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Synergistic affective analgesic interaction between delta-9-tetrahydrocannabinol and morphine

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Abstract

Evidence for an analgesic interaction between delta-9-tetrahydrocannabinol (Δ^9-THC) and morphine was sought using an experimental pain model applied to normal volunteers. The study incorporated a double blinded, four treatment, four period, four sequence, crossover design. Subjects received Δ^9-THC 5 mg orally or placebo and 90 min later morphine 0.02 mg/kg intravenously or placebo. Fifteen minutes later subjects rated the pain associated with the application of thermal stimuli to skin using two visual analog scales, one for the sensory and one for the affective aspects of pain. Among sensory responses, neither morphine nor Δ^9-THC had a significant effect at the doses used, and there was no significant interaction between the two. Among affective responses, although neither morphine nor Δ^9-THC had a significant effect, there was a positive analgesic interaction between the two ($p=0.012$), indicating that the combination had a synergistic affective analgesic effect. The surprisingly limited reported experimental experience in humans does not support a role for Δ^9-THC as an analgesic or as an adjunct to cannabinoid analgesia, except for our finding of synergy limited to the affective component of pain. Comparison of our results with those of others suggests that extrapolation from experimental pain models to the clinic is not likely to be a straight-forward process. Future studies of Δ^9-THC or other cannabinoids in combination with opiates should focus upon clinical rather than experimental pain.

Keywords: Narcotics; Opioid; Cannabinoid; Pain

1. Introduction

In the clinic opiate analgesia often is inadequate (Cherny et al., 2001). Some patients experience unacceptable, dose-related side effects, principally constipation, alterations in alertness and cognition, and nausea and/or emesis. Other patients experience inadequate pain relief despite administration of opioids in very high doses. This suggests a potential role for agents that would potentiate the analgesic effects of opiates, especially if these agents had a different side effect profile. In a series of investigations in rodents, Welch and others have demonstrated striking potentiation of opiate antinociception by various cannabinoids including delta-9-tetrahydrocannabinol (Δ^9-THC) (Welch et al., 1995; Smith et al., 1998a,b; Cichewicz et al., 1999; Mason et al., 1999; reviewed in Richardson, 2000). We were interested in whether Δ^9-THC might potentiate the analgesic effects of morphine in humans. We elected to study this question using an experimental pain model in volunteer subjects.

2. Methods

In order to investigate whether Δ^9-THC might potentiate the analgesic effects of morphine, we conducted a double blinded, four treatment, four period, four sequence, crossover study of the effects of Δ^9-THC and/or morphine upon sensory and affective responses to an experimental thermal pain stimulus in normal volunteers. Many aspects of our intervention — use of normal volunteers, application to the skin of a thermal stimulus as an experimental source of pain, rating of pain responses using a visual analog scale, and distinguishing between sensory and affective pain responses (see below) — were based upon previous reports (Price et al., 1983, 1985). The study was

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conducted as approved by an institutional review board for the protection of human subjects.

Eligible subjects were non-pregnant adults without serious intercurrent medical illness, recent ingestion of opioids or cannabinoids, or a history of allergy to either class of substance.

Subjects made five outpatient visits to the General Clinical Research Center. At the first visit subjects were informed about the study, signed an approved informed consent form, and were screened for eligibility including submission of a urine sample that was tested subsequently for the presence of opioids or Δ^9-THC using a high performance liquid chromatograph-based toxicology screen utilized by the VCU Health System for routine clinical practice. The methodology used would be expected to detect recent ingestion of morphine, codeine, hydromorphone, hydrocodone, and significant amounts of oxycodone, as well as any recent ingestion of Δ^9-THC. Enrolled subjects underwent a determination of baseline responses to thermal pain (described below).

Subsequently, subjects made four visits, each at least three days apart, for drug testing. Over the course of these visits each subject was exposed to four drug combinations, one combination at each visit, in a subject-specific random sequence. Drug combinations were Δ^9-THC and morphine, Δ^9-THC and placebo, placebo and morphine, and placebo and placebo. Subjects and investigators, other than the pharmacist, were blinded to drug assignments.

