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Naltrexone Maintenance: Effect on Morphine Sensitivity in Normal Volunteers

James W. Cornish, M.D.¹, David Henson, M.D.¹, Sanford Levine, M.D.^{1,2}, Joseph Volpicelli, M.D., Ph.D.¹, Charles E. Inturrisi, Ph.D.³, Byron C. Yoburn, Ph.D.⁴, and Charles P. O'Brien, M.D., Ph.D.¹

¹Department of Psychiatry, University of Pennsylvania and the Veterans Affairs Medical Center, Philadelphia

²The Medical College of Pennsylvania, Philadelphia

³Department of Pharmacology, Cornell University Medical College, Ithaca, NY

⁴The College of Pharmacy, Saint John's University, Jamaica, NY

Naltrexone has been tested in numerous clinical trials for both safety and efficacy in the treatment of relapse to opioid dependence. In the doses used for this purpose, it has been found to be safe and pharmacologically effective. Recently it has been found that chronic treatment with naloxone or naltrexone produces supersensitivity to opioid agonists in rodents. Seven normal human volunteers were tested for opiate sensitivity, using morphine 8 mg iv before and after 2 weeks of naltrexone treatment at 50 mg po qd. There were no significant differences in morphine-induced respiratory depression before or after naltrexone treatment. These results indicate that at the dose of morphine used in this study, it is unlikely that naltrexone maintenance would increase the risk of opiate toxicity.

Naltrexone maintenance treatment is an approved therapeutic modality for the treatment of opiate abuse.¹ Recent studies in rodents have clearly shown that when chronic treatment with opiate antagonists such as naloxone or naltrexone is discontinued, the analgesic and toxic potency of opiate agonists such as morphine is significantly increased (functional supersensitivity)^{2–5}. The basis of this increase in opioid potency appears to be an increase in brain and spinal cord opioid receptors (receptor upregulation)^{5–7}. The phenomenon of functional supersensitivity after chronic naltrexone in laboratory animals raises the possibility that both the toxic and analgesic effects of opiates in humans are enhanced after naltrexone maintenance treatment. If substantial shifts in morphine's potency are also observed in humans, there may be significant risk for increased incidence of morphine toxicity in patients who discontinue naltrexone and begin medical or nonmedical use of opiates.

To date, there has been no clinical indication of increased sensitivity to opioids after naltrexone treatment, but there has been no systematic study aimed at detecting such a

phenomenon. This is an important question because treatment with naltrexone tends to be intermittent. Thus, patients should be warned about possible supersensitivity to opioids after naltrexone. This study, therefore, examines whether there is clinically significant functional supersensitivity to morphine-induced respiratory depression in humans after naltrexone treatment.

METHODS

Subjects

Seven healthy, adult males (mean age = 29.7 years) participated in this study. Potential subjects were recruited through an advertisement posted at the university/medical center complex. Each subject had a psychiatric and medical evaluation, routine laboratory studies, and urine testing to exclude subjects with a prior or current history of medical or psychiatric disease or substance abuse. Each subject gave his informed consent to participate in the study after the procedures had been fully explained.

Study Design

The study consisted of three phases: pretreatment testing, treatment, and post-treatment testing.

Pretreatment testing—An 8 mg iv dose of morphine sulfate was selected because it was high enough to produce moderate respiratory depression and low enough to allow for the detection of supersensitivity. Morphine's respiratory effects were assessed by 1) measurement of end-tidal carbon dioxide ($P_{et}CO_2$) as a reflection of arterial carbon dioxide (P_ACO_2) and 2) ventilatory responses to hypercapnia. The measurements were determined at 15, 30, 45, and 60 minutes after morphine treatment.

Treatment phase—At 96 hours after pretreatment testing, each subject received naltrexone 50 mg po qd for the next 14 days (total naltrexone dose of 700 mg). Subjects came to the study clinic on weekdays to be evaluated for medication side effects and to take naltrexone. Each subject received medication to take home for weekend days.

Posttreatment testing—In humans, naltrexone has been shown to attenuate narcotic effects up to 72 hours after dosing.⁸ To ensure that opiate receptors were not blocked by residual naltrexone, we tested subjects on the fourth (3 subjects) or fifth (4 subjects) day after the final drug dose. Each subject was tested in an identical manner to the pretreatment testing; outcome parameters were determined at 15, 30, 45, and 60 minutes after a dose of morphine sulfate (8 mg iv).

To document the extent to which naltrexone had been eliminated at the time of testing, subjects had a blood sample drawn just before morphine injection as well as at 15, 30, and 60 minutes following morphine. Naltrexone and morphine concentrations were determined from the same blood sample by radioimmunoassays that are selective for each drug.^{2,9}

Specific Methodology

All respiratory studies were conducted using methods that were described previously.¹⁰ The subjects wore nose clips and breathed through a mouthpiece connected to a specially modified, two-way non-rebreathing respiratory valve (Hans Rudolph, Kansas City, MO). All respiratory parameters were derived from the following continuous direct measurements: inspiratory flow-rate, end-tidal concentration of oxygen (O_2) at the mouth, arterial oxygen saturation (SpO_2), and ECG. Inspiratory flow-rate was measured with a heated screen pneumotachograph (Hans Rudolph), a variable reluctance pressure transducer (Validyne), and a sine-wave carrier demodulator (Validyne). $PACO_2$ and alveolar tension of oxygen (PAO_2) were measured with a mass spectrometer (Perkin-Elmer), SpO_2 was measured with an ear oximeter (Hewlett-Packard, 47201A), and ECG was monitored by a manubriosternal lead interfaced with an ECG amplifier (E for M, V1205). All signals were monitored simultaneously on our polygraph recorders (E for M, VR-12) and digitized at 100 Hz onto magnetic tape by a PDP 11/23 computer. The data were then analyzed for all of the above parameters on our analytical computer (PDP 11/73).

