CLINICAL STUDIES OF INDUCTION AGENTS
XIV: A COMPARATIVE STUDY OF VENOUS COMPLICATIONS FOLLOWING
THIOPENTONE, METHOHEXITONE AND PROPANIDID

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SUMMARY
The incidence of venous complications was studied under comparable conditions in
700 patients following equipotent doses of 5 per cent thiopentone, 2 per cent metho-
hexitone and 3.5 per cent and 5 per cent propanidid, using two sizes of disposable
needles. There was no difference between the effects of thiopentone and methohexitone,
but propanidid, in 5 per cent solution, while acceptable for clinical use, was followed
by significantly more sequelae. This viscous solution was more easily injected through
the larger of the two needles, but there was a higher incidence of local ecchymosis.

A high incidence of venous thrombosis following
intravenous injection has been one of the major
problems in the development of non-barbiturate
intravenous anaesthetics and stable solutions of
barbiturates. This applied particularly to the
steriod anaesthetic, hydroxydione (Viadril,
Presuren). In a comprehensive study Robertson
and Wynn Williams (1961) found that none of the
modifications in the method of administration re-
duced the frequency of this complication to an
acceptable level. Gjöres (1958) and Gordh (1964)
both noted that Narkotal—a stable solution of a
barbiturate—also caused a high incidence of
thrombosis.

The newly introduced phenoxyacetic amines
(eugenol derivatives), while satisfactory as intra-
venous anaesthetics, are so insoluble in water that
various solvents have to be employed for their
clinical use. The first of these, G.29.505 (Detrovel,
Estil), is now largely abandoned because of the
high incidence of thrombosis following injection,
irrespective of its mode of presentation (Swerdlow
1961; Wright and Payne, 1962; Riding et al.,
1963). Propanidid (FBA.1420, Epontol) is pre-
pared in 5 per cent aqueous solution with the aid
of the solubilizing agent, Cremophor EL, and pre-
sented for clinical use as a viscous “oily” solution.

Preliminary clinical studies with propanidid
are promising and the incidence of venous damage
reported (Howells et al., 1964; Podlesch and Zind-
ler, 1965; Heinze, 1965) is similar to that found
with the established intravenous anaesthetics. How-
ever, in view of the previous experience with
G.29.505 it was felt necessary to study in detail
the venous sequelae following the administration
of propanidid and compare its effects with both
thiopentone and methohexitone, used in equiva-
 lent dosage under comparable conditions. This
paper reports the findings of this investigation.

METHOD
Concentration.
In the main part of the investigation 5 per cent
propanidid was compared with 5 per cent thio-
pentone and 2 per cent methohexitone, equal
volumes of which are approximately equipotent
as induction agents. In a further part of the study
propanidid was diluted to a 3.5 per cent solution,
with water for injection, B.P.

Technique.
Many anaesthetic techniques were employed,
but the use of the intravenous agent was limited
to a single induction dose of 6–8 ml of 5 per cent
thiopentone, 2 per cent methohexitone or 5 per
cent propanidid, or the equivalent dose (8–10 ml)
of 3.5 per cent propanidid. The needle was with-
drawn on completion of the injection and a sterile
swab firmly strapped to the arm. No further in-
jections were given into the same arm and no
arterial pressure readings made on that limb. A
record was made of the anatomical site of the in-
Injection (antecubital fossa, forearm, wrist or hand) and the size of the vein used (large, medium or small). A vein was not included in the series where there was any difficulty in venepuncture or a suspicion of extravascular leakage. Two sizes of disposable needles were used: 21 s.w.g. with external diameter 0.8 mm and 23 s.w.g. with diameter 0.6 mm (Gillette Scimitar or B-D Yale). The 3.5 per cent propanidid was used with the smaller needle only.

The investigation, comprising 700 patients, was arranged so that each series totalled 100. Each participant anaesthetized and followed up the same number of cases in each series. The patients were seen on the second or third postoperative day and the site of injection examined for the presence or absence of:

1. Tenderness on palpation of the vein.
2. Thrombosis in the vessel lumen.
3. Subcutaneous discolouration (ecchymosis).

From these signs the venous sequelae were classified into:

- Phlebitis (tenderness without thrombosis).
- Thrombosis (without phlebitis).
- Thrombophlebitis (combination of the above).
- Ecchymosis.

