COMPARISON OF THE RESPIRATORY EFFECTS OF ICI 35 868 AND THIOPENTONE IN THE RABBIT

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SUMMARY

The effects of thiopentone and ICI 35 868 on minute volume, respiratory frequency, tidal volume and arterialized venous $P_{CO_2}$, pH and standard bicarbonate have been compared in the rabbit. ICI 35 868 has two to three times the potency of thiopentone, but equivalent anaesthetic doses cause similar decreases in minute volume. ICI 35 868 decreased tidal volume to a greater extent than thiopentone. Whilst the time courses of the two drugs were similar in most respects, thiopentone produced a more prolonged increase in $P_{CO_2}$. This was accompanied by an increase in standard bicarbonate which was not seen in rabbits treated with ICI 35 868.

ICI 35 868, an i.v. induction agent, is being investigated currently in animals and man. Since the water solubility of this agent at room temperature is low the drug is available as a 1% solution solubilized in 16% Cremophor EL.

Preliminary studies at the ICI laboratories demonstrated minimal respiratory depression in pigs (Glen, 1980), but showed also that large doses of ICI 35 868 caused fatal respiratory depression in rabbits and a cat. The present study examined the time-course and the dose–response relationship of the respiratory effects of ICI 35 868 in the rabbit and compared these with the effects of an established i.v. induction agent, thiopentone.

METHODS

The study was performed on male and female New Zealand White, half lop rabbits weighing between 1.5 and 5.0 kg.

Measurements of minute volume, tidal volume and respiratory frequency

A padded face-mask attached to a one-way valve system was gently held over the rabbit's snout. A pneumotachograph (5 mm; Mercury Instruments) was connected to the inspiratory limb of the valve and the pressure changes across the pneumotachograph were measured using a Bell and Howell pressure transducer. The output of the transducer was displayed on a Grass Polygraph 79C incorporating a tachograph unit which gave a continuous trace of respiratory frequency. The apparatus was calibrated at the end of each day using a small animal ventilator set at respiratory frequencies corresponding to those exhibited by the rabbits during the experiments. The calibration graphs enabled the excursion of the pen on the pressure trace to be converted to tidal volume and minute volume was calculated from this value together with the respiratory frequency.

Following insertion of a 25-gauge metal needle to a lateral ear vein, control readings of tidal volume and respiratory frequency were taken until a steady state was achieved. The drug or vehicle control was administered i.v. and continuous readings were taken for the duration of the experiment.

Blood-gas analysis

Arterialized blood samples were taken from the rabbit's lateral ear vein. The ear was shaved, warmed and massaged gently to ensure a brisk circulation and samples were collected anaerobically in heparinized capillary tubes. The blood was mixed thoroughly and drawn into a Radiometer BMS3 Mk2 blood-gas analyser. Standard bicarbonate was calculated using a Siggaard-Andersen nomogram, assuming a normal haemoglobin. The opposite lateral ear vein was prepared and a metal needle inserted. Repeated blood samples were taken until a steady state had been obtained, and either drug or vehicle was administered.

In all experiments the rabbits were restrained in a purpose-built box, and were kept under controlled conditions of light and temperature. The
rabbits were fed on the same diet between experiments and the same animal was not used more frequently than once in 2 weeks. By randomizing the doses, no rabbit received the same dose of drug twice. On each occasion the rabbits received only one injection of drug.

Drugs
Thiopentone was used as the commercially available 2.5% solution in doses of 4, 8, 16 and 32 mg kg\(^{-1}\).

ICI 35 868 was prepared as a 1% solution in 16% Cremophor EL by the manufacturers and doses of 1, 2, 4 and 8 mg kg\(^{-1}\) were used.

Vehicle controls consisted of 0.9% sodium chloride in a volume equivalent to the greatest dose of thiopentone and 16% Cremophor EL in a volume equivalent to the greatest dose of ICI 35 868.

All drugs were administered i.v. over 30 s, and each dose was repeated a minimum of five times in different rabbits.

