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Antinociceptive Action of Tricyclic Antidepressant Drugs in the Rat

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The antinociceptive effects of controlled release amitriptyline, desipramine, and placebo pellets were studied over 3 weeks using the hot plate method in 45 rats. Animals treated with desipramine at total doses of 50 mg (8 mg/kg/day) and 100 mg (16 mg/kg/day) displayed analgesia for up to 48 hours compared with the matching placebo groups. Amitriptyline did not produce significant analgesia at the same doses. By 72 hours until the final evaluation period at 21 days, the antinociceptive action of desipramine was no longer evident. These results suggest that relatively small continuously released doses of desipramine produce analgesia within 24 hours in this animal model, but an apparent analgesic tolerance develops within 3 days.

Tricyclic antidepressants such as amitriptyline and desipramine are widely used as part of the treatment regimen in various chronic pain syndromes, including chronic pain in the orofacial region.[1–11] Their antidepressant action is thought to be due to a blockade of the biogenic amine reuptake pump which increases central serotonin and norepinephrine concentrations to more normal levels in depressed patients.[12] In addition, a down regulation of postsynaptic catecholamine receptors may also contribute to this effect.[12] Tertiary amine derivatives, such as amitriptyline and doxepin, block the reuptake of both serotonin and norepinephrine, while those with only two terminal methyl groups such as desipramine and nortriptyline preferentially block norepinephrine reuptake.

In most double-blind, placebo-controlled studies of chronic pain including lower back, arthritic, neuropathic, and headache, tricyclic antidepressants have outperformed the appearance-matched placebo treatments.[13,14] While mood elevation is certainly beneficial to the chronic pain patient, the available data suggest that these drugs possess analgesic activity that is distinct from their antidepressant action, as they have proven effective in patients with chronic pain who were not judged clinically depressed.[1,15,16] It has also been reported that the onset of analgesia tends to be more rapid than the onset of antidepressant activity (2–3 days vs 2–3 weeks).[13] However the efficacy of various tricyclic antidepressants has not been compared to one another or to more conventional analgesics in controlled clinical trials; nor have dose-response relationships been firmly established.[17]

Contradictory results on the analgesic efficacy of this class of drugs have been reported based on animal research. In one study, intraperitoneal nomifensine (a specific serotonin reuptake blocker) in doses up to 50 mg/kg was essentially devoid of analgesic activity in the mouse hot plate or tail immersion tests. However, the drug did potentiate morphine analgesia.[18] Similar results (absence of direct analgesia but potentiation of morphine) were reported after the subcutaneous injection of 30 mg/kg desipramine or 4 mg/kg amitriptyline in the rat tail-flick model.[19,20] In contrast, i.p. desipramine 10–40 mg/kg or clomipramine 20–50 mg/kg produced analgesia in the rat tail shock paradigm,[21,22] and in the rat tail pressure model.[23] Subcutaneous desipramine 25 mg/kg also significantly decreases the biting and scratching behavior induced by intrathecal substance P in rats.[24]

It should be noted that in all the mentioned animal studies, the antidepressant drugs were always administered via acute injection. However chronic pain patients are taking these drugs orally for more prolonged periods. The purpose of this study was to evaluate the antinoci-

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ceptive activity of amitriptyline and desipramine in the rat, while using a drug delivery system that more closely resembles the pharmacokinetic profile of these agents when used in the clinical setting.

METHODS

This investigation was approved by the University of Pennsylvania Animal Use and Care Committee. Forty-five male Sprague Dawley rats weighing 250–325 g were used in this study. Before drug administration the animals were placed on a heated surface (52°C) surrounded by a clear, 26-cm high plexiglass cylinder. Control thermal response time on the hot plate was defined as the time elapsed till the rat licked a back paw.[25] Occasionally an animal would jump to the top of the plexiglass dome instead of licking a paw. In these instances the onset of jumping behavior was considered the response time. Control and all subsequent thermal response times were determined twice within 30 min of each other and averaged.

