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Temporal factors in the enhancement of morphine analgesia by desipramine

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Summary Administration of desipramine, the tricyclic noradrenergic agent, for 7 days pre-operatively, had been found to potentiate postoperative morphine analgesia. In this study we investigated the necessary timing of administration of desipramine in its action to potentiate morphine analgesia. We report that the administration of desipramine for only 3 days, starting 7 days before surgery, also potentiated postoperative morphine analgesia and that the analgesia observed was not different from that in patients receiving a full 7 days of desipramine pre-operatively. The potentiation of morphine analgesia observed was most evident as a prolongation of the analgesic response. Patients who also received desipramine for only 3 days, but starting 3 days pre-operatively had an analgesic response to postoperative morphine that was the same as that in patients receiving placebo. The ability of the administration of desipramine early in the pre-operative week to interact with postoperative morphine and the lack of response when desipramine was given late in the week does not have an explanation at present. However, it may reflect the known latency in humans to the onset of the central effects of tricyclic antidepressants (TCAs).

Key words: Tricyclic antidepressant; Postoperative pain; Opiate analgesia; Noradrenergic; Desipramine

Introduction

Numerous agents have been used in combination with opiate analgesics to produce enhanced analgesia (Levine and Gordon 1988a; Levine et al. 1988b; Hasenbusch et al. 1991; Hogan et al. 1991; Lema et al. 1992; Taiwo et al. 1991). For example, in the study of combinations of adrenergic agents and opiates, it has been found that amphetamine and clonidine can enhance opiate analgesia while ephedrine does not (Ivy et al. 1944; Forrest et al. 1977; Levine et al. 1986; Gordon et al. 1992). We recently looked at the ability of 2 tricyclic antidepressants (TCAs) amitriptyline (a rela-

tively selective serotonin uptake inhibitor) and desipramine (a relatively selective noradrenaline uptake inhibitor) to enhance opiate analgesia in patients with postoperative pain. Although these agents have been found to exert an analgesic effect when administered alone in the setting of chronic pain (Walsh and Davis 1983), we found that in the presence of subacute postoperative pain, specifically, pain during a 6 h period immediately after dental surgery, neither agent given alone, daily for a week preceding surgery, resulted in analgesia (Levine et al. 1986). However, desipramine, but not amitriptyline, increased and prolonged morphine analgesia in the postoperative period. Animal studies have shown that opiate-tricyclic interaction is complex: single-dose administration of TCAs in general enhances opiate-induced analgesia (Kellstein et al. 1984, 1988; Sacerdote et al. 1987; Ventafridda et al. 1990) while chronic administration in general antagonizes opiate-induced analgesia (Fialip

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et al. 1986; O'Neill and Valentino 1986; Kellstein et al. 1988; Goldstein et al. 1990). The specific mechanisms underlying the interactions between TCAs and opiates as well as an explanation for the difference between the animal and human studies are not known. The TCAs are believed to influence opiate analgesia by influencing the endogenous pain control circuits, which are complex circuits through which opiates act. The circuits depend on noradrenergic and serotonergic mechanisms (Basbaum and Fields, 1984).

Since it is known that some of the actions of TCAs appear with a significant delay after the initiation of daily administration, we studied the effect of varying the schedule of the pre-operative administration of desipramine on the enhancement of morphine analgesia. We report that, as previously described (Levine et al. 1986), 7-day pre-operative administration of desipramine enhanced morphine analgesia but that administration for the 3 days immediately preceding surgery resulted in no enhancement of morphine analgesia. On the other hand, administration for only 3 days, but starting 1 week before surgery, resulted in enhancement of opiate analgesia similar to that after administration of desipramine for a full week.

Methods

Sixty patients (33 male, 27 female; aged 23.6 ± 0.5 years old ($x \pm S.E.M.$) and weighing 143.6 ± 3.6 lbs.) underwent standardized surgery for the removal of impacted third molars after premedication with intravenous diazepam. The extent of surgical trauma was similar in all groups. All patients had removal of at least 1 bony impacted third molar, the procedure that is more commonly associated with moderately severe postoperative pain than maxillary or non-bony (i.e., soft tissue) impactions. The surgical procedure and the visual analogue scale (VAS) used for pain measurement have been described in detail elsewhere (Levine and Gordon 1984; Levine et al. 1988b). The VAS used in this study consisted of a 10-cm horizontal line on which the subject indicates the degree of pain with the words 'no pain' at the left end and 'worst pain imaginable' at the right end. During the surgery, patients received nitrous oxide and local anesthesia (carbocaine without vasoconstrictor to assure a short duration of nerve block). The duration of the surgery and experiment, measured from the onset of local anesthesia, was approximately 5 h.

