Nontolerance to the Opioid Antagonism of Naltrexone

Herbert D. Kleber, Thomas R. Kosten, Joseph Gaspari, and Mark Topazian

Controlled opiate challenges of naltrexone-pretreated human subjects have established that naltrexone is an effective opioid antagonist. However, these challenges have been conducted after relatively acute dosing with naltrexone, and tolerance to this antagonism after chronic treatment is possible. We therefore administered morphine challenges in a double-blind, placebo-controlled design to nine ex-addicts who had been taking naltrexone for a mean of 9.4 months. None of the ex-addicts experienced euphoria; instead, most of these blockaded ex-addicts had a dysphoric histaminelike response to the intravenous morphine. The only physiological change was a slight increase in heart rate. We conclude that tolerance does not develop to the opioid antagonist properties of naltrexone up to as long as 21 months of treatment.

Introduction

Opioid antagonists have been explored as possible treatment alternatives to methadone maintenance or residential treatment. Because of problems with treatment using cyclazocine and naloxone, most recent studies have used naltrexone, a long-acting, orally effective opioid antagonist (National Research Council on Clinical Evaluation of Narcotic Antagonists 1978). Initial studies of naltrexone established it as an effective opioid antagonist by using controlled morphine challenges in naltrexone-pretreated subjects (Verebey et al., 1976). Former addicts pretreated with naltrexone reported no euphoria and showed no evidence of intoxication when given substantial intravenous doses of heroin (25 mg) or morphine (25–100 mg). These were acute studies and did not involve chronic treatment with naltrexone followed by quantitated morphine challenge. In the phase III clinical testing of naltrexone, former addicts were maintained on naltrexone for several months and reported not getting any euphoria or "high" when they used heroin (Table 5 in Hurzler et al. 1976). This finding suggested that the efficacy of naltrexone as an opioid

From the Department of Psychiatry, Yale University School of Medicine Connecticut Mental Health Center, Substance Abuse Treatment Unit, New Haven, Connecticut 06510.
Support for this work was provided by a grant from the DuPont Pharmaceutical Company.
Address reprint requests to: Dr. H.D. Kleber, Connecticut Mental Health Center, 34 Park Street, New Haven, Connecticut 06510.
Received May 24, 1984; revised July 6, 1984.

0006-3223/85/$03.30

antagonist was sustained and that subjects did not develop tolerance to this antagonism. In contrast, with narcotic agonists, tolerance develops to the euphoria produced by morphine after even a few days of regular dosing.

Although during these phase III trials no systematic studies were conducted on the continued efficacy of naltrexone as an antagonist, two studies have provided some indication that tolerance does not develop to the drug's opioid blockade. In rhesus monkeys, continuous intravenous infusions of naltrexone produced stable suppression of morphine self-administration over 4-week periods when the dose of morphine was held constant at 8 μg/kg/injection (Harrigan and Downs, 1978). The single human study by Martin et al. (1973) demonstrated that after 16 days of naltrexone at either 30 mg or 50 mg daily, no tolerance to its ability to block morphine euphoria at doses up to 240 mg/day occurred. In summary, several studies have suggested that tolerance does not develop. However, if tolerance to the opioid antagonism of naltrexone were to develop, a patient who is chronically taking naltrexone might run the risk of heroin overdose by overriding the opioid blockade of naltrexone. We therefore designed a double-blind, placebo-controlled study to test the efficacy of the opioid blockade of naltrexone after several months of maintenance.

Methods

Setting and Sample

Nine former heroin addicts in the Connecticut Mental Health Center Drug Dependence Unit took naltrexone for a mean of 9.4 months (range: 4.5–21 months) after giving written informed consent. The subjects were part of a comprehensive outpatient treatment program that has been previously described and had regular medical evaluations and biweekly urine toxicology screens for illicit drug use (Kosten and Kleber, 1984; Kosten et al., 1983). Program participants took naltrexone three times per week, i.e., 100 mg on Monday and Wednesday and 150 mg on Friday.

The former addicts had a mean age of 33 (range: 27–48) years; six were male and eight were white. They had been using primarily heroin for a mean of 10.4 (range: 1–21) years, and three had been on methadone maintenance in the past. Although no concurrent substance abuse was detected in the urine toxicology screens, only three participants reported never having tested the opioid blockade of naltrexone on their own. None of the participants had abused alcohol in the previous month, and none was taking any concurrent medications. Medical evaluations had excluded any potential subjects with significant hepatic, cardiovascular, or renal disease.