At the onset of each visit indwelling intravenous access was established. Subjects then swallowed Δ^9-THC 5 mg (Marinol®) or an identical-appearing placebo (kindly provided by Roxane Laboratories). Ninety minutes later subjects received an intravenous bolus injection of morphine sulfate 0.02 mg/kg in normal saline or a similar volume of normal saline only. Fifteen minutes later a research nurse initiated response to thermal pain stimulus testing. Prior to testing, the nurse instructed subjects on the difference between sensory and affective pain and the use of a Visual Analog Scale from the following script:

> There are two aspects of pain which we are interested in measuring: the intensity, how strong the pain feels, and the unpleasantness, how unpleasant or disturbing the pain is for you. The distinction between these two aspects of pain might be made clearer if you think of listening to a sound, such as a radio. As the volume of the sound increases, I can ask you how loud it sounds or how unpleasant it is to hear it. The intensity of pain is like loudness; the unpleasantness of pain depends not on intensity but also on other factors which may affect you.
>
> There are scales for measuring each of these two aspects of pain. Although some pain sensations may be equally intense and unpleasant, we would like you to judge the two aspects independently. Please mark on the line to indicate the relative intensity of your pain sensation; the further to the right the greater the intensity. Similarly, mark the line to indicate the relative unpleasantness of your pain sensation.

Thermal stimuli were provided by the application for 5 s (if tolerated) of a copper cylinder 2 cm in diameter to the volar aspect of the forearm opposite the intravenous access (ClinTherm, Adolor, Malvern, PA). Each of two groups of stimuli consisted of duplicate applications of copper cylinders preheated to 37, 49, and 51 °C. The stimuli were applied in one of four arbitrary sequences. Each stimulus was applied to a different area of the forearm. After each exposure, subjects rated stimulus-related pain using a visual analog scale. Six stimuli were rated for "sensory" pain indicated by a scale labeled "no sensation" and "the most intense sensation imaginable". The next six stimuli were rated for "affective" pain as indicated by a scale labeled "not bad at all" and "the most intense bad feeling possible". These visual analog scale ratings are referred to as "responses". At the conclusion of testing subjects completed an open-ended questionnaire concerning "any physical or mental sensations, other than those related to the heat probe testing, that you experienced after receiving the drugs today". Subjects were observed for adverse effects and released upon observation of an alert and oriented state with stable vital signs.

The primary study endpoints were sensory and affective responses at 51 °C and adverse events associated with drug administration. The sample size calculation was based upon response data approximated from graphs presented in Price et al. (1985). Using a two-sample one-sided test with a level of significance of 5% and power of 80%, a sample size of 6 was calculated to be large enough to detect a difference between the morphine group and the combination group for sensory analgesia. For affective analgesia, a two-sample, one-sided test with a significance level of 5% and power of 80%, a sample size of 12 was calculated to be large enough to detect a difference between the morphine group and the combination group. Accordingly, the study sample size is set at 12 with the option to do an interim analysis following evaluation of 6 subjects. The primary data analysis plan called for a comparison of the sensory and affective responses at 51 °C between placebo/morphine and Δ^9-THC/morphine and specified rejection of the null hypothesis (no difference in responses) at a confidence level of 0.05. Accordingly, sensory and affective response data were analyzed separately using a crossover mixed-effects model incorporating both random and fixed effects using Proc Mixed in SAS (SAS Institute Inc., Cary, NC). The general form of both models was:

$$y_{ijk} = \mu + T_i + \Pi_j + \lambda_{1-2} + \lambda_{1-3} + \lambda_{1-4} + p_j + \varepsilon_{ijk},$$
$$i = 1,2,3,4, \quad j = 1,2,3,4, \quad k = 1,\ldots,13$$

where

y_{ijk}	is the observed response of the kth subject in the ith treatment in the jth period
μ	is the grand mean
τ_i	is the effect of the ith treatment
Π_j	is the effect of the jth period
λ_{1-j}	is the linear combination of the carryover effects $\lambda_1 - \lambda_{1-j}$
p_j	is a random effect due to the kth subject and is $\sim N(0, \sigma_p^2)$
ε_{ijk}	is the random error associated with the y's and is $\sim N(0, \sigma_\varepsilon^2)$

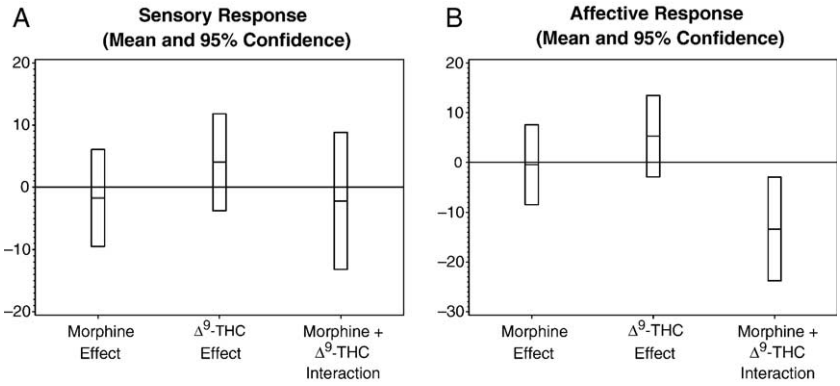

Fig. 1. Single agent effects and dual agent interactions of morphine and Δ^9-THC upon sensory (A) and affective (B) pain responses to a painful stimulus. Effects calculated using the average response per subject minus the average baseline response. Interactions calculated from a mixed-effects model as described in Methods. Vertical axis represents displacement of responses on a scale of 100 mm.

