CLINICAL STUDIES OF INDUCTION AGENTS

XXXIX: CT1341, A NEW STEROID ANAESTHETIC

BY

R. S. J. CLARKE, S. J. MONTGOMERY, J. W. DUNDEE AND J. G. BOVILL

SUMMARY

CT1341 is a new intravenous anaesthetic which appears to have overcome the dis-
advantages of the earlier steroid. The formulation is a mixture of two closely related
steroids with Cremophor EL and the optimum dose for induction is 50–60 μl/kg
though much larger doses can be given without serious side effects. As the dose is
increased the incidence of muscle movements, respiratory depression and hypotension
rises. Duration of action is intermediate between that of the barbiturates and propanidid
and postoperative sickness is rare.

The advent of propanidid and subsequent work
on this agent (Horatz, Frey and Zindler, 1965;
Doenicke et al., 1968) suggested that rapid and
complete recovery from anaesthesia was more
likely to follow the use of a non-barbiturate
whose reversal depended on breakdown or ex-
cretion than the use of a barbiturate dependent
mainly on redistribution. Recovery of conscious-
ness and mental clarity is probably as rapid after
propanidid as is ever desirable and this drug is
unlikely to be surpassed for anaesthetics of short
duration. However, anaesthesia with propanidid
is accompanied by a high incidence of involuntary
muscle movements and postoperative sickness
and, like the barbiturates, injection of large doses
in poor-risk patients leads to marked hypotension
(Clarke and Dundee, 1970).

Hydroxydione, the first steroid anaesthetic, was
introduced in 1955 by Laubach, Pan and Rudel
but its slow onset of action and the high incidence
of venous thrombosis (Robertson and Williams,
1961) led to its abandonment. Work on steroid
anaesthetics has continued since then but only
in the last few years have Glaxo Research Labora-
tories been able to prepare a rapidly acting
solution (CT1341) which was of low toxicity and
available in aqueous solution (Child et al., 1971).

CT1341 is a mixture of two steroids, 3α-
hydroxy-5α-pregnane-11,20-dione (Steroid I) and
21-acetoxy-3α-hydroxy-5α-pregnane-11,20-dione
(Steroid II). Both are anaesthetic agents but the
former has approximately twice the potency of the
latter. Steroid II, however, greatly increases the
solubility of Steroid I and the standard solution
contains 9 mg of the Steroid I with 3 mg of
Steroid II in each ml of 20 per cent Cremophor
EL. Investigations in a wide variety of animal
species (Child et al., 1971) have shown the mix-
ture to be rapidly acting, of short duration and
with few side effects. In particular it is free from
irritant properties to veins or arteries. Preliminary
work in man (Campbell et al., 1971) showed that
it caused no severe cardiovascular effects in the
clinical range of dosage and that recovery was
rapid and uncomplicated.

The present study was designed to determine
the optimum dose of CT1341 when used as an
induction agent and to obtain a dose/toxicity
curve over the range of doses likely to be used. A
preliminary report of this work has already been
published (Montgomery et al., 1971).

METHOD

The method of investigation was identical to that
used in studies carried out at this centre with
other induction agents (Dundee, Moore and

The patients were all undergoing minor gynae-
cological surgery. Premedication was standardized
as atropine 0.6 mg intramuscularly 1 hour before
anaesthesia. Induction was carried out by an intra-
venous injection of a predetermined dose of

F.F.A.R.C.S.; J. G. BOVILL, M.B., F.F.A.R.C.S.I.; Department of Anaesthetics, The Queen's University of
Belfast, Northern Ireland.
CT1341 and anaesthesia was maintained by 75 per cent nitrous oxide in oxygen. If deeper anaesthesia was required, as shown by patient movement, this was provided by giving supplemental intravenous doses of CT1341, usually of 100 microlitres. As stated previously, CT1341 is a mixture of two drugs and it was found convenient to refer to the dose of the drug in microlitres per kilogramme body weight (\( \mu l/kg \)).

Table I shows the number of patients studied in different dosage groups, with the average age, weight and duration of anaesthesia. As can be seen, the ages and weights at each dosage level are broadly comparable. There is some variation in the duration of operation, but as the study was primarily of induction characteristics, this was not considered to be important.

