COMPARISON BETWEEN BUPRENORPHINE AND PENTAZOCINE GIVEN I.V. ON DEMAND IN THE CONTROL OF POSTOPERATIVE PAIN

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SUMMARY

A double-blind comparison between buprenorphine and pentazocine was performed in 20 patients using an on demand analgesic system to provide analgesia after operation. The quality of analgesia, assessed subjectively, was good with both drugs and drug consumptions were compatible with previous potency estimates. The mean doses demanded in 24 h of buprenorphine (1.68 mg) and of pentazocine (382 mg) are consistent with those found in other trials although the between-patient variation was five- or six-fold. There was no significant difference in side-effects between the two groups. Buprenorphine and pentazocine may be used successfully in an on demand system to provide relief of severe pain after operation.

Several potent analgesic drugs were compared in a double-blind trial utilizing an on demand i.v. infusion system to provide analgesia for patients after cholecystectomy. We report here a comparison of buprenorphine and pentazocine.

Buprenorphine (N-cyclopropylmethyl-7α(1-(S)-1-hydroxy-1,2,2-trimethylpropyl) -6,14-endoethano-6,7,8,14-tetrahydro-nororipavine hydrochloride) is one of the partial agonist group of drugs. In animals it seems to have a low physical dependence liability (Cowan, Lewis and MacFarlane, 1977) and minimal effects on the cardiovascular system (Cowan, Doxey and Harry, 1977). In clinical use it has been shown to be an effective analgesic, with a dose of buprenorphine 0.3 mg being approximately equianalgesic to morphine 10 mg. Its duration of action appeared longer than morphine but cardiovascular and respiratory side-effects were similar (Hovell and Ward, 1977).

Pentazocine, (1, 2, 3, 4, 5, 6-hexahydro-6,11-dimethyl-3-(3-methylbut-2-enyl)-2,6-methano-3-benzazocin-8-ol) a benzomorphan derivative has been widely used in clinical practice. A review of the literature by Potter and Payne (1970) confirmed that, while the drug has good analgesic activity, there is no universal agreement as to the dose of pentazocine which is equianalgesic to morphine 10 mg; the suggested dose varies from 20 to 60 mg. It has been suggested that pentazocine has less respiratory depressant effects than morphine (Jennett, Barker and Forrest, 1968), but it is difficult to assess claims in this respect as the true equianalgesic dose is not yet known. Pentazocine has been found to have very limited dependence liability, but in large doses it has been associated with unpleasant dreams and hallucinations (Hamilton et al., 1967).

This trial was performed to determine the suitability of drugs of the partial agonist group for use in a patient demand system, and to derive estimates of the relative analgesic efficacy of pentazocine and buprenorphine.

METHODS

The patients were those presenting for cholecystectomy with no complications, aged between 16 and 75 yr and not pregnant. The trial was conducted double-blind, patients being randomly allocated into matched groups of 10, to receive one of the analgesics for 24 h after operation. The analgesic was administered i.v. by a patient-controlled syringe pump (Evans et al., 1976), available as the Cardiff Palliatior.

Each patient was visited on the day before surgery to obtain informed consent and instructed in the use of the apparatus. They were also introduced to the concept of the linear analogue (Revill et al., 1976) which was to be used to record pain and other subjective sensations.

The patients were premedicated with diazepam (approximately 0.15 mg kg⁻¹) administered orally 1–2 h before operation. Anaesthesia was induced with i.v. thiopentone, endotracheal intubation facilitated using suxamethonium or a non-
depolarizing relaxant and the patients were ventilated with nitrous oxide, oxygen and halothane supplemented with up to 0.2 mg of fentanyl. At the end of the operation residual neuromuscular blockade was antagonized using atropine and neostigmine.

On arrival in the recovery ward the Cardiff Palliator was connected to the patient's i.v. infusion using a valved Y-connector (Rosen and Williams, 1979). The Palliator was set to deliver an incremental dose of 1 ml of analgesic solution at a minimum interval of 10 min between demands. The analgesic solutions used were buprenorphine 0.09 mg ml\(^{-1}\) and pentazocine 20 mg ml\(^{-1}\).

On awakening and requesting analgesia the patient was given the demand control and reminded how to use it. Patients were kept in the recovery ward until proficient in the use of the Palliator and then returned to the surgical ward, to continue taking analgesics as required. Arterial pressure, heart rate and respiratory rate were recorded as usual by ward staff. Metoclopramide 10 mg i.m. was prescribed for any patient who complained of nausea or vomited, and an alternative i.m. analgesic regime was provided in case of rejection of the "on demand" system.