Measurement of end-tidal PCO_2 —Ventilatory parameters and $P_{et}CO_2$ as our measure of alveolar carbon dioxide (P_ACO_2) were continuously monitored on a breath-by-breath basis. Once a steady-state was achieved, we took the average $P_{et}CO_2$ over 5 minutes as our approximation of arterial pCO_2 . Measurement of ventilatory response to CO_2 .

In our laboratory, the ventilatory response to a hypercapnic stimulus under hyperoxic conditions was measured by the method of Read.¹¹ This method uses a rebreathing method in which expired carbon dioxide is constantly returned to the lungs. Once P_ACO_2 has been elevated to the mixed venous pCO_2 , ventilation (V_E) increases in a linear manner. Moreover, when V_E is plotted against $P_{et}CO_2$, a linear relationship is obtained. We used a least squares linear regression technique¹² to compute the change in minute ventilation that occurred in response to change in inspired carbon dioxide concentration, $V_E / P_{et}CO_2$.

RESULTS

During the 2-week naltrexone treatment, no subjects reported any side effects from medication. Side effects from the morphine infusions included a single episode of nausea and vomiting in one subject. Morphine subjective effects in pretreatment testing were the same as in posttreatment testing. No serious side effects occurred from either drug.

The mean plasma morphine levels from the seven subjects are shown in Figure 1. At 96 and 120 hours after naltrexone dosing, the plasma levels were below the lower limits of detection of the assay (1 ng/mL).

By use of a mixed-model analysis of variance, pre-morphine CO_2 responsiveness ($V_E / P_{et}CO_2$) before and after naltrexone treatment did not differ significantly ($F = 0.118$; $df = 1,6$; $P > 0.05$). Further, there was no difference in responsiveness to CO_2 in each of the three pre-morphine tests ($F = 1.179$; $df = 2,12$; $P > 0.05$). Therefore, these three pretests were combined. As shown in Figure 2, morphine 8 mg iv produced a significant decrease ($F = 5.211$; $df = 6,36$; $P < 0.001$) in ($V_E / P_{et}CO_2$) both before and after naltrexone treatment.

However, naltrexone did not significantly ($F= 1.022$; $df= 6,36$; $P> 0.05$) alter the morphine-induced decrease in $\dot{V}_E/P_{et}CO_2$.

DISCUSSION

We selected carbon dioxide responsiveness as a quantitative measure of respiratory depression. The dose of morphine selected, 8 mg iv, produced moderate respiratory depression in these normal volunteers, thus maximizing the chance of observing clinically significant enhancement of morphine's effects. These results suggest that at the doses of morphine used in this study, it is unlikely that naltrexone maintenance would increase the risk of opiate toxicity.

There are two possible reasons why our results in humans differ from those observed in animal studies. First, the development of supersensitivity in rodents is dependent upon the dose of naltrexone. Low chronic doses of naltrexone that were sufficient to antagonize morphine analgesia did not produce supersensitivity, whereas higher doses antagonized morphine as well as induced upregulation and supersensitivity.¹³ Perhaps the doses of naltrexone used in this study were too low to induce supersensitivity. Second, opioid receptor upregulation and supersensitivity have been shown to decline in rodents after termination of antagonist treatment.^{4,14,15} Typically, at the doses used in the animal studies, enough naltrexone has been eliminated by 24 hours after the end of dosing that there is no evidence of antagonism of opiate effects.⁹ Whereas the half-life of naltrexone is approximately 4–5 hours in both humans and rats, the half-life of the major metabolite in humans which is active, is approximately 12 hours.^{9,16} Studies suggest that the levels of naltrexol in biofluids of rodents are extremely low.^{17,18} Thus, in humans, the interval required for elimination of naltrexol may allow for down-regulation of opioid receptors, and this may mask functional supersensitivity and account for the differences in the animal and human studies. Finally, this study was not designed to assess whether any supersensitivity, at all, developed. In our protocol, morphine-induced respiratory depression was evaluated before and after naltrexone treatment. Since subjects were administered morphine twice, it is possible that some tolerance to the second administration may have occurred. The intervening naltrexone treatment may have actually produced some supersensitivity, but this effect may have been attenuated by the tolerance. However, this study modeled, in part, the use of opiates by abusers in that the opiate was stopped and restarted with naltrexone being administered in the interim. Under these conditions and using the present doses of morphine and naltrexone, naltrexone does not increase morphine-induced respiratory depression.

In summary, oral naltrexone treatment did not increase the potency of morphine in normal volunteers. These data suggest that the naltrexone maintenance is not likely to increase toxicity of opiates when a patient discontinues antagonist therapy.

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FIGURE 1.
Morphine plasma levels

FIGURE 2.

Carbon dioxide responsiveness

Note: Pre- and post-morphine groups demonstrated significantly different slope values ($F=5.21$; $P<0.001$)