Instances of thrombosis and thrombophlebitis were subdivided into localized or extended, the latter indicating involvement of a segment exceeding 1 inch in length. The ecchymoses were recorded as large (more than 1 inch in length) or small.

RESULTS

Table I lists the incidence of vein complications at the site of injection. In the three series with the 21 s.w.g. needle there were no significant differences between the drugs. On the other hand, with the smaller needle the incidence of venous sequelae following 5 per cent propanidid was significantly greater than that with 2 per cent methohexitone \((\chi^2=4.74; P<0.05)\) but not greater than that with 5 per cent thiopentone \((\chi^2=2.83; P<0.10)\).

When the data with the two sizes of needles are pooled, 5 per cent propanidid was followed by significantly more sequelae than either 5 per cent thiopentone or 2 per cent methohexitone \((\chi^2=4.39; P<0.05)\). When injected through the smaller needle, 3.5 per cent propanidid caused significantly less venous sequelae than either 5 per cent thiopentone or 2 per cent methohexitone \((\chi^2=4.39; P<0.05)\). When injected through the smaller needle, 3.5 per cent propanidid caused significantly less venous sequelae than the 5 per cent solution but not significantly less than when the latter was injected through the larger needle. There was a 6 per cent incidence of extended thrombosis with 5 per cent propanidid injected through the 23 s.w.g. needle as compared with 0–1 per cent in the other series. The size of needle did not significantly affect the incidence of venous sequelae with any particular drug; however, it was the main factor influencing the incidence of ecchymosis (which was similar for all drugs) as shown in table II.

<table>
<thead>
<tr>
<th>Needle size</th>
<th>21 s.w.g.</th>
<th>23 s.w.g.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Thio-pentone 5%</td>
<td>Methohexitone 2%</td>
</tr>
<tr>
<td>Number of cases</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Phlebitis (without thrombosis)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Thrombosis (without phlebitis)</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Localized</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Extended</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Thrombophlebitis</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Localized</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Extended</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total venous sequelae</td>
<td>5</td>
<td>7</td>
</tr>
</tbody>
</table>
TABLE II

Percentage incidence of large (over 1 inch diameter) and small ecchymoses following different sizes of needles, irrespective of drug used.

<table>
<thead>
<tr>
<th>Ecchymosis</th>
<th>Large needle (21 s.w.g.)</th>
<th>Small needle (23 s.w.g.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Small</td>
<td>37</td>
<td>29</td>
</tr>
</tbody>
</table>

TABLE III

Percentage incidence of total venous sequelae (excluding ecchymosis) related to size of vein.

<table>
<thead>
<tr>
<th>21 s.w.g.</th>
<th>Large</th>
<th>Medium</th>
<th>Small</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiopentone 5%</td>
<td>3</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>Methohexitone 2%</td>
<td>3</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>Propanidid 5%</td>
<td>5</td>
<td>14</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>23 s.w.g.</th>
<th>Large</th>
<th>Medium</th>
<th>Small</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiopentone 5%</td>
<td>7</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Methohexitone 2%</td>
<td>0</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Propanidid 5%</td>
<td>10</td>
<td>17</td>
<td>23</td>
</tr>
<tr>
<td>Propanidid 3.5%</td>
<td>0</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>All series</td>
<td>4</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

Further analyses of the data failed to reveal any relationship between the sex or age groups of the patients and the incidence of venous sequelae. The site of the vein had no influence on the frequency of complications, but table III shows that the size of the vessel was a factor. Medium and small veins were significantly more prone to the recorded sequelae than the large ones (P<0.05). The distribution of vein sizes was similar in each of the series.

DISCUSSION

The only finding in this study that is likely to be of clinical importance was the 6 per cent incidence of extended thrombosis when 5 per cent propanidid was injected using the smaller needle; this compares unfavourably with the other groups. The higher incidence of ecchymosis with the larger needle is also worthy of note particularly in relation to the use of the more viscous solutions such as 5 per cent propanidid which are most easily given through wider-bore needles.

The reduction in thrombosis with the more dilute solution of propanidid (and 23 s.w.g. needle) may be due to either a less irritant effect of the weaker solution or to the shorter time that this was in contact with the vein wall. (Although there was a larger volume of injectant with the 3.5 per cent solution, the reduction in viscosity was such that this could be injected over a shorter period of time). Stedtfeld (1957) and Galley and Lerman (1959) claimed that rapid injection lowered the incidence of sequelae with hydroxydione and the importance of this is being investigated with reference to propanidid.

