DOUBLE-BLIND COMPARISON BETWEEN DOXAPRAM AND PETHIDINE IN THE TREATMENT OF POSTANAESTHETIC SHIVERING

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SUMMARY

Sixty patients who shivered after routine surgery under general anaesthesia were allocated randomly to receive normal saline (n = 20), doxapram 1.5 mg kg\(^{-1}\) (n = 20) or pethidine 0.33 mg kg\(^{-1}\) (n = 20). Both doxapram and pethidine were effective in treating postoperative shivering 2–3 min after i.v. administration. In the group who received normal saline, 15 patients were still shivering 10 min after treatment, whilst in the doxapram group only three patients were shivering at that time. In the pethidine group, all patients had stopped shivering by 7 min after treatment. We conclude that both doxapram and pethidine were effective in the treatment of postoperative shivering.

KEY WORDS


Postanaesthetic shivering is a common phenomenon with a reported incidence varying from 5 to 65% [1-8]. It is important to prevent or treat postoperative shivering because of the distress it causes and the consequences involved, which may include an increase in metabolic rate of up to 400%, arterial hypoxaemia, lactic acidosis, increased intraocular pressure and difficulty in monitoring [5, 6, 9-11]. It has been shown that suppression of shivering decreases oxygen consumption and improves haemodynamic stability in the postoperative period [12].

Among the pharmacological methods of treating shivering, pethidine has been shown consistently to be effective [12-14]. Recently, Sarma and Fry found doxapram was effective [15], but there are no studies which compare doxapram with pethidine. In this study, we have compared the effectiveness of pethidine and doxapram in a placebo-controlled, double-blind manner.

PATIENTS AND METHODS

The study was approved by the local hospital Ethics Committee. We studied 60 patients (both genders), ASA I or II, who had undergone routine orthopaedic or otolaryngological surgery and developed shivering within 10 min of admission to the recovery room. As a consequence of the patients being selected as they were recovering from anaesthesia, their consent was not considered valid, and with the agreement of our Ethics Committee we did not obtain informed consent. Those patients with a history of hypertension, coronary artery disease, other cardiorespiratory or neuromuscular pathology were excluded.

Patients received the routine care undertaken for postoperative shivering in this hospital: they received oxygen by face mask and were covered by a heat-reflective blanket. In addition, each patient received an i.v. injection of doxapram 1.5 mg kg\(^{-1}\), pethidine 0.33 mg kg\(^{-1}\) or normal saline from identical syringes according to the randomization. All syringes were prepared by recovery nursing staff following written instructions removed from a sealed envelope.

The investigator who gave the i.v. injection was unaware of the treatment received by the patient, and assessed the shivering grade (table I) before (time 0) and then at every subsequent 1 min after treatment for 10 min. To limit between-observer bias, the number of investigators assessing the shivering grade was restricted to two (P.S. and V.D.). Each assessed an equal number of patients from all three groups. Oxygen saturation, heart rate and arterial pressure were recorded before and every 1 min after treatment for 10 min. Axillary temperature was measured immediately before the treatment was administered. Surgical procedure, duration of anaesthesia and anaesthetic technique were recorded for each patient.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Clinical signs</th>
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<tbody>
<tr>
<td>0</td>
<td>No shivering.</td>
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<tr>
<td>1</td>
<td>One or more of: piloerection, peripheral vasoconstriction, peripheral cyanosis without other cause, but without visible muscular activity.</td>
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<tr>
<td>2</td>
<td>Visible muscular activity confined to one muscle group.</td>
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<tr>
<td>3</td>
<td>Visible muscular activity in more than one muscle group.</td>
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<tr>
<td>4</td>
<td>Gross muscular activity involving entire body.</td>
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Statistical analysis was performed using ANOVA for evaluation of homogeneity of groups, by comparison of means between the different treatment groups with regard to age, weight, duration of anaesthesia, heart rate and arterial pressure. For comparison of gender, anaesthetic drugs, mode of ventilation and shivering between groups, chi-square test was used.

### RESULTS

The three groups were comparable with regard to age, weight and gender (table II). There were no statistically significant differences in the duration of anaesthesia, mode of ventilation, use of volatile inhalation agents or the use of intraoperative opioids between the three groups (table III), and no statistically significant difference in axillary temperature or shivering grade between the groups at the time of entry into the study. The temperature range for patients in the saline group was 35.6-37.7 °C, in the doxapram group 35.2-37.0 °C and in the pethidine group 34.8-37.5 °C. There was a preponderance of shivering grades 3 and 4 in all groups.

The effect of treatment may be seen in figure 1 and table IV. There was a statistically significant difference between groups in incidence and severity of shivering: $\chi^2 = 9.40$, $P < 0.01$ and $\chi^2 = 16.65$, $P < 0.05$, respectively at 2 min after treatment and $\chi^2 = 19.8$, $P < 0.001$ and $\chi^2 = 34.77$, $P < 0.001$, respectively at 3 min after treatment, remaining so until the end of the study.

