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NMDA-Receptor Antagonists: Evolving Role in Analgesia

Abuse Potential of Morphine/Dextromethorphan Combinations

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Abstract
The potentiation of morphine analgesia by dextromethorphan raises the issue of whether dextromethorphan also potentiates those actions of morphine that lead to abuse. Clinical pharmacology experiments indicated that dextromethorphan does not potentiate the euphorogenic and miotic actions of morphine. Morphine suppresses the dysphoric action of dextromethorphan. A second set of experiments indicated that dextromethorphan does not alter the response to naloxone-precipitated withdrawal. In a third set of experiments, dextromethorphan did not alter the morphine-induced depression in the slope of the increase in minute volume in response to breathing increased CO₂. In contrast to potentiation of analgesia, dextromethorphan does not enhance the euphorogenic, physical dependence, and respiratory depressant actions of morphine. These findings indicate that dextromethorphan does not enhance the abuse potential of morphine and that the potentiation of analgesia appeared to be selective. J Pain Symptom Manage 2000;19:S26–S30. © U.S. Cancer Pain Relief Committee, 2000.

Key Words
Abuse potential, euphoria, morphine/dextromethorphan, physical dependence capacity, respiratory depression capacity, selectivity

Introduction
Dextromethorphan is widely used as an over-the-counter antitussive that is recognized as effective and safe with little or no abuse potential.1,2 Even though structurally related to drugs having opioid activity, dextromethorphan lacks morphine-like properties. In recent years, dextromethorphan has been investigated as an N-methyl-D-aspartate receptor antagonist. Preclinical experiments demonstrate that dextromethorphan reduces tolerance in opiate-induced analgesia. In preclinical and clinical studies, dextromethorphan potentiates the analgesia of morphine and other opiates. Clinical studies show that potentiation of morphine by dextromethorphan is dose related. Studies indicate that this potentiation of morphine analgesia by dextromethorphan is not based on a pharmacokinetic interaction. An oral preparation, which combines morphine and dextromethorphan in a 1:1 weight ratio, is being introduced into therapeutics as an analgesic.

In nondependent substance abusers, use of dextromethorphan in doses up to 240 mg orally and 240 mg sc indicated that dextromethorphan lacks the euphoric properties...
Dextromethorphan is dysphoric, dilates pupils, and increases blood pressure. It does not produce morphine-like physical dependence. However, the addition of dextromethorphan to morphine raises issues concerning the abuse liability of the combination. First, dextromethorphan could enhance the abuse liability of the combination by potentiating those actions of morphine that lead to diversion, abuse, and public health and social problems. Alternatively, the addition of dextromethorphan could decrease the abuse liability of morphine by adding a dysphoric component to the combination, thereby limiting the euphorigenic action.

Clinical pharmacology studies were conducted to assess the abuse liability of the combination. In this context, abuse liability means the ability to be diverted, be abused, and create public health and social problems, including death, that occur with morphinelike drugs. Those pharmacological actions of morphine and other opiates responsible for this activity are: (1) the reinforcing or euphorigenic action of morphine as demonstrated in substance abusers; (2) the physical dependence capacity; and (3) the respiratory depressant capacity. Studies were conducted using clinical pharmacologic methods to assess abuse potential.

Study 1
The first study was a single-dose study conducted in 20 volunteer opiate abusers (17 male and 3 female). This was a double-blind crossover study in which drug combinations were administered at 48-h intervals in accordance with five 4×4 balanced Latin square design. Effects were measured predose and postdose at fixed intervals. In this study, four separate drug combinations were given orally to each subject. These were placebo/placebo, dextromethorphan 180 mg/placebo, placebo/morphine sulfate 180 mg, and dextromethorphan 180 mg/morphine sulfate 180 mg. A 2×2 factorial design was utilized. It was assumed that 180 mg of oral morphine is equivalent to 30 mg of a parenteral dose of morphine. The dose of dextromethorphan was approximately 6 to 18 times the usual adult antitussive dose of 10 to 30 mg.