The only comparable published study on the incidence of thrombosis with propanidid is that of Podlesch and Zindler (1965); these authors found a 10 per cent incidence of thrombosis and a 2 per cent incidence of thrombophlebitis after injection of the 5 per cent solution. They often gave a repeat injection and claimed that the incidence was higher with doses above 700 mg, but unfortunately they had no comparable data with thiopentone or methohexitone. Heinze (1965) studied the complications in 600 patients who received doses ranging from 250 to 500 mg in three concentrations (2.5, 3.5 and 5.0 per cent) and found no evidence of vein irritation over several postoperative days.

It is interesting to note that the incidence of thrombosis following thiopentone and methohexitone is very similar to that recorded by Riding and associates (1963) but the frequency with propanidid was very much less than with G.29.505. While it is difficult to compare findings obtained under different conditions, with different criteria of evaluation, there is little doubt that this present investigation shows that propanidid has a less deleterious effect on veins than that found with G.29.505 by Swerdlow (1962), Wright and Payne (1962) or by Stephen and Rippy (1963).

In this respect the new eugenol derivative has a definite advantage over its predecessor. The present form of propanidid is not ideal but at least the frequency of venous sequelae is acceptable for clinical use.

ADDENDUM

Since this paper was submitted for publication three additional series were completed using propanidid as induction agent given over 25–35 seconds (25 seconds was found to be the minimum time required to inject 7 ml 5 per cent solution with the smaller needle). The findings were:

- 5 per cent solution, 21 s.w.g. needle,
- 11 per cent total venous sequelae;
3.5 per cent solution, 21 s.w.g. needle,
8 per cent total venous sequelae;
5 per cent solution, 23 s.w.g. needle,
13 per cent total venous sequelae.

The speed of injection does not appear to be an
important factor influencing the incidence of
venous sequelae with propanidid, which again
showed a slightly higher incidence with the more
concentrated solution.

ACKNOWLEDGEMENT
The authors are indebted to Farbenfabriken Bayer AG
for ample supplies of propanidid for this study.

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BRITISH JOURNAL OF ANAESTHESIA

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ETUDE CLINIQUE DES AGENTS
D'INDUCTION

XIV: ETUDE COMPARATIVE DES COMPLI-
CATIONS VEINEUSES APRES L'INJECTION
DE THIOPENTONE, DE METHOHEXITONE
ET DE PROPANIDIDE

SOMMAIRE
On a étudié l'incidence des complications veineuses
dans des conditions comparables chez 700 malades
aprè des doses équivalentes de thiopentone à 5 pour
cent, de méthohexitone à 2 pour cent et de propani-
dide à 3,5 et 5 pour cent, en utilisant deux tailles
daiguilles. Il n'y a pas eu de différence entre les effets
de la thiopentone et de la méthohexitone, mais le
propanidide en solution à 5 pour cent, bien qu'accept-
able pour l'emploi clinique, a été suivi de beaucoup
plus de sequelles. Cette solution visqueuse a été plus
facilement injectée avec la plus grosse des deux
daiguilles, mais il y a eu une incidence plus élevée
d'ecchymose locale.

KLINISCHE PROFUNG VON DROGEN FOR
DIE NARKOSEEINLEITUNG

XIV: EINE VERGLEICHENDE UNTERSUCH-
UNG ÜBER DIE VENENVERÄNDERUNGEN
NACH VERABFOLGUNG VON THIOPENTONE,
METHOHEXITONE UND PROPANIDID

ZUSAMMENFASSUNG
Unter vergleichbaren Bedingungen an 700 Patienten
wurde die Häufigkeit von Venenveränderungen nach
Verabfolgung von gleichwirksamen Dosen von 5-
prozentigem Thiopentone, 2-prozentigem Metho-
hexitone und 3,5- und 5-prozentigem Propanidid untersucht, wobei zwei Größen von
Kanülen zum Einmalgebrauch Verwendung fanden.
Zwischen den Auswirkungen des Thiopentone und
des Methohexitone fand sich kein Unterschied, aber
nach Anwendung der 5-prozentigen Lösung des
Propanidids, die für den klinischen Gebrauch
durchaus zulässig ist, traten signifikant mehr Neben-
wirkungen auf. Durch die grössere der beiden Kanülen
lässt sich diese visköse Lösung leichter einspritzen,
aber dies war begleitet von häufigerem Auftreten von
lokaler Ecchymose.