THALAMONAL AS A PRE-OPERATIVE SEDATIVE

BY

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SUMMARY

In 100 healthy gynaecological patients the sedative properties of Thalamonal (2 ml) were studied using a standard scoring system and compared with morphine (10 mg). In 45 of the patients the changes in forearm blood flow which resulted from the application of the stimulus were studied. Both the scoring system and the measurements of the change in forearm blood flow showed that Thalamonal (2 ml) was a better pre-operative sedative than morphine (10 mg). Thalamonal also produced a significantly greater fall in systolic blood pressure and heart rate as compared with morphine, and the postoperative emetic sequelae were significantly lower. There was a disturbingly high incidence of "shivering" in the immediate pre-operative period in some 25 per cent of patients who had received Thalamonal and it is considered that this is a limiting factor to the routine use of the drug combination.

The combination of powerful sedative drugs with potent analgesic agents in the technique of neuroleptanalgesia is now well established for certain operations and diagnostic procedures. The advantages of the method, which is claimed to produce indifference to the environment and excellent analgesia while retaining conscious co-operation by the patient, are extolled by its advocates (Brown, 1963; Smith and Hollis, 1966).

The disadvantages of the combination are found mainly when the drugs are used at high dose levels without supplementary local or general anaesthesia. The sedative or neuroleptic drugs used—haloperidol, dehydrobenzperidol—while producing apparently quiet sedated patients, have caused very unpleasant subjective effects and Parkinsonian tremors (Brown, 1963). The potent analgesics in large doses, like other pethidine-like narcotics, produce respiratory depression and nausea and vomiting.

The use of the combination of drugs in neuroleptanalgesia is well reviewed by Robertson (1967) and it is not our purpose to pursue this aspect of the drugs in this paper. The use of a sedative with anti-emic effects such as dehydrobenzperidol and an analgesic such as fentanyl, which provides analgesia for a relatively short period, seemed attractive for premedication for routine surgery. It was hoped that by using low doses of the drugs many of the unpleasant side effects could be avoided. The drugs are combined in one ampoule as Thalamonal or Innovar, each 2-ml ampoule containing fentanyl 0.1 mg and dehydrobenzperidol 5 mg. In this study Thalamonal 2 ml (Janssen Pharmaceuticals) has been compared with morphine 10 mg made up to 2 ml.

METHOD

The method of study was as reported in a recent paper (Norris and Telfer, 1968). One hundred otherwise healthy patients from one gynaecological unit who were about to undergo minor surgical procedures were studied. Each patient received a 2-ml intramuscular injection 1 hour pre-operatively, the injection containing either morphine 10 mg or Thalamonal 2 ml. The study was double-blind, the drugs being allocated in a random fashion.

Scoring system.

Assessment of sedation was carried out using the scoring system of Nisbet and Norris (1963) which was again fully described by Norris and Telfer (1968). Points are awarded to a patient who appears relaxed in the anaesthetic room and who shows either a slight fall or no change in heart rate and blood pressure from the previous measurements made in the ward. A stimulus is provided by applying an anaesthetic face mask not connected to a machine or supply of gas, and...
points are awarded to patients who show no change in blood pressure or heart rate. A maximum score of 10 is possible and patients scoring 0–4 are considered poorly sedated, those scoring 5 and 6 fairly sedated, and those scoring 7–10 well sedated.

**Forearm blood flow.**

It has previously been reported that the application of a face mask to a resting subject results in an increase in the forearm blood flow (Bird and Telfer, 1966). In a recent paper comparing the sedative effects of morphine and pentazocine (Norris and Telfer, 1968) the forearm blood flow was measured in 30 patients as a pilot study. In this present series the assessment of forearm blood flow as an objective test of sedation was continued and the forearm blood flow was measured in 45 unselected patients out of the 100, using strain gauge plethysmography (Whitney, 1953). The details of the equipment and the technique of measurement, and the conditions under which the measurements were made have been reported by us previously (Norris and Telfer, 1968), and in this present study no departures were made from the procedures described therein. Comparison of the scores of the patients who had their blood flow measured with those for the whole series showed that, as before, the additional investigation had no significant effect on the score obtained. The mean score for the 26 patients who received morphine and had their blood flow measured was 5.7 ± 2.1 and for the 50 morphine patients in the series was 5.58 ± 2.08. The corresponding figures for the 19 Thalamonal patients were 8.6 ± 1.6 and 7.55 ± 1.92. In neither case is the difference between the score of the subgroup and the whole group significant.

