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A randomized, double-blind, placebo-controlled trial comparing pethidine to metamizol for treatment of post-anaesthetic shivering

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1 Shivering is frequent during the post-anaesthetic recovery period, and there is no clear consensus about the best strategy for its treatment. We tested the efficacy of two commonly used analgesic drugs, pethidine and metamizol.

2 A randomized, double-blind, placebo-controlled clinical trial was performed, including 104 adult patients who presented with post-anaesthetic shivering during the recovery from general anaesthesia. They were randomized to receive placebo ($n=32$), metamizol 25 mg kg^{-1} ($n=37$), or pethidine 0.4 mg kg^{-1} ($n=35$). The response to treatment was assessed 5, 15 and 45 min after drug administration, and the main outcome variable was complete suppression of shivering.

3 The efficacy at 5, 15 and 45 min was as follows: placebo 6%, 16% and 37%; metamizol 13.5%, 32% and 76%, and pethidine 89%, 91% and 89%. With both active drugs the efficacy at all three time intervals was significantly higher than that with placebo ($P<0.05$). The differences (at 5 and 15, but not at 45 min) between pethidine and metamizol were statistically significant ($P<0.05$). Both drugs were well tolerated.

4 The persistence of shivering at 45 min in two thirds of placebo-treated patients indicates that drug treatment is worthwhile; metamizol produces a better post-anaesthetic shivering response than placebo, especially 15 and 45 min after drug administration; the efficacy of pethidine was the highest and the response to it appeared more quickly; however, at 45 min it was similar to that observed with metamizol.

5 Both metamizol and pethidine suppress postanaesthetic shivering, but the latter induces a quicker and more reliable response.

Keywords postanaesthetic shivering recovery pethidine metamizol placebo trial

Introduction

Post-anaesthetic shivering (also called post-anaesthetic tremor) is a rhythmic oscillating movement, predominantly of upper limbs, neck and jaw, that can ensue in 20–40% of patients recovering from anaesthesia [1, 2]. Its main consequences are an increase of oxygen consumption and of CO_2 production, and tachypnea [3–6]. Other consequences are an increase of intraocular pressure, interference with monitoring of blood pressure and ECG, and general discomfort with a sensation of feeling cold [2, 7, 8].

Although hypothermia caused by anaesthetic procedures is the most frequently quoted risk factor, pre-anaesthetic stress, uncontrolled pain, opiate withdrawal, fever, blood loss, duration of the surgical procedure, and pyrogen and bacterial liberation have also been implicated [1, 2, 9–11]. As preventive measures are difficult to implement, various therapeutic approaches have been studied, in addition to oxygen therapy and

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warming measures [8, 12–15]. Although the efficacy of muscle relaxants, methylphenidate, vasodilators, ketanserin, opiates and other drugs has been studied [2, 5, 16–21], conclusions about which is the best therapeutic strategy are difficult, because scarce comparative data between the different drugs are available, and few patients have been included in controlled trials.

Although to date pethidine is the best studied drug in the treatment of post-anaesthetic shivering, comparative trials with non-opioid drugs have not been performed. In addition, its optimal dose has not been established; the usual recommendation of low dosages is based on the results of small trials [20]. Metamizol is an analgesic and antipyretic drug that does not have any antiinflammatory effect at usual doses. It does not exert the gastrointestinal effects typical of NSAIDs [22]. We therefore performed a double-blind, randomized clinical trial to assess and compare the efficacy of very low doses of pethidine and analgesic doses of metamizol in the treatment of post-anaesthetic shivering.

Methods

The protocol was approved by the Hospital Ethics Committee and by the Directorate General of Medicinal and Health Products (Ministry of Health).

Inclusion criteria were low risk adult patients (level I–II in ASA classification [23]) who presented with continuous post-anaesthetic shivering for 5 min or longer, during activity and at rest, in the first hour of recovery of general anaesthesia. Excluded were patients with one or more of the following: hyperthyroidism, insulin-dependent diabetes mellitus, hypersensitivity to metamizol, those pregnant and those under treatment with propranolol, opiates, theophylline, or sympathomimetics.

All patients were subject to a standard pre-operative evaluation. After written informed consent had been obtained from those eligible before the anaesthetic procedure, individuals who complied with the inclusion criteria were randomized to receive either pethidine ($0.4\ mg\ kg^{-1}$), metamizol magnesium ($25\ mg\ kg^{-1}$), or placebo. The study was double-blind. The level of preoperative stress was assessed on a three level scale based on the method described by Ramsay [24], in the operation theatre and prior to the administration of intravenous premedication.