The difference between the average reported pain at the *i*th visit and the average pain reported at baseline was the response used in the analysis. The crossover model was used to determine whether Δ^9-THC, when combined with morphine, had an interactive effect on either sensory or affective analgesia at a thermal stimulus of 51 °C. Akaike's Information Criterion was used to choose the most appropriate covariance structure for within-subject responses. Comparison of the unstructured covariance matrices and Akaike's Information Criterion indicated that a compound symmetry structure was most appropriate for sensory responses, whereas a Huynh–Feldt structure was best for affective responses. Tests for carryover effect and visit effect were done and found not to be significant. A random-coefficient model was used to determine whether the results were generalizeable across all three levels of thermal stimuli.

3. Results

Thirteen subjects, seven men and six women ranging in age from 18 to 49 years, were tested.[1]

Among the sensory responses, neither morphine ($p=0.608$) nor Δ^9-THC ($p=0.231$) had a significant effect at the doses used, and there was no significant interaction between the two ($p=0.645$) (Fig. 1A). Among the affective responses, although neither morphine ($p=0.8937$) nor Δ^9-THC ($p=0.1463$) had a significant effect, there was a positive interaction between the two ($p=0.012$), indicating that the combination had a synergistic affective analgesic effect (Fig. 1B).

Using a random-coefficients model, the pain responses by temperature slopes were not found to be significantly different from parallel across intervention groups for both sensory pain ($p=0.798$) and affective pain ($p=0.791$), indicating that the findings at 51 °C can be generalized across the temperature range studied (Fig. 2).

As gender may affect response to analgesics (Pleym et al., 2003), the data were reanalyzed with incorporation of subject gender into the models for both sensory and affective pain. There was no significant gender effect for either sensory or affective pain.

No serious or unexpected toxicities occurred. Subjects described a variety of mild euphoric or dysphoric effects, but these were not especially remarkable.

4. Discussion

We demonstrated an interaction with regard to the affective, but not the sensory, dimension of pain in an experimental pain model involving thermal stimuli applied to normal subjects. We undertook our study because previous experimentation with rodent models suggested that there might be such an interaction. Studies in rodents show up to a 20-fold potentiation of opiate effects by cannabinoids (Welch et al., 1995). Rodent models involve nociception and are based upon behavioral, not communicated, responses. One might surmise that these models are more relevant to the sensory as compared to the affective component of pain, but we did not observe an interaction with regard to sensory responses.

In this study neither morphine nor Δ^9-THC demonstrated a significant analgesic effect as a single agent. In the case of morphine, this can be attributed to the decision to study a very low dose. A previous report of a similar pain model involved up to 4-fold higher morphine doses and showed effective sensory and affective analgesia (Price et al., 1985). We chose to study a very low morphine dose out of concern that use of a high dose might obscure any interaction between morphine and Δ^9-THC.

In the case of Δ^9-THC, it is unclear whether an analgesic effect should have been expected. Studies of Δ^9-THC analgesia have yielded conflicting results, and its status as an analgesic is uncertain (Walker and Huang, 2002; see also below and Naef et al., 2003). Δ^9-THC is clinically indicated for the prevention or control of chemotherapy-induced nausea and vomiting and for appetite stimulation especially in patients with HIV/AIDS. The

[1] No candidate subjects tested positive for opioids or Δ^9-THC at the first visit. At one point it was uncertain whether data from a single subject taking prescribed psychotropic medications should be included in the analysis, and a potential replacement subject was enrolled. At the conclusion of the enrollment period and prior to data analysis, a decision was made to include all data from all subjects.

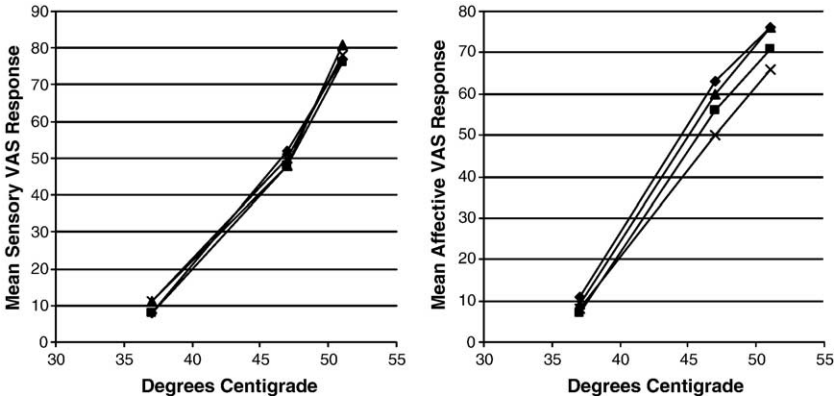

Fig. 2. Mean sensory and affective responses at three thermal stimulus temperatures. Conditions are: placebo/placebo (♦), placebo/morphine (■), Δ^9-THC/placebo (▲), Δ^9-THC/morphine (×).

