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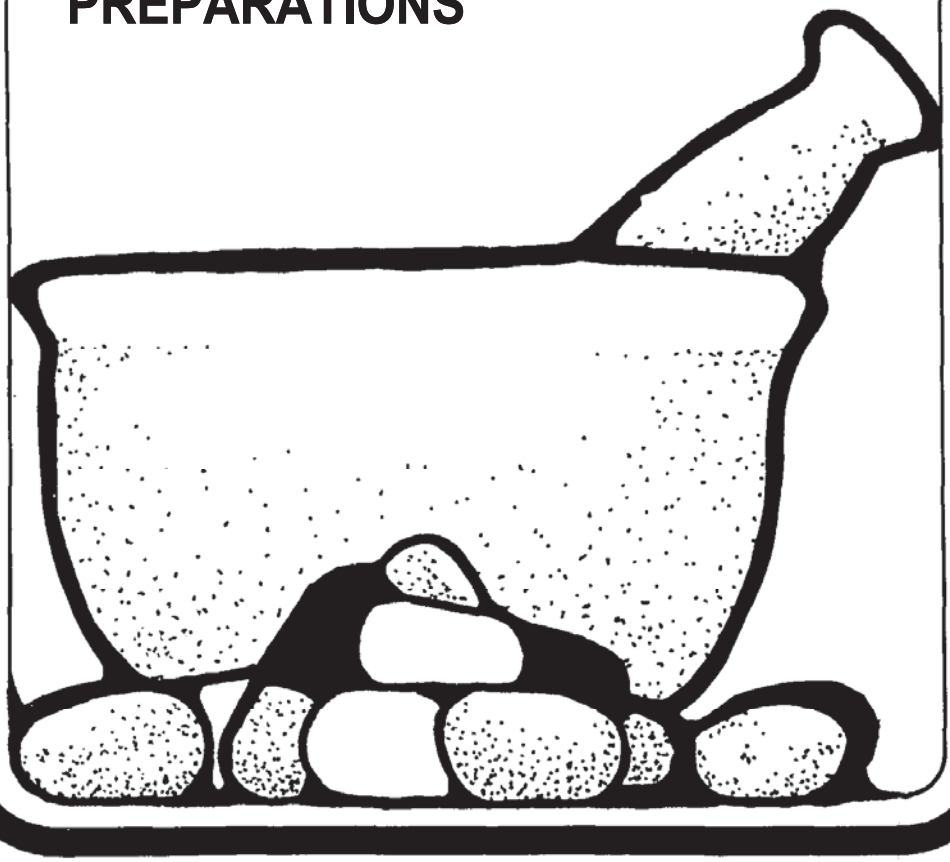
Narcotic Antagonists:

NALTREXONE PHARMACOCHEMISTRY AND SUSTAINED-RELEASE PREPARATIONS



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service • Alcohol. Drug Abuse • and Mental Health Administration

Narcotic Antagonists:

Naltrexone Pharmacochemistry and Sustained-Release Preparations

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The Clinical Pharmacology of Naltrexone: Pharmacology and Pharmacodynamics

Karl Verebey

The time-action of opiate antagonist activity of naltrexone was evaluated in detoxified ex-opiate addicts, using 25 mg intravenous heroin challenges. A 100 mg naltrexone dose provided 96% blockade at 24 hr, 86.5% blockade at 48 hr and 46.6% blockade at 72 hr. Following oral administration, naltrexone was rapidly and completely absorbed. Peak levels of naltrexone and its major metabolite 6ß-naltrexol were reached 1 hr after the dose. The high 6ß-naltrexol plasma concentrations only 1 hr after drug administration indicate a rapid biotransformation process, convertin a large fraction of the dose to less active metabolites. Over 70% of the dose was excreted in the 24 hr urine and less than 0.5% in the feces. No change was observed in the rate of naltrexone disposition during chronic dosing vs. the acute study, indicating no metabolic induction. The rapid achievement of steady state naltrexone plasma levels eliminates the need of stepwise induction at the beginning of nal trexone treatment.

After intravenous administration of 8 mg naltrexone, the plasma levels were unexpectedly high for the low dose, ranging between 32 and 3 ng/ml. The intravenous drug administration eliminated direct exposure to hepatic biotransformation; this is the likely reason for the higher naltrexone and the significantly lower metabolite (6ß-naltrexol) plasma levels.

A rising dose efficacy study from 100 to 800 mg per day provided an opportunity for studying naltrexone at much higher than thera-

peutic doses. No undesirable naltrexone-related side effects were observed during the study. Two weeks after the 800 mg/day doses were stopped, the plasma was free of naltrexone and its metabolites, indicating efficient elimination of the drug from the body.

Based on these human studies, a 100 mg dose of naltrexone provided 2 to 3 days protection against 25 mg of intravenous heroin. Naltrexone seems to be well tolerated even at doses well above those suggested for opiate antagonist therapy. No toxicity or accumulation of naltrexone and its metabolites was observed in any of the studies. The lack of dependence liability and absence of pharmacologic or metabolic tolerance during chronic treatment make naltrexone a safe and efficacious orally effective opiate antagonist.

INTRODUCTION

Naltrexone (N-cyclopropylmethylnoroxymorphone) was synthesized by Blumberg et al. in 1965 (1). In animal (2) and clinical studies (3,4) it demonstrated longer duration of action and greater potency than its N-allyl congener, naloxone. Naltrexone was also orally efficacious at significantly lower doses than naloxone. This is important for a drug which is a candidate for the treatment of ex-opiate addicts. The initial trials of naltrexone in man indicated good efficacy (opiate antagonism), practicality (long time action and oral effectiveness) and safety (low doses). In this overview of naltrexone the available data will be combined to examine naltrexone's opiate receptor blocking activity as it relates to its total biological disposition in human subjects.

