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Blockade of Morphine Abstinence by Δ^9-Tetrahydrocannabinol

Hine *et al.* (*1*) reported that Δ^9-*trans*-tetrahydrocannabinol (THC) suppresses certain symptoms of naloxone-precipitated morphine abstinence in rats. However, the title of their report, "Morphine-dependent rats: Blockade of precipitated abstinence by tetrahydrocannabinol," is quite misleading since three important abstinence signs, including ear blanching, ptosis, and vocalization, were not significantly reduced even by the highest dose of THC (two were induced by THC alone). Thus, the most that can be claimed is that THC reduced two of the symptoms of precipitated abstinence, wet shakes and defecation.

At the doses of THC that were effective in suppressing abstinence symptoms in the study, THC has a substantial sedative effect (*2*) (although the authors state that doses of 5 mg/kg or less did not produce sedation in their rats). It is not surprising that THC might suppress a variety of behavioral symptoms of precipitated abstinence because of its general sedative properties. Unfortunately, the study failed to include controls that were treated with other sedative drugs such as benzodiazepines or barbiturates, which do not exhibit cross dependence with narcotics. It is possible that these drugs would be as effective as THC in suppressing certain signs of precipitated abstinence.

Finally, the authors propose that their data suggest that further exploration of the therapeutic utility of THC in narcotic detoxification is warranted. They argue that THC, if it were effective in suppressing abstinence signs, would be preferred to drugs such as methadone since the latter produces physical dependence, while the former does not. However, the doses of THC required for effective suppression of abstinence symptoms in their study, 5 to 10 mg/kg, were far beyond the range of doses required to produce intoxication in human subjects (about 0.02 mg/kg) (*3*). I am not familiar with any other reports of doses in this range administered to human subjects. If such extremely high doses of THC are required to suppress abstinence signs in humans, there is no strong reason to believe that THC would be desirable as an agent for detoxification.

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The only agents capable of specifically suppressing all components of a narcotic abstinence syndrome are opiates or their derivatives (*1*). At sedative doses, barbiturates may not block or even attenuate narcotic abstinence signs in humans (*2*) or rodents (*3*). Benzodiazepines, clinically effective in controlling seizure activity (*4*), also do not suppress all abstinence signs when used to treat neonatal or adolescent narcotic withdrawal (*5*), notwithstanding evidence of effective suppression by low doses of benzodiazepines of naloxone-induced jumping in morphine-pelleted mice (*6*). Thus, the question of which abstinence signs in animals dependent on narcotics are most "important" is a complex one which cannot be easily answered.

The purpose of our report was to determine the effect of pharmacologically active doses of Δ^9-*trans*-tetrahydrocannabinol (THC) in the rat on nine (by no means exhaustive) components of a precipitated abstinence syndrome in this species. When abstinence scores for each animal were determined from the total number of the nine signs present, the data clearly indicated a THC dose-dependent decrease in number of signs displayed, statistically significant at doses of 2 mg per kilogram of body weight and at higher doses. Moreover, wet shakes, one abstinence sign in the rat elicited at moderate (*7*) to high (*8*) degrees of dependence only with high naloxone doses (*8*), was the sign most affected by THC. Our conservative statistical presentation did not emphasize the fact that, even at 1 mg/kg (the lowest dose used), prior treatment with THC resulted in significantly ($P = .048$, one-tailed Fisher test) fewer rats exhibiting wet shakes compared to control animals. Frequencies of occurrence of two other signs (not one, as Carder suggests), presence of diarrhea at 30 minutes and an elevated fecal bolus count at 15 minutes, were also significantly reduced—to zero in some cases.

Finally, there are two problems with Carder's extrapolation of appropriate THC doses for humans and rodents on a milligram per kilogram basis. There is at least a tenfold difference in doses required for psychopharmacological effects in these species, attributable, in part, to differences in absorption and distribution with different routes of administration. This difference is illustrated in acute toxicity studies in the rat and mouse by a median lethal dose (MLD) after intraperitoneal administration that is 10 to 13 times higher than the MLD after intravenous administration (*9*), since most of the drug remains at the injection site after intraperitoneal injection and relatively little enters the brain or is converted to active metabolites (*10*). Second, 0.02 mg/kg was the approximate average intravenous dose at which autonomic and subjective effects of THC were first perceived by the subjects of the study cited in Carder's reference 3, whereas "intoxicating" human doses generally range from 100 to 250 μg/kg for the inhalation route (*11*). This route is at least as effective as the intravenous one for producing psychoactive and toxic effects (*12*), although impaired performance on some cognitive tasks may not occur even at these doses (*13*). Thus, doses of THC found effective in our study are within a reasonable range for extrapolation to clinical use.

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