clinical dose range extends from 2.5 mg to about 25 mg (Unimed Pharmaceuticals, Inc., 2002). We chose to study only a moderate dose of 5 mg out of concerns for possible additive or synergistic toxicities.

The interaction effect size we observed for affective responses was smaller than we had hoped, but our expectations may have been unrealistic. In a previous report of a similar pain model, morphine 0.08 mg/kg induced about a 25% reduction in mean affective responses to a 51 °C thermal stimulus (Price et al., 1985), whereas we observed mean reductions of 6% (not significant) and 13% (statistically significant) following morphine 0.02 mg/kg alone and Δ^9-THC plus morphine, respectively. In retrospect, we consider this effect size to be promising.

To our knowledge only one other report addresses the potential for an analgesic interaction between a cannabinoid and an opioid in humans, that is, a report of Naef et al. (2003). Their report is more comprehensive, and there are remarkable similarities and some potentially significant differences between the two studies. Naef et al. used a much higher Δ^9-THC dose, 20 mg, formulated as Δ^9-THC encapsulated in sesame seed oil, and a higher dose of morphine, that is, 30 mg administered orally (which would correspond to an intravenous dose of 0.14 mg/kg, assuming an oral to intravenous potency ratio of 3 to 1 and an average subject mass of 70 kg). Naef et al. applied four types of painful stimuli: pressure, heat, cold, and transcutaneous electrical stimulation. They observed many differences among Δ^9-THC, morphine, and the combination among their four pain models. A consistent finding was that Δ^9-THC was not analgesic; in two tests, it was hyperalgesic. Using a value $p<0.05$ and Wilcoxon signed ranks tests, they observed a "slight additive" analgesic effect for the combination in the electrical stimulation test only.

In the heat test, Naef et al. used different endpoints: during a continuous ramping up of the applied temperature from a baseline of 30 °C to a peak of 52 °C, subjects were asked to indicate when the stimulus became painful and when it became intolerable. With this model, Naef et al. observed no analgesic effects of Δ^9-THC, morphine, or the combination, and they observed hyperalgesia with Δ^9-THC. They comment that their results were limited by the participation of subjects who were intolerant of the 52 °C thermal stimulus. As Price et al. observed both sensory and affective morphine effects in the model upon which our study was based (Price et al., 1985), it appears that, despite remarkable similarities, the two models test different aspects of experimental thermal pain analgesia.

There is precedent for Δ^9-THC interacting in a positive manner with another analgesic. In a study of patients with disease-related chronic pain, the combination of Δ^9-THC 10 mg and aspirin 600 mg was a more potent analgesic than either Δ^9-THC or aspirin alone (Noyes et al., 1975).

Although there has been considerable interest in cannabinoids as analgesics, they are not currently used as such (Foley, 2001), and there are surprisingly few published studies of cannabinoid analgesic effects in humans (Walker and Huang, 2002; but also see Buggy et al., 2003). Although based exclusively upon experimental pain models, two more recent reports (Naef et al. and this one) further reduce the possibility that Δ^9-THC as a single agent has clinical promise as an analgesic.

Our study suggests that Δ^9-THC may synergistically interact with opioids in analgesia. Our study showed an interaction limited to the affective component of pain. Management of the affective component of pain may be especially relevant to the clinical problem of chronic pain.

Results from our study in comparison with those of Naef et al. suggest to us that extrapolation from experimental pain models to the clinic is not likely to be a straight-forward process. We believe that future studies of Δ^9-THC in combination with opiates should focus upon clinical rather than experimental pain as an approved clinical formulation is readily available; results to date in experimental pain models show some promise, and further studies in experimental pain models in normal subjects are unlikely to further clarify its potential clinical role.

We also consider our results to offer promise for combinations of other cannabinoids and opioids in clinical analgesia. It may be particularly appropriate to study new, selective cannabinoids (Walker and Huang, 2002). For example, whereas Δ^9-THC activates both cannabinoid CB_1 and CB_2 receptors, analgesic effects may be predominantly mediated through CB_1. Further, some cannabinoid CB_1 agonists demonstrate

differential stimulation of G-proteins and differential activation of downstream signaling pathways in a therapeutically favorable manner.

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