**Table I**

<table>
<thead>
<tr>
<th>Dose (( \mu l/kg ))</th>
<th>No. of patients</th>
<th>Age (yr)</th>
<th>Weight (kg)</th>
<th>Duration (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>20</td>
<td>29</td>
<td>64</td>
<td>7.0</td>
</tr>
<tr>
<td>30</td>
<td>20</td>
<td>35</td>
<td>61</td>
<td>11.2</td>
</tr>
<tr>
<td>40</td>
<td>50</td>
<td>32</td>
<td>60</td>
<td>6.5</td>
</tr>
<tr>
<td>50</td>
<td>50</td>
<td>32</td>
<td>60</td>
<td>9.7</td>
</tr>
<tr>
<td>60</td>
<td>50</td>
<td>35</td>
<td>56</td>
<td>8.7</td>
</tr>
<tr>
<td>75</td>
<td>50</td>
<td>34</td>
<td>61</td>
<td>8.5</td>
</tr>
<tr>
<td>100</td>
<td>20</td>
<td>37</td>
<td>60</td>
<td>11.2</td>
</tr>
<tr>
<td>150</td>
<td>20</td>
<td>33</td>
<td>55</td>
<td>11.0</td>
</tr>
<tr>
<td>200</td>
<td>20</td>
<td>29</td>
<td>55</td>
<td>8.1</td>
</tr>
</tbody>
</table>

Blood pressure was measured (using an oscillotonometer) before induction and at 1-minute intervals during anaesthesia. All patients were carefully observed during induction and anaesthesia for the occurrence of any side effects, such as involuntary muscle movements, coughing, hiccups and marked respiratory depression.

Each induction was carefully graded by the anaesthetist in one of four categories:

1. Smooth, uncomplicated induction.
2a. Induction with minor side effects not interfering with anaesthesia or surgery.
2b. Side effects which interfered with anaesthesia or surgery but did not endanger the patient's life.
3. Major side effects which could endanger the patient's life or make surgery impossible.

Grades 2b and 3 were classed as unacceptable inductions.

On completion of surgery nitrous oxide was withdrawn and the patients were given 100 per cent oxygen for 1 minute. Two minutes after cessation of nitrous oxide the patients were observed and classified as “awake”, “safe” or “unsafe”. Patients were regarded as awake when they responded to questioning, e.g. opened eyes on command; safe was taken as return of protective pharyngeal reflexes and maintenance of a clear airway, and unsafe meant that the patient's airway needed support or that protective reflexes were still absent.

All patients were visited by the anaesthetist 1 hour and 6 hours following anaesthesia and asked about nausea and vomiting. The patients were also asked whether they recalled any dreams during the anaesthetic and if so whether the dreams were pleasant or unpleasant. Finally, they were asked if they found the anaesthetic pleasant or not and whether they would have the same anaesthetic again if the need arose.

**RESULTS**

All patients lost consciousness within one arm–brain circulation when the dosage was adequate. However, 30 per cent of the patients receiving 25 \( \mu l/kg \) and 20 per cent of those receiving 30 \( \mu l/kg \) failed to become unconscious. Above this dosage all patients were anaesthetized for a variable period.

Table II shows that the incidence of excitatory side effects is strongly correlated with dose, the incidence rising from 5 to 75 per cent. Hiccups are less frequent and less closely correlated with dose.

**Table II**

<table>
<thead>
<tr>
<th>Dose (( \mu l/kg ))</th>
<th>Excitatory effects</th>
<th>Hiccup etc.</th>
<th>Marked respiratory depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>15</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>30</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>40</td>
<td>24</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>50</td>
<td>18</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>60</td>
<td>24</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>75</td>
<td>32</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>100</td>
<td>50</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>150</td>
<td>65</td>
<td>40</td>
<td>0</td>
</tr>
<tr>
<td>200</td>
<td>75</td>
<td>35</td>
<td>60</td>
</tr>
</tbody>
</table>
Respiratory depression prolonged enough to require ventilatory assistance only occurred with the 200 μl/kg dose.

The changes in arterial blood pressure are shown in figure 1. In the dose range 25–70 μl/kg falls of pressure were mainly in the 0–20 mm Hg range though the incidence of significant hypotension did increase with the dose. Even with the highest dose studied there were no instances of severe hypotension (60 mm Hg or more).

The incidence of undesirable induction characteristics, together with failure to be anaesthetized have been taken into account in table III and figure 2. The table shows that the optimum dose is 50–60 μl/kg and in this range almost three-quarters of all cases have completely smooth inductions while above 100 μl/kg, less than one-quarter. However, many of the changes noted are trivial and the classification into acceptable and unacceptable is probably more useful in clinical practice (fig. 2). On this basis also, the 50–60 μl/kg dose is ideal but the range 40–100 μl/kg is quite acceptable for the great majority of cases.

The recovery after CT1341 can be assessed by the percentage of patients classified as awake, safe and unsafe, after differing total doses of CT1341.