As in the previous series the measurements of total forearm blood flow were made at rest in the ward before and 1 hour after administration of the drug under test and again in the anaesthetic room before and during the application of the stimulus. Only the changes in flow produced by the application of the stimulus are considered in this paper. Ten consecutive readings were obtained prior to the application of the stimulus and a further ten consecutive readings while the mask remained on the face. From these readings three values for the blood flow were calculated:

(a) the mean pre-stimulus value;
(b) the mean post-stimulus value;
(c) the peak post-stimulus value.

The percentage changes in blood flow between the mean pre-stimulus value and both the mean and the peak post-stimulus values have been calculated and are presented in table II.

**Side effects.**

The incidence of nausea and vomiting in the first hour after administration of the drug was noted and the incidence of nausea and vomiting up till 9 p.m. (when the nursing staff changed)—a period of 9–12 hours—was also recorded.

The occurrence of postoperative restlessness was also noted.

**RESULTS**

**Sedation.**

The results of the trial are shown graphically in figure 1. In table I the distribution of the scores is again shown. The mean score for Thalamonal is 7.55 ± 1.92, significantly better than morphine 10 mg at 5.58 ± 2.08 (t = 4.92; P < 0.001). There are significantly more patients well sedated (7–10) with Thalamonal and significantly fewer poorly sedated (0–4).

**TABLE I**

The classification of the patients into groups "good" "fair" and "poor".

<table>
<thead>
<tr>
<th></th>
<th>Poor (0–4)</th>
<th>Fair (5, 6)</th>
<th>Good (7–10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine 10 mg</td>
<td>14</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Thalamonal 2 ml</td>
<td>4</td>
<td>14</td>
<td>32</td>
</tr>
</tbody>
</table>

Good χ² = 7.84; P < 0.01.
Poor χ² = 6.80; P < 0.01.
THALAMONAL AS A PRE-OPERATIVE SEDATIVE

TABLE II
The mean percentage increase in blood flow after stimulation in the 45 cases studied.

<table>
<thead>
<tr>
<th></th>
<th>Morphine 10 mg</th>
<th>Thalamonal 2 ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean pre-stimulus to</td>
<td></td>
<td></td>
</tr>
<tr>
<td>max. post-stimulus</td>
<td>Mean</td>
<td>Mean</td>
</tr>
<tr>
<td></td>
<td>Standard error of mean</td>
<td>Standard error of mean</td>
</tr>
<tr>
<td>Morphine</td>
<td>109</td>
<td>45.7</td>
</tr>
<tr>
<td>Thalamonal</td>
<td>23.5</td>
<td>13.2</td>
</tr>
<tr>
<td>Mean pre-stimulus to</td>
<td>54</td>
<td>10.2</td>
</tr>
<tr>
<td>mean post-stimulus</td>
<td>14.4</td>
<td>8.55</td>
</tr>
</tbody>
</table>

Forearm blood flow.
The majority of the patients showed a rise in blood flow following application of the face mask but in the change from mean to peak 3 patients (2 Thalamonal, 1 morphine) showed a reduction in blood flow, and in the mean-to-mean figures 13 patients showed a reduction in blood flow (9 Thalamonal, 4 morphine). The mean results with their significance are presented in table II. Figure 2 shows the mean percentage increase in blood flow plotted against that part of the score which was derived from the application of the stimulus. With the relatively small number of patients involved, the difference between the mean blood flow change in those patients who scored zero and the change in those who scored 2 is barely significant (0.05<P<0.1).

