Fentanyl Challenges

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Abstract

This report describes effective prolonged opiate blockade by subcutaneous depot-naltrexone (d-NTX) preparation. The d-NTX is a 1000 mg pellet inserted at opiate detoxification. The assay of effective opiate blockade was direct opiate challenge. Fifteen challenges were performed. Opiate challenges occurred from 21 to 70 days after d-NTX implantation (mean 40.9 days). All patients were refractory to the opiate. The data suggest that this d-NTX preparation is effective for at least 4 weeks after implantation. While not a “cure” for opiate dependence, d-NTX may allow a prolonged interval after detoxification during which addicts will have time to benefit from social/psychological interventions.

Naltrexone (NTX) is a potent and effective narcotic antagonist.(1) People with drug levels $\geq 1$ ng/ml are refractory to the effects of intravenous opiates,(2) and it has potential efficacy as an adjunct to help maintain abstinence in opiate addicts after detoxification. Naltrexone was discovered in the late 1960s and evaluated at some length in the 1970s.(1,3) After it aroused clinical excitement in the early 1970s,(4) Second, although it is orally available and has a longer duration of effect than the other available
narcotic antagonists, oral NTX still needs to be given a minimum of three times a week, making compliance an issue.(5) We feel that the first issue has a solution in the use of accelerated opiate detoxification under sedation or anesthesia.(6) The second issue may have a solution in the use of slow-release subcutaneous depot-NTX (d-NTX).

Early recognition of the issue of compliance with oral NTX after detoxification led to some initial work in the development and evaluation of d-NTX preparations,(2,7-10) but the surge of interest apparent in the 1970s has not yet led to a published study demonstrating the effective use of d-NTX in a clinical setting. This report describes such a clinical experience.

**Methods**

Detailed written consent was obtained from every patient before any intervention. Consents were obtained for precipitated withdrawal and for pellet insertion.

All patients were initially detoxified under anesthesia, with propofol the principle anesthetic.(6) After induction with the propofol, patients were intubated and paralyzed. Withdrawal was then effected via administration of opiate receptor blockade with opiate antagonists. Pellet insertion occurred before the patient awoke from anesthesia.

All patients described herein were treated with pellets of NTX mixed with pharmacologically acceptable excipients and compressed into a cylindrical form. The preparation was a single pellet which contained 1000 mg of NTX in a cylinder 12.5 mm in diameter 9.5 mm high.

Insertion involved a small incision and subcutaneous deposition of the pellet approximately 3.5 cm away from the incision site using blunt dissection of the subcutaneous tissues. Some patients later returned for repeat pellet insertion approximately two months later. In these cases, the insertion was performed using lidocaine with 1/1000 epinephrine.

Initial assay attempts involved NTX blood levels from different commercial laboratories, but the blood levels appeared not to correlate with clinical experience; patients who reported being refractory to street-taken opiates had
unmeasurable levels at the time. This could have been due to levels below the sensitivities of the assays but nonetheless clinically effective, due to degradation of the NTX or its metabolites prior to assay, or it could have been due to errors in testing. Because of these issues, the assay was changed to a classic clinical assay of efficacy, direct opiate challenge.\(1-3\) Fentanyl was used as the challenge agent.

Fifteen challenges were performed on ten d-NTX recipients. One patient had three challenges, 3 had two challenges, and the remaining 6 had one challenge each. Of the fifteen challenges, 9 were given to men and 6 to women. One patient, patient four, had one challenge after each of two successive d-NTX insertions. In the other cases with more than one challenge, all were done after a single pellet insertion. The mean age of the patients being challenged was 30.3 with a range of 19 to 39. Patients were challenged with 250 mcg of fentanyl, a synthetic opioid with approximately 80 times the potency of morphine.\(11\) It has a short duration of action,\(11\) making it a good candidate for opiate challenge. The dose given was the pharmacologic equivalent of a 20 to 25 mg bolus of morphine.

**Results**

The results of the fentanyl challenges are presented in table 1. Challenges were performed a mean of 40.9 days after implantation of the 1000 mg tablet, with the earliest challenge at day 21 and the latest at day 70. As can be seen, no patient had a significant response. After fentanyl challenge, there were no significant changes in pupillary size or respiratory rate despite the significant narcotic load. In patient nine, there was a subjective impression of slight pupillary change which, if present, was too slight to be reflected in a change in measured pupillary size. The most significant adverse event after Fentanyl administration was what appeared to be a vasovagal response in patient five which was short-lived and not accompanied by evidence of opiate intoxication.