Anaesthesia was standardized as follows: (1) intravenous premedication with midazolam $0.04\ mg\ kg^{-1}$, fentanyl $1.2\ \mu g\ kg^{-1}$, and atropine $0.01\ mg\ kg^{-1}$, (2) induction with thiopentone 4-5 $mg\ kg^{-1}$ and atracurium $0.5\ mg\ kg^{-1}$, and (3) maintenance with oxygen 40%, nitrous oxide 60%, isoflurane 0.5–1%, fentanyl 2–4 $\mu g\ kg^{-1}\ h^{-1}$, and atracurium 0.5–1 $mg\ kg^{-1}\ h^{-1}$.

Fluid therapy was carried out with fluids previously mantained at 21–24° C according to Miller's guide [25]. To reverse muscle relaxation all patients received neostigmine ($0.04\ mg\ kg^{-1}$) in combination with atropine ($0.02\ mg\ kg^{-1}$). Occasionally naloxone (a 0.04 mg dose repeated as needed) was administered when patients presented signs of respiratory depression. The operating theatre was maintained at 21–23° C and room humidity was around 60–70%.

The severity of post-anaesthetic shivering was measured at 5, 15, 30, and 45 min after the administration of the tested regimens. Shivering or tremor severity was classified as follows: 0 (absent), 1 (present only in action), and 2 (present in action and at rest). Shivering response was assessed as follows: null (shivering intensity not changed), improvement (shivering intensity decreased or changed from a continuous pattern to an intermittent one), and disappearance (absence of shivering). The presence of fasciculations in face, neck, trunk and limbs was recorded. All patients were asked about sensation of feeling cold. We also recorded any event (mainly haemodynamic, neurologic or respiratory) that could be related to one of the drugs under study.

The number of patients ($n = 90$) to be included in the trial was calculated by assuming an alpha error of 0.05, power of 0.80, placebo response of 10% at 5–15 min, pethidine response of 80% at 5–15 min, and metamizol response of 40% at 5–15 min. Results were analyzed with the chi-square test and ANOVA for continuous variables. The Kruskall-Wallis test was applied to look at differences in the duration of the surgical procedure.

Results

Five hundred patients undergoing general anaesthesia were approached to obtain their informed consent and followed up, of whom 215 had post-anaesthetic shivering. Of these, 104 fulfilled the inclusion criteria and were included in the trial. The surgical procedures were mainly orthopaedic, general and gynaecological surgery. The baseline characteristics of the three groups did not differ significantly (Table 1).

Five minutes after drug administration, post-anaesthetic shivering had partially or totally disappeared in 97% of patients in the pethidine group, in 38% of those in the metamizol group, and in 16% of those in the placebo group (Table 2). However, at 45 min the response to both pethidine and metamizol was similar, and consistently better than that to placebo; the results at 15 and 30 min were intermediate (Table 2). Both pethidine and metamizol produced better results than placebo, but metamizol had a more gradual effect (Figure 1).

Fasciculations were present in 49 patients (47% of the whole study population) and the response of each of the three groups was very similar to that observed for post-anaesthetic shivering (an earlier and greater response to pethidine and an intermediate and delayed response to metamizol). Sensation of feeling cold was present in 67 patients (64% of the whole study population) and a significant improvement was observed only in the pethidine group—at 45 min coldness persisted only in 17% of the patients treated with pethidine,

Table 1 Patients' baseline characteristics. No statistical differences ($P > 0.05$) between the three groups were observed

	Placebo (n = 32)	*Metamizol* (n = 37)	*Pethidine* (n = 35)
Age (years) [mean (s.d.)]	46 (18)	42 (18)	45 (16)
Sex (female), *n* (%)	16 (50)	20 (54)	19 (54)
Weight (kg) [mean (s.d.)]	61 (10)	64 (11)	66 (11)
Preoperative stress, level 1, *n* (%)	9 (28)	10 (27)	12 (34)
Duration of surgery, min, median (range)	105 (30–195)	105 (40–240)	90 (45–240)
Use of naloxone during the anaesthetic procedure, *n* (%)	8 (25)	11 (28)	9 (26)