<table>
<thead>
<tr>
<th>Dose (μl/kg)</th>
<th>Acceptable 1</th>
<th>Acceptable 2a</th>
<th>Unacceptable 2b</th>
<th>Unacceptable 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>45</td>
<td>25</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>30</td>
<td>60</td>
<td>25</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>40</td>
<td>64</td>
<td>22</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>50</td>
<td>72</td>
<td>26</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>60</td>
<td>68</td>
<td>30</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>75</td>
<td>48</td>
<td>42</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>100</td>
<td>30</td>
<td>65</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>150</td>
<td>20</td>
<td>65</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>200</td>
<td>0</td>
<td>35</td>
<td>65</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Induction</th>
<th>Total</th>
<th>Awake</th>
<th>Safe</th>
<th>Unsafe</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>45 ± 3.0</td>
<td>75</td>
<td>20</td>
<td>5</td>
</tr>
<tr>
<td>30</td>
<td>62 ± 6.2</td>
<td>75</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>40</td>
<td>57 ± 3.3</td>
<td>82</td>
<td>16</td>
<td>2</td>
</tr>
<tr>
<td>50</td>
<td>70 ± 3.2</td>
<td>86</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>60</td>
<td>72 ± 2.9</td>
<td>86</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>75</td>
<td>89 ± 3.0</td>
<td>68</td>
<td>30</td>
<td>2</td>
</tr>
<tr>
<td>100</td>
<td>118 ± 5.8</td>
<td>45</td>
<td>50</td>
<td>5</td>
</tr>
<tr>
<td>150</td>
<td>155 ± 3.1</td>
<td>15</td>
<td>70</td>
<td>15</td>
</tr>
<tr>
<td>200</td>
<td>200 ± 0.1</td>
<td>5</td>
<td>45</td>
<td>50</td>
</tr>
</tbody>
</table>
TABLE V

Percentage incidence of induction side effects and state of recovery 2 minutes after four intravenous anaesthetics.

<table>
<thead>
<tr>
<th>Drug and dose</th>
<th>Excitatory effects</th>
<th>Respiratory upset</th>
<th>Hypotension (mm Hg)</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>20-40*</td>
<td>40+</td>
</tr>
<tr>
<td>CT1341 50 µl/kg</td>
<td>18</td>
<td>4</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Thiopentone 4 mg/kg</td>
<td>9</td>
<td>6</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>Methohexitone 1.6 mg/kg</td>
<td>33</td>
<td>26</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Propanidid 4 mg/kg</td>
<td>11</td>
<td>3</td>
<td>10</td>
<td>0</td>
</tr>
</tbody>
</table>

* The remainder had blood pressure falls of less than 20 mm Hg.
† The remainder were awake after 2 minutes.

Results for thiopentone, methohexitone and propanidid from Dundee and Clarke (1964).

The largest number awake after 2 minutes occurred in the 40–60 µl/kg dose range and as the total dose rose the degree of recovery at the 2-minute stage diminished (table IV).

Table V shows a comparison of the induction characteristics of CT1341 with those of thiopentone, methohexitone and propanidid after atropine premedication. Excitatory effects occur more frequently than after comparable doses of thiopentone but less frequently than after methohexitone. As with thiopentone and propanidid, the incidence of respiratory upset is low following induction with CT1341 and this contrasts markedly with the effects of methohexitone. The occurrence of hypotension with CT1341 is similar to that with other agents. The rapid recovery after CT1341 is illustrated here also, where it is seen to compare favourably with propanidid when used in a similar manner.

The relative frequency of postoperative nausea and vomiting is illustrated in figure 3. CT1341 was preferable to the other induction agents in this respect, in similar groups of patients undergoing minor gynaecological operations. Anaesthesia with CT1341 was followed by remarkably little nausea (7 per cent) or vomiting (5 per cent).

The patient acceptance of CT1341 anaesthesia was high, as shown in table VI. Over 90 per cent of patients liked anaesthesia with this agent, which was slightly higher than the acceptance after methohexitone and distinctly better than after ketamine in similar series. Comparable figures for recall of dreams during anaesthesia are not available for methohexitone but 14 per cent recalled dreams after CT1341 anaesthesia compared with 62 per cent after ketamine. Only 6 per cent reported unpleasant dreams after CT1341.

TABLE VI

Percentage incidence of patient acceptance and dreams after CT1341 compared with methohexitone and ketamine (Knox et al., 1970).