RESULTS
ICI 35 868 proved to be an anaesthetic agent with a rapid onset of action. The approximate duration of sleep with ICI 35 868 and thiopentone (table I) was judged as duration of head drop. Transient apnoea was a feature of both agents at the greater doses and, in the case of thiopentone 32 mg kg\(^{-1}\), this proved fatal in three rabbits out of five. This dose was not used in the measurement of blood-gas tensions.

**Table I. Approximate duration of sleep in rabbits treated with thiopentone or ICI 35 868**

<table>
<thead>
<tr>
<th>Dose (mg kg(^{-1}))</th>
<th>Sleep (min)</th>
<th>Dose (mg kg(^{-1}))</th>
<th>Sleep (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICI 35 868</td>
<td></td>
<td>Thiopentone</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>8</td>
<td>0–1</td>
</tr>
<tr>
<td>4</td>
<td>1–1.5</td>
<td>16</td>
<td>2–3</td>
</tr>
<tr>
<td>8</td>
<td>3–5</td>
<td>32</td>
<td>Over 50% mortality</td>
</tr>
</tbody>
</table>

Figure 1 shows the changes in minute volume produced at 1 min by various doses of thiopentone and ICI 35 868. Thiopentone, given in two to three times the dose of ICI 35 868, produced similar degrees of respiratory depression. Both agents depressed the rate of respiration with increasing dosage, but the slope of the dose-response relationship appeared steeper for thiopentone than for ICI 35 868 (fig. 2).

![Figure 1](image1.png)

**Fig. 1.** The effects of thiopentone ■ and ICI 35 868 ● on the respiratory minute volume \((V)\) of the rabbit. The results are expressed as percentage change (mean ± SEM) from pre-drug values 1 min after injection. This is equivalent to maximum change. Means without standard errors include values of 100%.

![Figure 2](image2.png)

**Fig. 2.** The effect of thiopentone ■ and ICI 35 868 ● on the respiratory frequency \((f)\) of the rabbit. The results are expressed as maximum percentage change (mean ± SEM) from pre-drug values 1 min after injection. Means without standard errors include values of 100%.

Figure 3 shows the time-course of the effects of equivalent doses of thiopentone and ICI 35 868 on minute volume. There were no obvious differences
between the two agents. Neither saline nor Cremophor controls produced any significant changes in tidal volume, respiratory rate or minute volume.

Small doses of ICI 35 868 and thiopentone produced no increase in carbon dioxide tension, but at anaesthetic doses both agents caused an increase in arterialized venous $P_{CO_2}$ (fig. 4). The time-course of these effects (fig. 5) shows that thiopentone caused a significant increase of $P_{CO_2}$ for up to 20 min ($P<0.05$) whilst $P_{CO_2}$ had returned to normal in 10 min in the animals receiving ICI 35 868. The doses of thiopentone and ICI 35 868 illustrated in figure 5 decreased pH similarly, and control values were regained 10 min after the injection of both agents.

There was no change in standard bicarbonate after ICI 35 868 8 mg kg$^{-1}$, but there was an increase following thiopentone 16 mg kg$^{-1}$ which was significantly greater than pre-drug values 20 min after injection ($P<0.05$) (fig. 6).
There were no convulsions with either drug, although rapid eye movement occurred at even the smallest doses of both drugs. At the end of the experiments all the surviving rabbits were able to walk. With the exception of the three deaths following thiopentone 32 mg kg\(^{-1}\), there were no undesirable sequelae and venous thrombosis following injection was not a problem. The time lapse between injection and anaesthesia appeared to be the same for the two agents.

DISCUSSION

This study has shown that ICI 35 868 is two to three times as potent as thiopentone in the rabbit both as an anaesthetic agent (table I) and as a respiratory depressant (fig. 2). However, the relative potencies of ICI 35 868 and thiopentone vary in different animals. In mice the ED\(_{50}\) for hypnosis was 11.88 mg kg\(^{-1}\) with ICI 35 868 and 21.68 mg kg\(^{-1}\) with thiopentone—a ratio of 1 : 1.8 (Glen, 1980). In pigs the same worker found ICI 35 868 2.5 mg kg\(^{-1}\) to be equivalent to thiopentone 10 mg kg\(^{-1}\)—a ratio of 1 : 4. In humans the potency ratio is similar to that obtained in rabbits. The hypnotic dose of ICI 35 868 is about 1 mg kg\(^{-1}\) in man (Kay and Roily, 1977) and the anaesthetic dose is 2 mg kg\(^{-1}\) (Rogers et al., 1980). Equivalent doses of thiopentone are generally accepted to be 2–3 mg kg\(^{-1}\) for hypnosis and 4–5 mg kg\(^{-1}\) for anaesthesia.