Following control measurements, animals were anesthetized with intraperitoneal pentobarbital 35 mg/kg. The back of the animal's neck then was shaved and a small vertical incision (0.5–1.0 cm) was made. A 2-cm subcutaneous tunnel was created with the use of a blunt surgical hemostat for the placement of a controlled time-released pellet containing either active drug or vehicle (Innovative Research, Toledo, OH).

The drug pellets evaluated in this study included placebo, amitriptyline, and desipramine at total dosages of 5, 50, and 100 mg. Five animals were allocated to each of the nine possible treatment groups. These drug pellets have been shown to release a constant amount of drug over three weeks.[26,27] For example, a 100-mg pellet slowly releases approximately 4.8 mg of drug per day for 3 weeks. Following subcutaneous placement of the drug pellet, the surgical site was closed with one or two silk sutures.

Thermal response time was then reevaluated at 1, 2, 3, 7, 14, and 21 days postpellet implantation. The percent change in response time from baseline was calculated for each individual animal using the formula:

$$\% \text{ Change} = \frac{\text{postimplantation response time} - \text{baseline response time}}{\text{baseline response time}} \times 100.$$

A one-way ANOVA was used to compare the efficacy of matching dosages of the various treatments. Statistically significant differences ($P < 0.05$) were identified using a Least significant difference test.

Table 1. Percent Change in Thermal Response Time (mean ± SEM) at One Day for the 50-mg Treatments

Drug	*N*	*% Change from Baseline*
Placebo	5	−10.8 ± 16.7
Amitriptyline	5	12.1 ± 19.8
Desipramine	5	40.7 ± 12.0*

* Significantly different than placebo, $P < 0.05$.

RESULTS

The mean control response times for the nine treatment groups ranged from 7.2 ± 0.6 to 10.9 ± 1.8 s (mean ± SEM). At a total dose of 5 mg neither amitriptyline nor desipramine exerted an antinociceptive effect compared with the matching (5 mg) placebo treatment. Rats treated with 50 and 100 mg desipramine displayed significantly longer response times than their matching placebo counterparts. On day one, both desipramine doses exerted an analgesic effect (Tables 1, 2); but by day 2 only the 100-mg desipramine group displayed analgesia (Table 3). A positive dose-response curve is apparent for the doses of desipramine that were evaluated (Figure 1). Animals treated with the 50- and 100-mg doses of amitriptyline did not significantly differ from those treated with placebo; although a trend toward analgesia was seen with the 100-mg dose.

The analgesic effect of desipramine was no longer evident by day 3. From this point until the final 21-day evaluation period, thermal response times in the 100-mg desipramine group did not differ from the 100-mg placebo treatment (Figure 2).

Animals from all treatment groups gained body weight in a normal fashion during the course of the study. The mean increase in body weight among the different treatments ranged from 93–116 g.

DISCUSSION

Desipramine 50 and 100 mg incorporated into time-released pellets exerts antinociceptive activity for up to 48 hours in the rat. The early onset of analgesia agrees with reported clinical findings.[13] Considering the initial body

Table 2. Percent Change in Thermal Response Time (mean ± SEM) at One Day for the 100-mg Treatments

Drug	*N*	*% Change from Baseline*
Placebo	5	15.7 ± 13.5
Amitriptyline	5	69.0 ± 33.6
Desipramine	5	119.9 ± 41.0*

* Significantly different than placebo, $P < 0.05$.

Table 3. Percent Change in Thermal Response Time (mean ± SEM) at Two Days for the 100-mg Treatments

Drug	*N*	*% Change from Baseline*
Placebo	5	10.2 ± 11.7
Amitriptyline	5	34.9 ± 12.1
Desipramine	5	101.5 ± 44.3*