Fifteen patients (75%) in the saline group and three patients (15%) in the doxapram group were still shivering 10 min after treatment, whilst all patients stopped shivering at 7 min after treatment with pethidine. Throughout the study, more patients shivered in the doxapram group than in the pethidine group, although this was significant only at 3 min and 7 min after treatment ($\chi^2 = 5.23$ and 4.44 respectively, $P < 0.05$ at both times). No patient who was successfully treated subsequently returned to shivering during the study period.

### DISCUSSION

Our results indicate that both doxapram and pethidine were effective in treating postoperative shivering. Pethidine had a significantly better success
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rate at 3 and 7 min after administration of treatment, with a success rate of 100%, compared with 85% for doxapram.

Shivering grade 1 was not an exclusion criterion, but there were no patients of shivering grade 1 entered into the study. Their absence may be explained by two possible mechanisms. It is possible that grade 1 represents a stage of recovery from postoperative shivering, so that patients who are stopping shivering after operation (either spontaneously or secondary to treatment) pass through this stage before they ultimately stop shivering. This view is supported by data from a previous study [8]. An alternative explanation may be that grade 1 is easy to miss unless it is specifically sought.

The aetiology of postanaesthetic shivering remains inadequately understood. This has led to various suggestions regarding the possible mechanisms and the mode of therapy. Amongst the suggested mechanisms are uninhibited spinal reflexes [4], pain [16], decreased sympathetic activity [17], adrenal suppression [7] and a normal thermoregulatory response to intraoperative heat loss [7, 18]. It has also been appreciated that shivering may not always be related to hypothermia in the postoperative period [19, 20].

A variety of drugs have been used to control postanaesthetic shivering, including methylphenidate [21], orphenadrine [22], magnesium sulphate [23], pancuronium [5] and various opioids [12—14]]. It has been suggested that postoperative shivering is perhaps a result of differential recovery of various neuronal centres after discontinuing the anaesthetic—spinal activity recovering earlier than the higher inhibitory centres, resulting in uninhibited spinal activity in the form of rigidity and clonic spontaneous tremor [4, 21, 24, 25]. This theory is substantiated by the successful use of a cerebral stimulant such as methylphenidate, which may enhance recovery of the brain from depression by anaesthetic agents and thereby establish normal control over spinal reflex activity [21]. Sarma and Fry [15] found that doxapram, another cerebral stimulant, was effective in treating postoperative shivering in 73% of patients. Fifty percent of their patients stopped shivering in less than 1 min after i.v. injection of doxapram 100 mg. In the present study, 85% of patients treated with doxapram stopped shivering within 10 min of administration. Success rates of 50% and 75% occurred at 3 and 5 min, respectively, compared with only 10% at both times after treatment with saline. Our study confirms the effectiveness of doxapram in treating postoperative shivering, but differs from the earlier study in its time course. We are unable to comment on this difference, as Sarma and Fry [15] did not grade shivering according to severity and their patients may therefore have been different from ours with regard to the severity of shivering at the time of entry into the study.

Doxapram is known to stimulate the respiratory centre, whilst pethidine may cause respiratory depression, although none of our patients had clinically obvious respiratory depression. All of the patients in the study maintained an oxygen saturation greater than 94%, but all were receiving oxygen via a Hudson mask as a part of their routine care. Doxapram may also transiently increase heart rate and arterial pressure. We did not compare circulatory variables after treatment in the three different groups because of the questionable reliability of non-invasive cardiovascular measurements in shivering patients [11]. However, none of the patients in the doxapram group had a clinically significant episode of hypertension as defined as a diastolic arterial pressure greater than 100 mm Hg.

It is difficult to find an appropriate explanation for the effectiveness of pethidine in treating postoperative shivering. It has been reported as effective in treating shaking chills associated with amphotericin B, and granulocyte and platelet infusions [26]. It has also been shown to control shivering in patients undergoing Cesarean section under extradural anaesthesia, by either i.v. [27] or extradural routes [28]. After general anaesthesia, Claybon and Hirch [13] reported that, after general anaesthesia, pethidine 25 mg arrested shivering within 5 min in 73% of patients. Later, it was shown to be superior to both morphine and fentanyl in this respect [14]. A more recent study shows that 11 of 14 patients stopped shivering within 5 min after pethidine 25 mg i.v., and that pethidine was effective in reducing the increased metabolic demand of shivering [12]. Our results agree with these studies, in demonstrating the effectiveness of pethidine and suggest that pethidine may be marginally superior to doxapram in this respect. However, in the absence of full dose—response curves to both agents, we have no direct evidence that each drug was administered in optimal doses.

REFERENCES