The depression of minute volume produced by equivalent doses of ICI 35 868 and thiopentone were similar. However, a comparison of figures 1 and 2 show that the depression of minute volume produced by thiopentone was almost solely a result of depression of respiratory frequency, whilst that caused by ICI 35 868 was caused by a diminution of both tidal volume and respiratory frequency. Neither drug exhibited an opioid type of respiratory depression, in which tidal volume may be increased (Hunter, Pleuvry and Rees, 1968).

Although Glen (1980) demonstrated that repeated doses of ICI 35 868 were considerably less cumulative than thiopentone, our study has shown that the time-course of changes in minute volume for single equivalent doses of the two drugs was similar. However, the time-course of the changes in \(P_{CO_2}\) was not the same: thiopentone produced an increase in \(P_{CO_2}\) for almost twice as long as ICI 35 868. This could be a result of differences in the effects of the two agents on carbon dioxide production or an alteration in deadspace.

The increase in standard bicarbonate produced by thiopentone in this study suggests also that thiopentone has more intrinsic metabolic activity than ICI 35 868, at least in the rabbit.

ACKNOWLEDGEMENTS

We wish to thank Miss Stephanie Maddison for invaluable technical assistance with the blood-gas analyses. We are also indebted to I.C.I. Pharmaceutical Limited for supplies of ICI 35 868 and for some financial assistance with this project. Finally, we would like to thank Dr B. Kay for suggesting that we should examine the respiratory effects of ICI 35 868 in animals.

REFERENCES

RESPIRATORY EFFECTS OF ICI 35 868 AND THIOPENTONE


COMPARAISON DES EFFETS RESPIRATOIRES DE L’ICI 35 868 ET DU THIOPENTONE SUR LES LAPINS

RESUME
On a comparé sur des lapins les effets du thiopentone et de l’ICI 35 868 sur le débit cardiaque, la fréquence respiratoire, le volume courant et la $Pco_2$ veineuse artérialisée, le pH et le bicarbonate standard. ICI 35 868 a de deux à trois fois la puissance du thiopentone, mais des doses anesthésiantes équivalentes entraînent des diminutions similaires du débit cardiaque. L’ICI 35 868 fait diminuer le volume courant dans des proportions beaucoup plus grandes que le thiopentone. Bien que la durée d’efficacité des deux produits ait été similaire sous de nombreux aspects, le thiopentone a été à l’origine d’une prolongation de la $Pco_2$. Ceci a été accompagné d’une augmentation du bicarbonate standard, ce que l’on n’a pas vu sur les lapins traités à l’ICI 35 868.

VERGLEICH DER RESPIRATORISCHEN WIRKUNGEN VON ICI 35 868 UND VON THIOPENTON BEIM KANINCHEN

ZUSAMMENFASSUNG

COMPARACION DE LOS EFECTOS RESPIRATORIOS DE LA ICI 35 868 Y DE LA TIOPENTONA EN EL CONEJO

SUMARIO
Se compararon en el conejo los efectos de la tiopentona y del ICI 35 868 sobre el volumen minuto, la frecuencia respiratoria, el volumen periódico y el $Pco_2$, venoso arterializado, el pH y el bicarbonato típico. El ICI 35 868 posee de dos a tres veces la potencia de la tiopentona, pero las dosis anestésicas equivalentes causan similares disminuciones, en el volumen minuto. El ICI 35 868 reduce el volumen periódico en mayor grado que la tiopentona. Aunque los transcurso de tiempo fueron similares en la mayoría de los aspectos para las dos drogas, la tiopentona produjo un incremento en $Pco_2$, más prolongado. Esto vino acompañado por un incremento del bicarbonato típico que no se vió en los conejos tratados con ICI 35 868.