Blood pressure and heart rate.
The changes in blood pressure and heart rate from the levels obtained in the ward on the day before operation to the levels in the anaesthetic room are shown in table III. The mean fall in systolic blood pressure and heart rate is significantly greater after Thalamonal than after morphine. The fall in diastolic blood pressure after Thalamonal is greater though not significantly so.

Nausea and vomiting.
The incidence of nausea and vomiting after administration of the two drugs is shown in table IV. Only one patient (given morphine) was nauseated pre-operatively. The incidence of total emetic sequelae after morphine was significantly greater than after Thalamonal ($\chi^2=58.34$, P<0.0001).

Restlessness.
Muscular movement similar to shivering was noted in 25-30 per cent of patients who received Thalamonal. The exact incidence is lacking as the first cases occurred in a spell of cold weather and some were attributed to the change in temperature. No patients showed this change after morphine.
TABLE III
The changes in blood pressure and heart rate from the resting level in the ward on the day before operation to those obtaining in the anaesthetic room 1 hour after administration of the drug and before application of the stimulus.

<table>
<thead>
<tr>
<th></th>
<th>Morphine</th>
<th>Thalamonal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic (mm Hg)</td>
<td>$-3 \pm 27.0$</td>
<td>$-17.1 \pm 23.8$</td>
</tr>
<tr>
<td>Diastolic (mm Hg)</td>
<td>$-4.7 \pm 16.73$</td>
<td>$-10.7 \pm 17.44$</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>$+1 \pm 14.42$</td>
<td>$-6.2 \pm 11.0$</td>
</tr>
</tbody>
</table>

The $t$ test results obtained by comparing the means are shown.

Postoperative restlessness after Thalamonal was greater than after morphine, but the difference was not statistically significant ($\chi^2 = 2.168$; $0.2 > P > 0.1$).

TABLE IV
The incidence of postoperative nausea, vomiting and restlessness within 9–12 hours after operation.

<table>
<thead>
<tr>
<th></th>
<th>Morphine</th>
<th>Thalamonal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>25</td>
<td>3</td>
</tr>
<tr>
<td>Total emetic sequelae</td>
<td>38 (76%)</td>
<td>11 (22%)</td>
</tr>
<tr>
<td>Restlessness</td>
<td>7 (14%)</td>
<td>11 (22%)</td>
</tr>
</tbody>
</table>

The total emetic sequelae after morphine were significantly greater than after Thalamonal ($\chi^2 = 58.34$; $P < 0.0001$). The incidence of postoperative restlessness was greater after Thalamonal but the difference was not statistically significant ($\chi^2 = 2.168$; $0.1 < P < 0.2$).

DISCUSSION
The results, both from the scoring system and from the blood flow study, show that Thalamonal is a much more effective pre-operative sedative than morphine at the dose levels tested. The lower level of postoperative emetic sequelae with Thalamonal is also very desirable. This finding is in keeping with previous published reports of the use of this combination of drugs (Robertson, 1967). No patient complained of unpleasant subjective symptoms after Thalamonal and, although these were not specifically sought after, each patient was questioned as to how she felt in the anaesthetic room. The lesser response to the stimulus in terms of forearm blood flow suggests that anxiety was more effectively reduced by the Thalamonal.

The shivering type of movement was, however, a considerable nuisance and appeared to upset the patients concerned, although not always reflected in the sedation score obtained. The shivering, which was often intermittent, in some cases delayed the blood flow measurement. It invariably disappeared after a few ml of the thiopentone induction dose had been given and was not noted postoperatively. Even at this low dose level, therefore, this combination of drugs is still not free from some of the undesirable effects of the neuroleptic drugs.

The effects of the Thalamonal on blood pressure and heart rate probably reflect the better sedation produced and the mean changes are well within the limits obtaining during normal sleep. The restlessness seen postoperatively with Thalamonal may in part be due to the shorter duration of action of the fentanyl (about 45 minutes), thus leaving the patient under the influence of the droperidol but without the protective analgesic action in the immediate postoperative period.