In this study, dextromethorphan alone and morphine alone were active controls. Morphine produced the expected response, which
included constriction of pupils, increase on the “liking” scale and the Morphine Benzedrine Group (MBG) scale (measures of euphoria), (Fig. 1) and a slight increase in both supine and mean blood pressure readings. In contrast, dextromethorphan alone slightly dilated pupils, was not liked, produced no significant responses on either the “liking” or the MBG scale, and produced “disliking” (Fig. 1) and a slight increase in blood pressure and standing pulse. When the effects of the combination of morphine/dextromethorphan were compared to the effects of morphine alone, there was no greater effect on the euphorogenic measures of “liking” and MBG response. On the other hand, morphine reduced the dysphoric reaction, the pupillary dilatation, and the blood pressure effects of dextromethorphan. The significant findings of this study were that: (1) dextromethorphan does not potentiate the euphorogenic effects of morphine; (2) morphine suppresses the dysphoric effects of dextromethorphan; and (3) morphine suppresses the increases in pupil size, pulse, and blood pressure produced by dextromethorphan. It is therefore concluded that dextromethorphan neither enhances nor reduces the euphorogenic action of morphine.

**Study 2**

The physical dependence capacity of an opiate can be demonstrated either through abrupt withdrawal of the opiate or by the administration of a competitive opiate antagonist such as naloxone. It is also known that short-term 24- to 36-h administration of morphine will result in the development of acute physical dependence. This can be seen when the administration of large doses of naloxone precipitates a withdrawal syndrome. Using this model, a second study was conducted in eight subjects in which the drug conditions were administered according to two 4×4 balanced Latin squares with a 1-day washout between experiments. Each experiment consisted of 2 days of drug administration. On the first day, each subject received morphine sulfate orally in a 60-mg dose at 6 AM, noon, 6 PM, and midnight. This was accompanied either by a dose of placebo or by a dose of dextromethorphan 30 mg, dextromethorphan 60 mg, or dextromethorphan 120 mg on each of the four occasions. At 6 AM on the second day, subjects received their original dose of dextromethorphan; at 6:30 AM, they were given morphine sulfate 30 mg im, and at 8:30 AM, naloxone was administered intramuscularly in a dose of 2.5 mg.
Naloxone resulted in precipitated withdrawal as measured by a significant increase in pupil size, increases in tympanic temperature, pulse rate, and respiratory rate, and reports by both subjects and observers of withdrawal sickness. These effects lasted for about 1 h. The increasing doses of dextromethorphan had no significant effect on this acute precipitated withdrawal, as shown in Figure 2. Based on this study, it is concluded that dextromethorphan has no effect on naloxone-precipitated abstinence. This finding implies that dextromethorphan does not alter the physical dependence capacity of morphine.

Study 3

The third clinical pharmacology study evaluated the effect of dextromethorphan on the respiratory depressive action of morphine. This study was conducted in 12 normal volunteers, defined as individuals without a history of opiate abuse. The study was a crossover, 2×2 factorial study in which four drug conditions were administered according to three 4×4 balanced Latin squares. Study drugs were given at 48-h intervals. The four drugs were: a placebo combination, morphine sulfate 60 mg alone, dextromethorphan 60 mg alone, and the combination of morphine sulfate 60 mg and dextromethorphan 60 mg. These doses represent the proposed therapeutic dose of the morphine/dextromethorphan combination. The procedure for assessing respiratory depression involved breathing fixed concentrations of carbon dioxide (CO₂): 2%, 4%, 6%, and 8% CO₂ in combination with 21% oxygen and the balance nitrogen. Subjects breathed from tanks for 2 min each, progressing from the lowest to the highest concentration. After each 2-min period, the subjects were allowed to breathe room air until they were comfortable; they then proceeded to the next CO₂ concentration. The minute volume was calculated from the last 15 breaths and was corrected for temperature, pressure, and water vapor. The measure of respiratory depression was the decrease in the slope of the minute volume/CO₂ dose response curve.

Morphine alone depressed the slope at the 2-, 4-, and 6-h postdrug observations, which can be seen in Figure 3. There was no evidence that dextromethorphan potentiated the decrease in the slope of the minute volume dose response curve more than morphine alone. On the basis of this study, it is concluded that dextromethorphan does not alter the respiratory depressant action of morphine.

In summary, these three clinical pharmacology studies indicate that dextromethorphan does not alter the euphoric, physical de-
pendence, or respiratory depressant capacities of morphine. These studies suggest that the potentiation of morphine analgesia by dextromethorphan is selective.

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References