One week before surgery patients were randomly assigned to receive either desipramine 50 mg QHS for 7 days; desipramine 50 mg QHS for the 3 days immediately preceding surgery; desipramine 50 mg QHS for 3 days starting 7 days pre-operatively; or placebo QHS for 7 days. (All patients received, double blind, 7 days of QHS medication, with oral placebo given as needed.) No patient chose to discontinue the TCA medication due to side effect and none reported a significant side effect, probably due to the low dose used. Pain was evaluated in the immediate postoperative period, up to 6 h after surgery. Pain ratings were made every 20 min starting immediately when the surgery was completed. Each patient received, via an indwelling intravenous line, a single blind, open injection of 6 mg morphine sulfate, given immediately after a pain rating of at least one-quarter (2.5 cm) of the VAS but no sooner than 80 min after the onset of local anesthesia.

Since baseline pain levels in the different groups did not differ significantly before opiate administration ($P > 0.05$ by 1-way

ANOVA), the magnitude of the morphine analgesia was defined as the change, at each time point, from the pain intensity before morphine administration. The magnitudes of the analgesic effect for the various drug treatments were evaluated using a 2-tailed Student's t test. Comparison between treatments was performed using a 2-factor (group, change in pain level), repeated measures (time) ANOVA (Zar 1984) and the Fisher's least squares difference post-hoc test (Fisher 1949).

Results

Patients who received placebo pre-operatively demonstrated a statistically significant analgesia after 6 mg of morphine sulfate ($P < 0.05$ by Student's t test), peaking at about 40 min postinjection, with a return to near baseline level at approximately 100–120 min postadministration (Fig. 1). As we had previously found (Levine et al. 1986), patients given 7 days of pre-operative desipramine showed a significant enhancement of

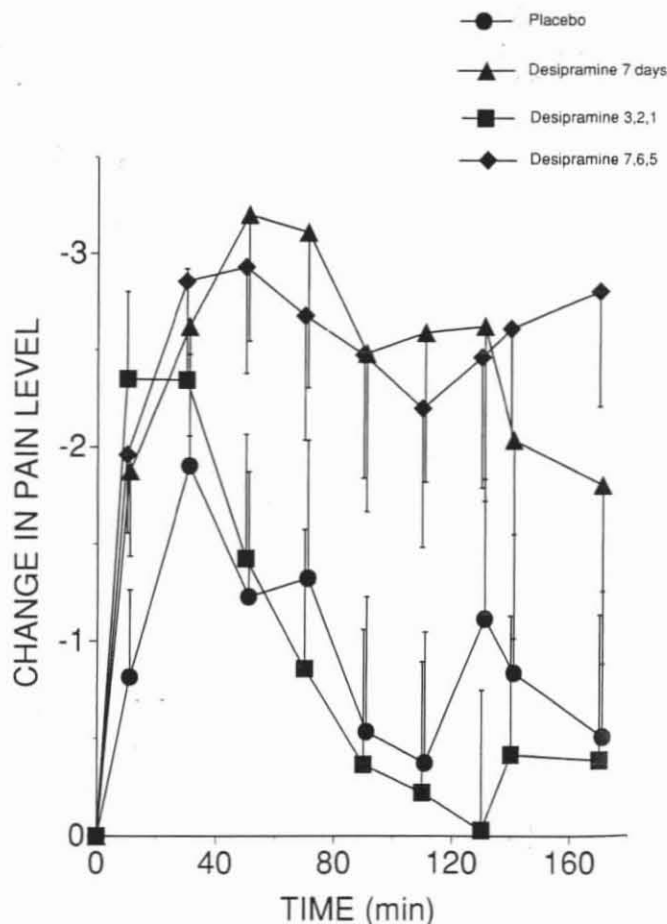


Fig. 1. Change in pain level measured on the VAS after the administration of 6 mg morphine (i.v.) at time 0 in postoperative dental patients who had previously received desipramine. ▲, patients who received 50 mg desipramine (p.o.) for 7 days pre-operatively; ■, patients who received 50 mg desipramine (p.o.) for the immediate 3 pre-operative days only; ◆, patients who received 50 mg desipramine (p.o.) for 3 days only, but starting 7 days pre-operatively; ●, patients who received placebo (p.o.) for 7 days pre-operatively.