CONCLUSIONS
Thalamonal (2 ml) produced better pre-operative sedation than morphine (10 mg) both as judged by the scoring system and on the results of the blood flow measurements. The total postoperative emetic sequelae were also significantly less with Thalamonal than with morphine (10 mg) and the incidence of postoperative restlessness, though higher, was not significantly so. Judged on these findings Thalamonal (2 ml) would appear to be a good pre-operative sedative which is better than morphine (10 mg). The incidence of the pre-operative shivering movements, however, which proved unpleasant for the patients, is in our opinion a limiting factor to the routine use of this combination of drugs. It may be that the replacement of fentanyl by a longer-acting analgesic would further reduce the incidence of postoperative restlessness at the cost of prolonging the other side effects of the narcotic analgesic at a time when many would not welcome this.

REFERENCES
THALAMONAL AS A PRE-OPERATIVE SEDATIVE


THALAMONAL CONSIDERE COMME SEDATIF PRE-OPERATOIRE

SOMMAIRE
Chez 100 patientes gynécologiques en bonne santé, les propriétés sédatives du Thalamonal (2 ml) ont été étudiées grâce à un système standard de pointage et comparées avec celles de la morphine (10 mg). Chez 45 des patientes les altérations observées dans le flux sanguin de l’avant-bras provoquées par l’administration du stimulus ont été examinées. Le système de pointage et les variations des constantes du flux sanguin de l’avant-bras ont montré que le Thalamonal (2 ml) était un sédatif pré-opératoire meilleur que la morphine (10 mg). Le Thalamonal a produit également une chute nettement plus grande sur la pression sanguine systolique et le rythme des pulsations cardiaques comparé à celui déclenché par la morphine; les séquelles émettantes étaient notablement moins. En période pré-opératoire immédiate, il existait une incidence perturbante élevée de frissonnement chez quelque 25 pour cent des patientes qui avaient reçu du Thalamonal, et ce phénomène est considéré comme limitatif de l’usage routinier de la combinaison médicamenteuse.

THALAMONAL ALS PRÖOPERATIVES SEDATIVUM

ZUSAMMENFASSUNG
Bei 100 gesunden gynäkologischen Patientinnen wurden die sedierenden Eigenschaften von Thalamonal (2 ml) unter Verwendung eines Standardprüfsystems untersucht und mit Morphin (10 mg) verglichen. Bei 45 von diesen Patientinnen wurde die Durchblutungsänderung im Unterarm erforscht, die sich bei der Anwendung des Mittels einstellte. Sowohl das Prüf-system als auch die Messung der Durchblutungsänderung im Unterarm zeigten, daß Thalamonal (2 ml) ein besseres präoperatives Sedativum war als Morphin (10 mg). Thalamonal verursachte im Vergleich zu Morphin auch eine signifikant größere Abnahme des systolischen Blutdrucks und der Herzfrequenz. Ferner waren postoperativ die emetischen Folgeerscheinungen signifikant geringer. Beunruhigend häufig kam es bei etwa 25 Prozent der Patientinnen, die Thalamonal erhalten hatten, unmittelbar vor der Operation zum "Schüttelfrost". Es wird die Ansicht vertreten, daß dies den begrenzenden Faktor für eine Routineanwendung der Substanzkombination darstellt.

REGISTRARS’ PRIZE (ANAESTHETICS)

Applications are invited by the Royal Society of Medicine, Section of Anaesthetics, for a prize of £50 provided by Messrs. May & Baker Ltd., for a paper written by a medical practitioner of Senior Registrar or Registrar status holding an appointment in anaesthesia in a department or hospital, or in the armed forces of the Commonwealth or of the Republics of South Africa or Eire. Fellowship of the Royal Society of Medicine is not necessary for entry. The subject will be of the author’s choice, but must be connected with anaesthesia. All papers for the 1969 award must be submitted in triplicate by January 1, 1969.

Further details and rules of the prize can be obtained from the Assistant Secretary, Royal Society of Medicine, 1 Wimpole Street, London, W.1.

A further prize of £25 may be awarded on the recommendation of the judges.