Study Design

The study design was a double-blind, placebo-controlled trial involving intravenous boluses of either morphine or placebo on different days. On the basis of previous acute studies of naltrexone (Verebey et al. 1976; Martin et al. 1973; Meyer and Mirin, 1979), a single 60-mg dose of morphine was considered the upper limit for a challenge dose, and the initial two participants were given doses of 20 mg followed by the next two participants receiving 40 mg. The last five participants received 60 mg. The challenge was given as a bolus through an intravenous line maintained for at least 60 min postinjection with 5% dextrose solution. To prevent participants from knowing when the in-

jection was given, subjects were placed in an isolation room and the intravenous tubing was run through an opening in the wall to the observation room. The experimenter could view the subject through a video monitor and give the intravenous challenge through the line without the subject knowing when the injection was given. The order of placebo and morphine injections was randomized. The challenge testing occurred in the afternoon, 4 hr after a 100-mg dose of naltrexone.

After obtaining written informed consent, the participant was asked to give a urine sample for toxicology, and a brief psychiatric interview and physical examination were conducted. Several standard outcome measures were also administered before the challenge testing began, and these outcome measures were repeated at intervals of 2 min after the injection, then at every 20 min for 1 hr, and then at 2 hr after the injection. The initial four subjects were also assessed at 3 hr after injection.

Outcome Measures

Both physiological and psychological assessments of the participants were made. Physiological assessments included blood pressure, heart rate, respiratory rate, and pupillometry. Blood pressure was assessed with an AMR Dinamap Automated Noninvasive monitor using the oscillometric method. These readings were checked with manually obtained blood pressures and were found to correspond well. Heart rate was monitored using a three-lead electrocardiogram connected to a Gould brush 480 amplifier and chart recorder. Respiratory rate was measured using changes in the electrical impedance of the chest wall. The impedance change was processed by a Hewlett-Packard respiration monitor and was written on the chart recorder. Pupillometry was performed using a Polaroid CU-5 closeup 3 : 1 camera with polarizing filter. The pupil size in the photographs was then measured.

Psychological assessments included both self-reports and observer ratings. The self-reports were six analog scales ranging from 0 to 10 for feeling "high," feeling a "rush," feeling sleepy, feeling pleasant, craving, and dollar value of the injection. From the Addiction Research Center Inventory (ARCI) (Hill et al. 1963) the 45 items known to detect a weak opioid response were also administered. Observer ratings were completed at the baseline and at five subsequent time intervals using 10-point analog scales that included "nodding," sedation, dysphoria, withdrawal, and intoxication.

Data Analysis

This experiment had a balanced repeated-measures design, with nine subjects having measurements repeated six times under the two challenge conditions of morphine and placebo. For statistical analysis, a two-way repeated-measures analysis of variance (ANOVA) was used to determine any differences between the two challenge conditions. Interaction effects were important, because they indicated a difference between the morphine and placebo challenges. This difference was related to the pattern of change over time in the physiological (i.e., heart rate) or psychological (i.e., dysphoria) measure. If a significant interaction effect was demonstrated, the pattern of change over time was visually examined to determine at which time points the major differences occurred (i.e., at 2 min after the injection). To assess the significance of these differences, matched sample Student's *t*-tests were used.

Table 1. Physiological Measures During the Baseline and After Placebo and Morphine Challenges (n = 9)

	Placebo		Morphine		Significance[b]		
Measure	Base	Post[a]	Base	Post[a]	Chal.	Rep.	Inter.
Systolic BP	125	123	124	124	—	—	—
Diastolic BP	76	76	77	78	—	*	—
Respiration	17	17	18	17	—	—	—
Pupil size (mm)[c]	5.0	5.0	5.3	5.1	—	*	—
Heart rate	73	71	70	74	—	**	**

[a]Base: 20-min baseline assessment of physiological measures; Post: average of five postinjection assessments at 2, 20, 40, 60, and 120 min.

[b]Significance determined using two-way repeated-measures ANOVA for six sampling times. Chal: challenge effect overall for morphine vs. placebo; Rep: repeated measure, i.e., change in response measure over time for both challenges combined; Inter: interaction term for difference between morphine and placebo challenge in pattern of response measure change over time. * = $p < 0.05$, ** = $p < 0.01$, with $F(1,80)$ for challenge effect and $F(5,80)$ for repeated-measures and interaction effects.

[c]For pupil size, assessments were made only at 2, 20, 40, and 60 min postinjection for the last six participants.

Results

Physiological Responses

The only physiological outcome to demonstrate a significant difference between the morphine and placebo injection was heart rate, but no other physiological index suggested that morphine intoxication had occurred. For heart rate, the repeated measure [$F(5,80) = 5.8$, $p < 0.01$] and interaction [$F(5,80) = 6.2, p < 0.01$] effects were both significant. Upon visual examination of the change in heart rate over time, the largest difference between the morphine and placebo challenges occurred at 2 min after the injection. At that time, the morphine rate rose to 88.4 beats/min, while the placebo rate remained at 70 beats/min ($t = 2.2$, $p < 0.05$). After this initial rise during the morphine challenge condition, the heart rate fell to the same rate as the placebo condition and remained stable. For the other physiological outcomes, the two challenge conditions did not differ. Table 1 compares the blood pressure, respiratory rate, and pupil size during the placebo and the morphine challenge conditions for the baseline and for the postinjection times. The values for the five postinjection ratings were averaged, as no significant differences were demonstrated using the repeated-measures ANOVA. Although the repeated-measures effect was significant for diastolic blood pressure and pupil size, the direction of the change in these was the opposite of what would be expected from an opioid response.