Between 2 and 4 h after operation the patients were visited on the ward by a research nurse, assessed with regard to their physical and conscious states, and questioned as to the degree of pain, dizziness, nausea and change of mood. At 24 h after operation, patients were again visited and asked to mark linear analogues representing overall pain, dizziness, drowsiness, and nausea. The placement of a mark on the linear analogue was to represent the patient's average degree of sensation over the whole 24 h. At this visit patients were also questioned directly concerning pain and the occurrence of unpleasant dreams. The Palliator was then removed and the patient prescribed a standard analgesic to be given i.m. when required.

Mean score and SEM were calculated for each set of linear analogues and results for the two drugs compared using the Mann-Whitney U test to estimate statistical significance. Qualitative and non-continuous data were analysed with Fisher Exact Probability and Mann-Whitney U tests as appropriate.

### RESULTS

The patients included in this comparison consisted of 14 females and six males. The full details of each patient are shown in Table I.

The number of demands made in the 24 h and the quantity of drug used by each group of patients are shown in Table II.

The 2-4 h observations consisted of assessing conscious level on a 1-4 scale (1 representing fully awake) and noting the presence of sweating, pallor, retching or wincing. Patients were also questioned regarding pain, dizziness, nausea and mood change, using a 1-5 scale for degree (1 representing no pain and 5 very severe pain). The 2-4 h assessment scores were compared and showed no significant differences between the patients receiving buprenorphine and those receiving pentazocine.

The linear analogue obtained at 24 h for each

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### Table I. Patient details (all patients underwent uncomplicated cholecystectomy). *Fentanyl 0.1 mg; **metoclopramide 10 mg administered after operation

<table>
<thead>
<tr>
<th>No.</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Wt (kg)</th>
<th>Analgesia during operation*</th>
<th>Total dose (mg)</th>
<th>Analgesia during operation*</th>
<th>Total dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUPRENORPHINE</td>
<td>PENTAZOCINE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>64</td>
<td>F</td>
<td>63</td>
<td>None</td>
<td>1.89</td>
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<td>60</td>
<td>None</td>
<td>2.24</td>
<td>None</td>
<td>2.24</td>
</tr>
<tr>
<td>3</td>
<td>24</td>
<td>F</td>
<td>59</td>
<td>None</td>
<td>1.44</td>
<td>None</td>
<td>1.44</td>
</tr>
<tr>
<td>4**</td>
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<td>F</td>
<td>59</td>
<td>None</td>
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<tr>
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<td>44</td>
<td>F</td>
<td>59</td>
<td>None</td>
<td>0.63</td>
<td>None</td>
<td>0.63</td>
</tr>
<tr>
<td>6</td>
<td>52</td>
<td>M</td>
<td>65</td>
<td>Fentanyl</td>
<td>2.52</td>
<td>None</td>
<td>2.52</td>
</tr>
<tr>
<td>7</td>
<td>20</td>
<td>F</td>
<td>82</td>
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<td>2.07</td>
</tr>
<tr>
<td>8</td>
<td>61</td>
<td>M</td>
<td>68</td>
<td>Fentanyl</td>
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</tr>
<tr>
<td>10**</td>
<td>51</td>
<td>F</td>
<td>59</td>
<td>Fentanyl</td>
<td>0.81</td>
<td>None</td>
<td>0.81</td>
</tr>
<tr>
<td>Mean</td>
<td>45</td>
<td>65</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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BUPRENORPHINE AND PENTAZOCINE FOR ON DEMAND ANALGESIA

sensation ranged from none at one end to the greatest imaginable degree at the other. The subject of each analogue and the results, expressed as a percentage of the whole line, are shown in table III.

Analysis of linear analogue scores by non-parametric testing showed that the degree of analgesia and frequency of side-effects were not different for the two drugs. Both groups showed a reasonably high degree of drowsiness.

In addition to the linear analogue, patients were questioned directly as to the overall degree of pain felt, using a five-point scale ranging from no pain to very severe pain. A similar scale was used to assess unpleasant dreams. The dream and pain ratings were compared and there was no significant difference between the two groups (P<0.05).

From the collected data it was possible to calculate the mean analgesic consumption for selected intervals within the 24-h period. This information is presented in table IV.

**DISCUSSION**

The two groups of patients in this double-blind trial were similar with respect to age, weight, sex and operation. The degree of analgesia which each group attained, as assessed by the linear analogue, was again similar and comparable to previous studies using an on demand analgesic system (Chakravarty et al., 1979). The mean analgesic linear analogue score for buprenorphine was 33.5±9.5 (mean±SEM) compared with 36.6±6.5 for pentazocine. These linear analogue scores represent good levels of analgesia, and are lower than those reported by similar patients receiving staff-administered i.m. analgesics (Slattery et al., 1982).