TABLE I

INDIVIDUAL AVERAGE PAIN RELIEF SCORES (from Fig. 1) FOR CHANGE IN PAIN AFTER ADMINISTRATION OF THE i.v. AGENT (morphine)

Pre-surgery medication	Individual average pain relief scores
Placebo	-4.9, -2.9, -1.9, -1.8, -1.4, -1.4, -0.9, -0.7, -0.7, -0.6, -0.4, -0.3, +0.4, +0.6, +2.9
Desipramine 7 days	-6.6, -5.5, -4.9, -4.0, -4.1, -3.9, -2.6, -2.5, -2.2, -1.9, -1.2, -0.3, +0.2, +0.5, +1.9
Desipramine days 7, 6, 5	-7.9, -3.5, -3.4, -3.0, -3.0, -3.0, -2.7, -2.7, -2.5, -2.4, -2.3, -2.0, -1.4, +0.7, +0.8
Desipramine days 3, 2, 1	-4.5, -4.4, -4.2, -2.8, -0.9, -0.8, -0.8, -0.6, -0.2, -0.2, 0.0, +0.3, +1.0, +1.4, +2.6

morphine analgesia throughout the study period (Fig. 1; $P < 0.05$ by repeated-measures ANOVA with Fisher's least squares difference post-hoc test). Patients that received desipramine daily for 3 days, immediately preceding surgery, demonstrated analgesia after morphine that was similar to that of subjects receiving placebo pre-operatively (Fig. 1). Patients that received desipramine for only 3 days pre-operatively, but starting 7 days before surgery, demonstrated analgesia after morphine that was greater than after placebo ($P < 0.05$ by repeated-measures ANOVA with Fisher's least squares difference post-hoc test) and not different than that after 1 week of pre-operative treatment with desipramine ($P > 0.05$ by repeated-measures ANOVA with Fisher's least squares difference post-hoc test).

Patients that had received TCAs pre-operatively, compared to the placebo group, demonstrated significantly greater analgesia at the first measurement (10 min after i.v. morphine) ($P < 0.05$ by Student's *t* test).

Table I presents the average pain relief, over the course of the experiment, after the administration of morphine for each individual in the 4 groups studied.

Discussion

In this study we found, as previously demonstrated (Levine et al. 1986) that desipramine, a relatively selective noradrenaline uptake inhibitor, when given daily for 1 week before surgery, was able to enhance morphine analgesia administered postoperatively. The additional protocols used in the present study, namely administration for only 3 days, either at the beginning or the end of the pre-operative week revealed that the ability of desipramine to enhance postoperative morphine analgesia appears to require administration starting more than 3 days pre-operatively and that there is no effect after only 3 daily pre-operative doses just before surgery.

Our findings are consistent with the known long latency in humans (days to weeks) to central effects of the TCA group of drugs (Baldessarini 1990). The data, therefore, suggest that such a central effect is involved in the enhancement of opiate analgesia, consistent with

the role of the central endogenous pain modulating system in opiate analgesia. However, the specific mechanism mediating this action remains unknown. There are confounding data from the experimental literature. For example, in rats, acute administration of desipramine or other antidepressants potentiates opioid analgesia (Kellstein et al. 1984; Sacerdote et al. 1987; Kellstein et al. 1988; Ventafridda et al. 1990). On the other hand, if administered chronically, these same agents attenuate opioid analgesia (Fialip et al. 1986; O'Neill and Valentino 1986; Kellstein et al. 1988; Goldstein et al. 1990). Since metabolism is much more rapid in rats than in humans (Sasaki et al. 1988; Baldessarini 1990; Ardid and Guilbaud 1992), it is difficult to base interpretation of our finding on the animal data.

The potentiation of opiate analgesia by desipramine consisted mainly of a prolongation of the action of the dose of morphine administered. A persisting effect on norepinephrine re-uptake is unlikely since this prolongation is also seen in the group given desipramine only during days 7, 6 and 5 pre-operatively, in which most of the desipramine would be expected to be gone at the time of surgery. An effect retarding morphine metabolism or influencing its distribution may be responsible for the effect observed. While a lingering effect of a TCA 5 days after last administration is not an unexpected clinical finding, there is no known mechanism to explain this observation.

We also found that patients who received TCA pre-operatively demonstrated a significantly greater analgesia at the first measurement, 10 min after morphine, compared to patients who had received placebo. The group that received desipramine for the immediate 3 pre-operative days had the greatest analgesia at 10 min, but did not demonstrate enhanced analgesia over the study period. If substantiated this would suggest that the production of enhanced early opiate analgesia (i.e., more rapid onset) represents a different effect than the prolongation of opiate analgesia.

In summary, we demonstrate that even a short course of the noradrenergic tricyclic, desipramine, given a considerable time before dental surgery, can enhance opiate analgesia administered for postoperative pain, mainly by prolonging analgesia. Further studies are

needed to evaluate the apparent additional effect of a more rapid onset of opiate analgesia after tricyclics. The data suggest that depending on doses needed there might be a role for the clinical use of noradrenergic tricyclics, as part of treatment of moderate to severe subacute pain, in addition to the present use of TCAs for chronic pain. Pain which would be anticipated, such as that after elective surgery, might also appear to be a possible use, but likely interactions with anesthetics mitigate against this. Further studies are needed to characterize the TCA-opiate interaction.

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