**Discussion**

Using fentanyl challenge, clinical efficacy of d-NTX has been demonstrated in a small group of patients for up to 70 days after implantation of a single 1000 mg NTX pellet. No patient demonstrated any evident response to direct opiate challenge.
While the times after pellet insertion at which Fentanyl challenge was performed varied, the data strongly suggest that the d-NTX pellet provides effective opiate receptor blockade for at least 4 weeks in most subjects. This duration is potentially crucial, as it would allow more time for post-detoxification programs to be effective. In the absence of opiate blockade, the highest relapse rate after detoxification occurs within the month following detoxification,(12) a time during which the patients described herein were refractory to opiate effect. Note that an alternative approach, maintenance therapy, has not been an obvious answer to the problem of relapse; even maintenance has high recidivism rates, with failure rates of 66% within the first month of treatment using high-dose levomethadyl acetate (LAAM) the best of the results reported in a recent study.(13) This is not the first attempt at development of a subcutaneous, slow-release form of NTX. As mentioned, several articles in the early 1980s described the manufacture of NTX-containing pellets and of their biological release in both animals and human beings. (2,7-10) This form of subcutaneous d-NTX was demonstrated to give a promising release profile with reasonable drug levels, and prolonged resistance to opiates in both human and non-human subjects after implantation was demonstrated.(2,7-10) Work with these preparations tapered off after the mid-1980s. We posit three reasons for this tapering. First, the system used for the preparation of pellets in those studies was protracted and expensive. Second, the methods described involved injectable preparations that could not be removed, in contradistinction to the pellets used for this study, which can be removed in any emergent situation. A third possibility is that incomplete detoxification made it difficult to initiate NTX therapy. To our knowledge, this is the first description of ongoing clinical experience with any d-NTX preparation.

One other experience with the d-NTX tablets used in this study has been reported. Brewer and Gastfriend placed successive d-NTX tablets in a young heroin addict after an initial detoxification.(14) The second tablet was placed five weeks after the first. Two weeks after the second implant, the patient was given a double challenge. First he was challenged with intravenous fentanyl in 50 mcg increments until a total of 1000 mcg had been given (roughly equivalent to 80 mg of morphine). There was no subjective or objective change. The same subject was then given 0.4 mg of intravenous naloxone and 50 mg of oral NTX. Again, there was no change. The data are consistent with the findings reported herein. It is important to note that d-NTX did not prevent experimentation with street
drugs post-detoxification. It did prevent a slip from becoming a relapse. This allows a longer period for meaningful intervention.

The patients given fentanyl challenge and reported herein represent only a fraction of those in whom pellets have been inserted in the last 2 years. From that experience, the only complication of d-NTX implantation which has occurred with frequency has been inflammation at the insertion site. A local response at the insertion sites is relatively common (~15%), although very few of the events (~1.3%) appear to be infectious and none have required more than oral antibiotic therapy and local soaks/dressings. Of note, earlier animal studies with a different d-NTX preparation have demonstrated that individual animals exhibited a non-necrotic inflammatory response which appeared to be caused by the NTX itself. (10) This is probably the same inflammatory response seen in our patients, and it may even play a positive role in the effective slow absorption over time reflected in the clinical efficacy of the d-NTX preparation. No systemic side-effects have been reported by any d-NTX patient. This is not surprising, as drug levels from the slow release of the subcutaneous NTX would be significantly lower than those obtained by oral administration,(2,7,15) and even orally administered drug has minimal side-effects.(16,17,18)

We would argue that maintenance of abstinence with d-NTX is more rational than maintenance of opiate dependence with a long-acting opiate such as Methadone. There are, however, several potential problems with NTX which need to be acknowledged. First, a patient with active NTX blockade will not be susceptible to routine narcotic analgesia for emergent situations. One d-NTX patient needed surgery for an arm fracture while he had a NTX pellet in place, and non-narcotic analgesia needed to be provided. Another patient developed symptomatic cholelithiasis with a d-NTX pellet in place and underwent laparoscopic cholecystectomy with non-steroidal analgesics for pain control. She was able to maintain abstinence throughout the process. Second, the effects of NTX on pregnancy have not been established. While one could argue that it may be safer to administer tiny doses of NTX via a slow-release system than to allow intermittent opiate usage during pregnancy, there is no available clinical information which one can use to apportion risk. This clinical issue needs desperately to be addressed. Third, the use of subcutaneous deposition does require an invasive technique, albeit minor.
We must emphasize that rapid detoxification coupled with d-NTX is not curative. Even if d-NTX is effective for up to 70 days, it is not a “solution” to drug dependence. We believe that all detoxifications need to be accompanied by attempts at social support and social change, such as a 12-step program. D-NTX is not that therapeutic environment; d-NTX is an adjunctive therapy whose goal is to give patients who are capable of change the opportunity to change over an extended interval during which drug-taking will not renew physical dependence.

In summary, we have described the use of a subcutaneous NTX pellet inserted at the end of detoxification which is capable of blocking opiate responses for extended periods after implantation. We believe that the use of this pellet may be a valuable adjunct to the process of helping addicts to break the vicious cycle of opiate dependence.

Reference
15. Wall ME, Brine DR, Perez-Reyes M. Metabolism and disposition of naltrexone in man after oral and intravenous administration. Drug Metab Dispos 1981;9:369-375
Table 1. **Responses to Fentanyl Challenge**

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<th>Pt #</th>
<th>Age</th>
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July 30, 1998

Sheldon I. Miller, MD, Editor
_The American Journal on Addictions_
7301 Mission Road #252
Prairie Village, KS 66208

Re: Depot Naltrexone (d-NTX) for Protection Against Opiate Effect in the Post-Detoxification Period

Dear Dr. Miller:

We appreciate the request for manuscripts sent to Dr. Gooberman after the Toronto meeting of the American Psychiatric Society. In response, we have prepared this manuscript, which covers an aspect of the detoxification work being done out of U.S. Detox, Inc. We have in addition submitted an abstract covering this material for the 9th annual AAAP meeting. The material has not been published elsewhere and is not being considered for publication elsewhere. We understand and appreciate the fact that your request for submission does not in any way obviate the need for peer review. We look forward to hearing the comments and critiques of your reviewers.

Sincerely,

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