Analysis of the frequency of side-effects showed no significant difference between the two groups, both drugs appeared to cause a similar moderate degree of drowsiness but we were unable to confirm the occurrence of dysphoric phenomena associated with large doses of pentazocine (Hamilton et al., 1967). The frequency of nausea and vomiting was low in both groups and would have had little influence on analgesic consumption.

Any trial comparing different analgesic drugs has the problem of setting parameters so that groups may be assessed in a uniform manner. The choice, basically, is between using a set dose regime and then accurately measuring the response (a difficult procedure as pain, nausea, dizziness and dysphoria are subjective sensations), or producing a comparable response in all patients and using the amount of each drug required and the frequency of side-effects to compare the effectiveness of the drugs.

If an on demand analgesic system is used, then within the limits of efficacy of the drugs used, all patients are able to achieve optimal pain relief, where the concept of optimal pain relief relates to a compromise between the desirable (analgesic) effects of a drug and the undesirable (emetic and dysphoric) effects.

If patients using different drugs are generally similar with respect to operation type (and hence degree of pain) then the amount of analgesic consumed per unit time will provide an index of relative “potency”, where potency is defined in terms of the amount of analgesic needed to produce a desired...
TABLE V. Equianalgesic doses of studied drugs given i.v. on demand

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine</td>
<td>0.27 mg</td>
</tr>
<tr>
<td>Pentazocine</td>
<td>60 mg</td>
</tr>
<tr>
<td>Pethidine</td>
<td>100 mg</td>
</tr>
<tr>
<td>Meptazinol</td>
<td>240 mg</td>
</tr>
</tbody>
</table>

The relative doses derived in this manner for buprenorphine, pentazocine and pethidine are consistent with previously published estimates established from extensive clinical trials (Jaffe and Martin, 1980).

This agreement between analgesic potencies of established drugs found in our studies and those derived by extensive clinical usage suggests that an on demand system may provide a relatively rapid method of screening analgesic potencies of newer agents.

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REFERENCES


COMPARAISON ENTRE BUPRENORPHINE ET PENTAZOCINE ADMINISTREE PAR VOIE INTRAVEINEUSE SUR LA DEMANDE DANS LE CONTROLE DE LA DOULEUR POST-OPERATOIRE

RESUME

Une comparaison en double aveugle entre buprénorphine et pentazocine a été effectuée chez 20 patients en utilisant un système d'analgesie à la demande pour fournir une analgésie post-opératoire. La qualité de l'analgesie, estimée subjectivement, était bonne avec les deux produits et les consommations médicamenteuses étaient compatibles avec les estimations antérieures de puissance. Les doses moyennes demandées en 24 h de buprénorphine (1,68 mg) et de pentazocine (382 mg) étaient compatibles avec celles retrouvées dans d'autres études bien que les différences individuelles s'entretiennent d'un ordre de grandeur de cinq ou six fois. Il n'y a pas eu de différences significatives dans les effets secondaires entre les deux groupes. La buprénorphine et la pentazocine peuvent être utilisées avec succès dans un système d'administration à la demande pour soulager des douleurs post-opératoires sévères.

VERGLEICH ZWISCHEN BUPRENORPHIN UND PENTAZOZIN, DAS BEI BEDARF I.V. VERABREICHT WURDE, BEI DER BEHANDLUNG VON POSTOPERATIVEN SCHMERZEN

ZUSAMMENFASSUNG

COMPARACIÓN ENTRE LA BUPRENORFINA Y LA PENTAZOCINA ADMINISTRADAS I.V. SOBRE PEDIDO EN EL CONTROL DE LOS DOLORES POSTOPERATORIOS

SUMARIO

Se llevó a cabo una comparación doble-ciega entre la buprenorfina y la pentazocina en 20 pacientes al usar un sistema analgésico sobre pedido para proveer analgesia después de una operación. La calidad de la analgesia, evaluada subjetivamente, fue buena con ambas substancias y los consumos de las mismas fueron compatibles con las cifras estimadas previas de potencia. Las dosis medias durante 24 h de buprenorfina (1,68 mg) y de pentazocina (382 mg) son compatibles con las recogidas durante otros ensayos aunque la variación entre pacientes era de cinco a seis veces mayores. No hubo diferencia significativa en los efectos secundarios en ambos grupos. La buprenorfina y la pentazocina pueden usarse con éxito en un sistema sobre pedido para proveer un alivio de los dolores agudos después de una operación.