<table>
<thead>
<tr>
<th></th>
<th>CT1341</th>
<th>Methohexitone</th>
<th>Ketamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acceptance</td>
<td>Yes</td>
<td>96</td>
<td>83</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Dreams</td>
<td>Pleasant</td>
<td>8</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Unpleasant</td>
<td>6</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Nil</td>
<td>86</td>
<td>—</td>
</tr>
</tbody>
</table>

DISCUSSION

The new steroid anaesthetic CT1341 appears to be a satisfactory induction agent in the dose range 40–100 µl/kg. Induction is rapid with only minor excitatory effects and hypotension; it behaves like most other intravenous anaesthetics when given in optimum dosage which appears to be 50–60 µl/kg. Recovery, however, does seem to be more rapid than after the barbiturates, without the
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emetic sequelae which mar recovery after propanidid. The euphoria described by Campbell et al. (1971) was not noted in the present series but certainly patients found the anaesthesia pleasant, as shown by the high acceptance rate.

Below the ideal dose range induction of anaesthesia is often unpredictable and above this range side effects become more frequent and severe. On the other hand, the safety margin is high and even severe muscle movements are not life-threatening compared with the hypotension found with certain other induction agents in high dosage (Clarke and Dundee, 1970). The involuntary muscle movements found with CT1341 occurred soon after its injection and usually subsided spontaneously. There was no indication that administration of a further dose counteracted these movements. Certainly the suggestion of Campbell et al. (1971) that 150 μl/kg was a more suitable dose in fit patients does not agree with the present experience. It seems likely that these involuntary muscle movements are directly related to dose, rate of injection and premedication, though the relevance of the two latter factors has still to be investigated.

ACKNOWLEDGEMENTS

The authors would like to thank Dr Snell and Glaxo Pharmaceuticals Ltd for generous supplies of CT1341 and help with the investigation.

REFERENCES


ETUDES CLINIQUES D’AGENTS D’INDUCTION

XXXIX: CT1341, UN NOUVEL ANESTHESIQUE STEROIDE

Sommaire

CT1341 est un nouvel anesthésique intraveineux qui ne semble plus présenter les désavantages des stéroïdes précédents. La formule est un mélange de deux stéroïdes étroitement apparentés avec Cremophor EL et la dose optimale pour l’induction est 50–60 mcg/kg, mais des doses beaucoup plus grandes peuvent être administrées sans effets secondaires graves. Avec l’augmentation de la dose s’accroît la fréquence des mouvements musculaires, de la dépression respiratoire et de l’hypotension. La durée d’action est intermédiaire entre celle des barbituriques et propanidid et les malaises postopératoires sont rares.

KLINISCHE UNTERSUCHUNGEN VON INDUKTIONSSUBSTANZEN

XXXIX: CT1341, EIN NEUES STEROIDNARKOTIKUM

ZUSAMMENFASSUNG

Este formulación es una mezcla de dos esteroides estrechamente relacionados y Cremophor EL, siendo la dosis óptima para la inducción 50–60 μl/kg, aunque dosis mucho más elevadas pueden ser administradas sin efectos secundarios graves. A medida que es incrementada la dosis, aumenta la frecuencia de movimientos musculares, depresión respiratoria e hipo-tensión. La duración de la acción es intermedia entre la de los barbitúricos y la del propanidid y la enfermedad posoperatoria es rara.

ASSOCIATION OF ANAESTHETISTS OF GREAT BRITAIN AND IRELAND

Research and Education Grants

The Research Committee of the Association of Anaesthetists will consider applications from Members needing financial assistance for educational or research purposes. The award of grants falls into two main categories:

1. For research projects carried out by an individual working under supervision, or for a specific piece of research as part of a Departmental project. Grants of more than £1000 (towards salary or equipment) are unlikely to be exceeded, except in special circumstances.

2. For travel grants towards the expenses of a tour abroad which includes either teaching, learning, or research. Grants will not be made for the purpose of taking up a post abroad, but may be made for extending the candidate’s travel within the terms already stated. Grants in the region of £100–£150 may be given.

CRITERIA IN MAKING AWARDS

In considering applications, the Committee will bear the following in mind:

1. Research Projects
   - The amount of local support promised.
   - Where salaries or large sums are involved, the amount of support likely to be given by the Medical Research Council, the Wellcome Foundation, etc.
   - The suitability of the project, and the effectiveness of a contribution from the Association.

2. Travel Grants
   - The purpose of the proposed visit abroad.
   - The suitability of the itinerary in regard to the purpose.
   - Contributions, if any, from other organizations or the applicant’s employing authority.
   - Value of emoluments to be received during the visit, including salary.

WHERE AND HOW TO APPLY

Application form obtainable on application to the Hon. Secretary, Association of Anaesthetists, Room 126, Tavistock House North, Tavistock Square, London W.C.1.

CLOSING DATES

End of April and October for research projects. Any time for travel grants.

FOLLOW-UP REPORTS will be asked for, and published in the Association’s Annual Report.