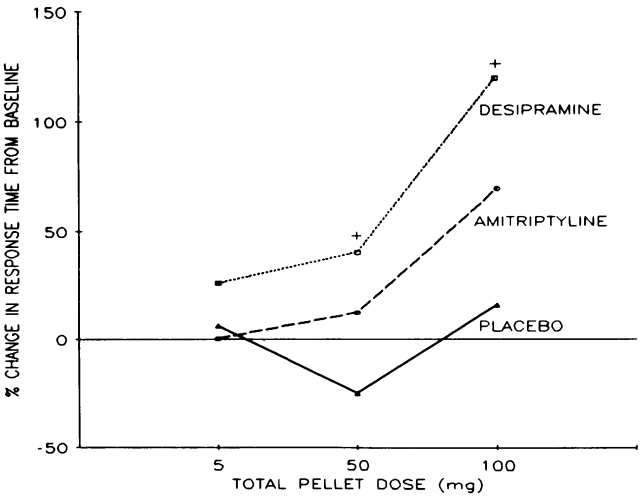
* Significantly different than placebo, $P < 0.05$.

weight of our animals, and the normal increase in body weight of about 100 g displayed by rats in all treatment groups during the course of the study, the above total pellet doses represent approximately 6–10 and 12–20 mg/kg/day of drug, respectively, delivered during the 21-day period. In contrast amitriptyline, at the same dosages, lacked significant analgesic activity.

Whereas others have reported that desipramine produces analgesia after acute injection in the rat,[21–24] the same effect can apparently be achieved when the drug is delivered by a continuous time-release system at much lower doses. This drug delivery system also allowed us to study the efficacy of the antidepressant drugs over a 21-day period without repeatedly injecting the animals. We believe that continuous drug release over 21 days more closely resembles the clinical situation than single-dose injections, as chronic pain patients usually receive relatively low doses of tricyclics over extended periods.[13]

Intriguingly, the rats in the present study exhibited an apparent tolerance within 3 days to the analgesic effect of desipramine. Normal growth of the rats during the 3-week period slowly reduced the milligrams per kilogram of drug delivered per day. While this could account for a partial diminution of analgesic activity toward the end of the study, it would not explain the rapidity and magnitude of analgesic decrement. A recent investigation in rats showed that the potentiation of intrathecal morphine analgesia by subcutaneous desipramine disappeared in 22 days with chronic desipramine injections.[28] The appearance of tolerance to desipramine induced analgesia in animal studies may have clinical significance and should be studied further.

Figure 1. Antinociceptive action of the various controlled release drugs 24 h following subcutaneous implantation. Each point represents the mean response in five experimental animals. $^{+}$ $P < 0.05$ compared to matching placebo dose.



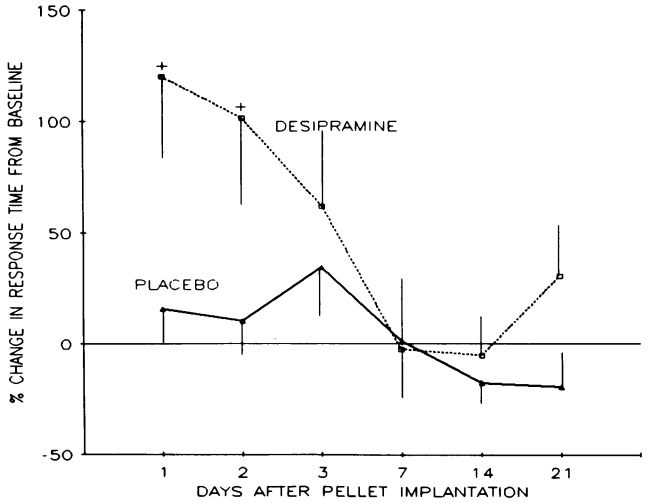


Figure 2. Time-action curves of the 100 mg desipramine and placebo treatments. The data points on each curve represent the mean responses ± the standard error of the mean in five experimental animals over 21 days. $^{+}$ $P < 0.05$ compared to placebo treatment.

The mechanism of tricyclic analgesia is thought to involve the activation of descending noradrenergic and serotonergic pathways, which in turn stimulates the release of spinal enkephalins in the dorsal horn.[29] Although we can only speculate on the mechanism of tolerance to desipramine, a down regulation of spinal opiate receptors may occur.

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