Psychological Responses

The psychological ratings did not demonstrate the expected effects of morphine intoxication; instead, a significant dysphoric response was found during the morphine challenge. Among the subjective responses, the ARCI scale indicated a slight morphine effect beginning at 2 min after the injection, as shown in Table 2. Three of the analog scales also indicated a subjective response to the morphine. The rush scale rose from a baseline of 0 to 5.4 at 2 min after the morphine injection [$F(1,80) = 11.5$, $p < 0.01$, for the challenge effect, and $F(5,80) = 13.9$, $p < 0.01$, for the interaction]. The "high" scale rose from 0.1 to 2.2 at 2 min [$F(1,80) = 6.7$, $p < 0.05$, for the challenge effect, and $F(5,80) = 4.8$, $p < 0.05$, for the interaction]. The feeling-pleasant scale dropped from

Table 2. Psychological Measures During the Baseline and After Placebo and Morphine Challenges (n = 9)

Measure	Placebo			Morphine			Significance[b]		
	Base	Post[a]		Base	Post[a]		Chal.	Rep.	Inter.
ARCI[c]	3.7	3.8	3.3	3.6	6.6	5.0	—	*	—
Feel high	0	0.1	.02	0.1	2.2	0.5	*	**	**
Feel rush	0	0.1	.07	0	5.4	1.1	**	**	**
Dollar value	0	0	0	0.9	0.8	0.8	—	—	—
Pleasant	4.8	4.6	4.4	5.4	2.8	4.1	—	*	*
Dysphoric	0.6	0.1	.07	0.1	2.8	0.8	—	**	**
Sedated	0.7	1.3	1.3	1.1	1.0	0.7	—	—	—

[a]Base: 20-min baseline assessment of physiological measures; Post: the 2-min postinjection rating (see Table 1). It is given in addition to the average of the postinjection ratings because these ratings were often markedly different from the other four postinjection ratings.

[b]Significance determined using two-way repeated-measures ANOVA for six sampling times. Chal: challenge effect overall for morphine vs. placebo; Rep: repeated measure, i.e., change in response measure over time for both challenges combined; Inter: interaction term for difference between morphine and placebo challenge in pattern of response measure change over time. * = $p < 0.05$, ** = $p < 0.01$, with $F(1,80)$ for challenge effect and $F(5,80)$ for repeated-measures and interaction effects.

[c]ARCI: Addiction Research Center Inventory, consisting of weak opioid response scale of 45 true/false items.

5.4 to 2.8 at 2 min and had a significant interaction effect [$F(5,80) = 2.44$, $p < 0.05$]. Thus, the rise in ARCI score and the "rush" and "high" analogs were associated with an unpleasant response.

This unpleasant response was corroborated by observer ratings. Among the observer ratings, only the dysphoria rating demonstrated a significant interaction effect using ANOVA [$F(5,80) = 8.4$, $p < 0.01$]. When the dysphoria rating during the morphine challenge was compared with this rating during the placebo challenge, a major difference was apparent at 2 min after the injection. The ARCI weak opioid response occurred at the same time as the peak dysphoria rating. The values at the baseline and at 2 min after injection and the average of the other four ratings are shown in Table 2 for all the scales except craving, "nodding," withdrawal, and intoxication. These four scales are not included in the analysis because they never demonstrated any change during either challenge condition.

Clinical Responses to Morphine Challenge

Below 60 mg of morphine, only two of the four participants reported any response to morphine. At 20 mg of morphine, one participant felt a "buzz in his head" for about 1 min after the injection, and at 40 mg another participant said he was "getting a rush" followed by paresthesia, nausea, and a pounding bitemporal headache for 20 min. At 60 mg, every participant easily identified the morphine injection by a feeling of "pins and needles" in the injected arm, and the observer noted diffuse erythema in all five participants. These symptoms cleared within 20–30 min. Other symptoms described by some participants included pruritis, feeling warm all over, a "pounding heart, puffy face" and a metallic taste. No respiratory distress or major allergic-type responses occurred.

Discussion

The present study with former addicts maintained on naltrexone for a mean of 9.4 months indicates that subjects do not become tolerant to its opioid antagonism, but may become dysphoric when challenged by intravenous morphine. The only physiological assessment

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.