The Time Course of Action of Opiate Antagonism

The opiate receptor blocking activity of naltrexone was studied by challenging it with intravenous heroin injections in four opiate ex-addicts (5). Control data of various objective and subjective responses to heroin, collected in the absence of naltrexone, in response to a 25 mg heroin injection was considered as 100%. In the test period, during naltrexone therapy (100 mg/day), 25 mg heroin challenges were performed 24, 48 and 72 hr after the last naltrexone dose. Individual challenges were at least 10 days apart in the same patients. The results are shown in figure 1. Averaging both the objective and subjective results, 96% of heroin-related responses were blocked at 24 hr, 87% at 48 hr and 47% at 72 hr. It is apparent from the figure that the blockade seems to hold longer and to a greater extent for subjective responses than for objective ones. Pooling pupillary miosis and respiratory depression data (ob-

jective), the blockade was 89% at 24 hr, 73% at 48 hr, and only 20% at 72 hr after naltrexone. The blockade for the subjective responses was 99% at 24 hr, 92% at 48 hr and a respectable 57% at 72 hr after naltrexone. The proposed function of naltrexone is to block the subjective (or euphorogenic) effects of heroin which, in fact, were blocked more efficiently than the objective ones. It should be emphasized that 25 mg of heroin is a substantial dose and few addicts can obtain such large quantities of heroin routinely. Thus the duration and magnitude of the blockade seem highly effective for most practical situations.

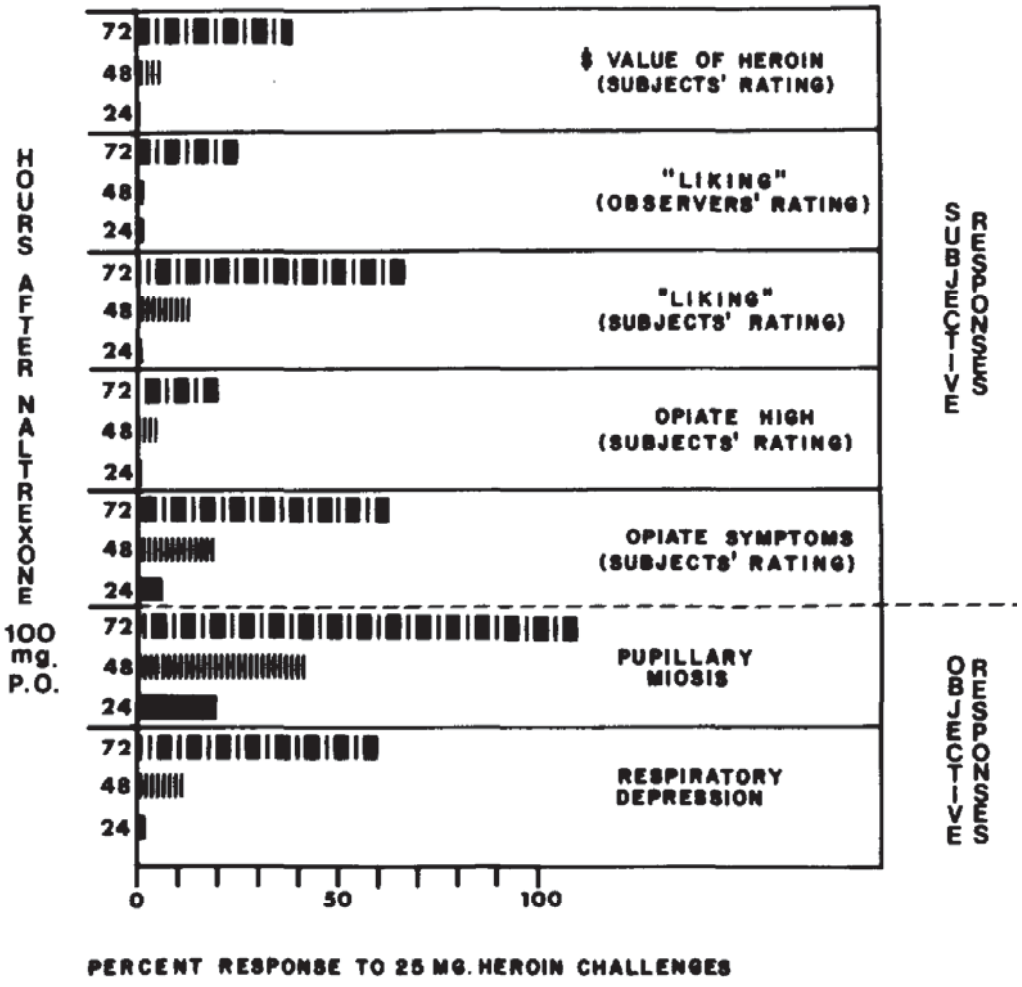

FIGURE 1. The percent objective and subjective responses are shown after 25 mg i.v. heroin 24,48 and 72 hr after 100 mg oral naltrexone. The 100% heroin responses were determined in the absence of naltrexone. For detailed description of the specific tests, see reference 5.

An interesting observation is that pupillary constriction at 72 hr is greater than the 100% control heroin effect. It is possible that some metabolic N-dealkylation occurs, producing the strong agon-

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