Table 2 Response of post-anaesthetic shivering (PAS) at 5–45 min

PAS response	*Null effect* n (%)	*Improvement* n (%)	*Disappearance* n (%)	*Total* n
5 min[a]				
Placebo	27 (84.4)	3 (9.4)	2 (6.2)	32
Metamizol	23 (62.2)	9 (24.3)	5 (13.5)	37
Pethidine	1 (2.9)	3 (8.6)	31 (88.6)	35
15 min				
Placebo	21 (65.6)	6 (18.8)	5 (15.6)	32
Metamizol	12 (32.4)	13 (35.2)	12 (32.4)	37
Pethidine	3 (8.6)	0 (0)	32 (91.4)	35
30 min				
Placebo	15 (46.8)	6 (18.8)	11 (34.4)	32
Metamizol	4 (10.8)	10 (27.0)	23 (62.2)	37
Pethidine	3 (8.6)	3 (8.6)	29 (82.8)	35
45 min[b]				
Placebo	9 (28.1)	11 (34.4)	12 (37.5)	32
Metamizol	2 (5.4)	7 (18.9)	28 (75.7)	37
Pethidine	0 (0)	4 (11.4)	31 (88.6)	35

[a]The differences between the three groups were statistically significant; the metamizol group showed better response than the placebo group (Chi-square test; $P = 0.03$), but the pethidine group showed the highest response (Chi-square test *vs* placebo and *vs* metamizol; $P < 0.001$).

[b]The differences between the three groups were statistically significant; metamizol and pethidine ellicited a better response than placebo (Chi-square; $P < 0.005$), but there were no significant differences between both drugs (Chi-square test; $P = 0.16$).

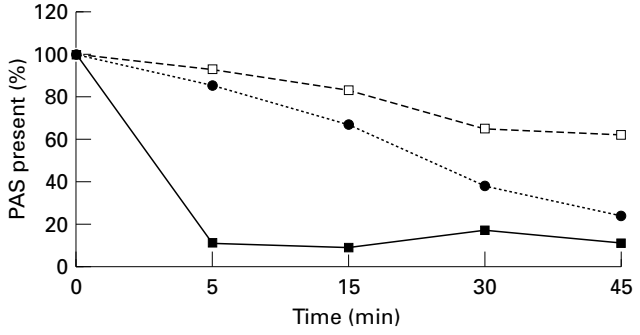

Figure 1 Time response to treatment (■ pethidine; ● metamizol; □ placebo). Post-anaesthetic shivering (PAS) was considered to be present if a null effect or a partial response to treatment were recorded.

compared with 40% in the metamizol group and 48% in the placebo group.

Regarding adverse events, there were no differences between the three groups in blood pressure or heart rate during the follow-up period. Slight CNS depression was recorded in five patients (four in the pethidine group, one in the metamizol group). An episode of bradypnoea which did not need any specific action was recorded in one patient of the pethidine group. Two patients in the pethidine group had nausea and vomiting.

Discussion

We have shown that two simple and easy to implement therapeutic measures are effective for the treatment of

post-anaesthetic shivering. Previous well controlled trials on this condition had not involved direct comparisons between different regimens. Our findings are important because post-anaesthetic shivering is common among patients undergoing standard general anaesthesia. In addition, both pethidine and metamizol are established effective drugs for the treatment of post-operative pain.

Post-anaesthetic shivering improved spontaneously in the placebo group. However, at 45 min tremor was still present in 62% of these patients, indicating the need for drug treatment.

The therapeutic response was greater and of more rapid onset in the pethidine group. Our results are slightly better than those described in other studies [18–20]; these differences could be related to the anaesthetic technique. On the other hand, metamizol magnesium at doses of 25 mg kg^{-1}, produced a better response than placebo, especially at 30 and 45 min. The efficacy of metamizol magnesium in the treatment of shivering may be related to the analgesic action of metamizol and/or to the spasmolytic action of magnesium [17]; the delayed onset of its effect could be because metamizol acts through active metabolites [26]. Both pethidine and metamizol were well tolerated, even though some non-severe and well known adverse effects were recorded in the group treated with pethidine.

The response of fasciculations was very close to that of post-anaesthetic shivering; this is probably because fasciculations are a nonspecific accompanying sign of muscle hyperactivity. A sensation of cold was present in a large number of patients with post-anaesthetic shivering; at 45 min it persisted in 48% of placebo-treated patients, in spite of using cotton blankets. With pethidine, a good response was achieved, but not in all patients. This underlines the need to apply active warming for the comfort of the patient.

Post-anesthetic shivering is frequent and difficult to prevent. It can produce a number of unfavourable respiratory and haemodynamic changes. Our results indicate that it can be treated specifically, at least in high risk patients. Pethidine in low doses is highly effective, but it needs medical supervision. Metamizol magnesium at usual analgesic doses is an effective alternative due to the low incidence of adverse effects [22, 28].

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