discomfort in the hand and arm during injection whereas there were no such
complaints following Althesin (table III). However, there were no abnormal sequelae in the vein used for injection in any patient.

Involuntary movement occurred in four patients receiving Althesin and one receiving ICI 35 868. The response to application of a towel clip to the leg was similar for the two drugs (table III).

All of the patients appeared to be satisfied with their experience of the induction of anaesthesia and there were no obvious untoward events such as dreaming or hallucinations.

There were no obvious abnormalities in the haematological data or in the serum electrolyte concentrations before and 24 h after anaesthesia. Neither were there any obvious abnormalities in liver function tests. However, we noted a small increase in the serum bilirubin concentration in seven of the patients who received ICI 35 868. In all but one instance the values remained within the normal range for the hospital laboratory.

**DISCUSSION**

These preliminary studies indicate that when used in the manner described in this study a suitable induction dose of ICI 35 868 is approximately 2 mg kg\(^{-1}\). However, the method of dose-finding employed by us was crude as a consequence of the limited number of injections which we were permitted to administer. In spite of our uncertainty about the dose, it seemed appropriate to compare our initial experience of the new agent with Althesin as an example of a better known i.v. anaesthetic, the pharmacological profile and formulation of which was not dissimilar to that of the new compound.

The results suggest that, as with Althesin, ICI 35 868 provides a reliable induction of anaesthesia with no unpleasant after-effects. Although no patient found the experience unpleasant in retrospect, the complaints of pain in the hand and arm during injection of ICI 35 868 must be regarded as an important disadvantage of the compound. It may be that changes in the formulation can lead to a lessening of this problem. The cardiovascular stability associated with ICI 35 868 was impressive. The respiratory depression produced by the new compound was slightly more marked than that with Althesin, but we would not regard this as a serious disadvantage in clinical practice.

The pharmacokinetic profile of ICI 35 868 in animals (Adams, Glen and Hoyle, 1980) indicates a compound that might be expected to provide rapid recovery from anaesthesia and to be particularly suitable for administration to outpatients. Similarly, a compound with these characteristics would be worthy of evaluation as a continuous i.v. anaesthetic although it is not possible to predict from the present studies that it would be a satisfactory anaesthetic if used as the sole agent.

**ACKNOWLEDGEMENTS**

We wish to acknowledge the help of Mr Robert Watson, the technicians of the University Department of Anaesthesia, the resident medical staff of Wards G6 and 7, Western Infirmary and ICI Pharmaceuticals Ltd, for supplies of ICI 35 868.
In einer kleinen offenen Studie zur Dosisfeststellung von intravenös gegebenem ICI 35 868 zur Einleitung von Narkose war die erforderliche Dosis bei gesunden Erwachsenen 2 mg kg$^{-1}$. Ein Vergleich dieser Dosis mit Althesin 0,05 ml kg$^{-1}$, beide über 30 sek injiziert, zeigt, dass die Drogen ähnliche Wirkungen auf die Herztätigkeit, den arteriellen Druck und die Atemrate haben. Die mittlere Zeit für den Verlust des Lidreflexes war 57±SD 10,1 sek (ICI 35 868) und 46±SD 3,9 sek (Althesin). Die neue Droge bewirkte Schmerzen und Unbehagen bei der Injektion bei sieben von 10 Patienten, aber bei weniger unwillkürlichen Bewegungen als bei Althesin.

DURANTE UN PEQUEÑO ESTUDIO PARA AVERIGUAR LA DOSIS NECESARIA PARA INDUCIR ANESTESIA EN ADULTOS SANOS, MEDIANTE ICI 35 868, SE CONCLUSÓ QUE ÉSTA ERA DE 2 mg kg$^{-1}$. LA COMPARACIÓN DE ESTAS DOSIS CON 0.05 ml kg$^{-1}$ DE ALTESINA PARA PRODUCIR INDUCCIÓN INTRAVENOSA, AMBAS DOSIS INYECTADAS A LO LARGO DE 30 SEGUNDOS, SIGUIÓ QUE ESTAS CANTIDADES EJERCÍAN EFECTOS SIMILARES SOBRE EL RITMO CARDíACO, LA PRESIÓN ARTERIAL Y LA RESPIRACIÓN. EL PROMEDIO DE TIEMPO PARA PERDER EL REFLEJO DEL PáRPADO FUE DE 57±DEVIACiÓN TíPICA DE 10,1 (PARA EL ICI 35 868) Y DE 46±DEVIACiÓN TíPICA DE 3,9 (PARA LA ALTESINA). LA INYECCIÓN DE LA NEUVA DROGA VINO ASOCIADA CON DOLOR Y MOLESTIAS EN 7 DE LOS 10 PACIENTES, PERO CON UN MENOR MOVIMIENTO INVOLUNTARIO QUE EL ADECUADO CON LA ALTESINA.