PRODUCT MONOGRAPH

[Pr]RPC-NALTREXONE

Naltrexone Hydrochloride Tablets

50 mg

Opioid Antagonist

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PRODUCT MONOGRAPH

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Naltrexone Hydrochloride Tablets

50 mg

THERAPEUTIC CLASSIFICATION

Opioid Antagonist

ACTION AND CLINICAL PHARMACOLOGY

Pharmacodynamic Actions

Naltrexone hydrochloride (naltrexone hydrochloride) is a pure opioid antagonist. It markedly attenuates or completely blocks, reversibly, the subjective effects of intravenously administered opioids. [In this context, the term *opioid* is used to describe 1) classic morphine-like agonists and 2) analgesics possessing agonist and antagonist activity (e.g., butorphanol, nalbuphine and pentazocine)].

When co-administered with morphine, on a chronic basis, naltrexone hydrochloride blocks the physical dependence to morphine and presumably other opioids. naltrexone hydrochloride has few, if any, intrinsic actions besides its opioid blocking properties. However, it does produce some pupillary constriction, by an unknown mechanism.

While the mechanism of action is not fully understood, the preponderance of evidence suggests that naltrexone hydrochloride blocks the effects of opioids by competitive binding (i.e., analogous to competitive inhibition of enzymes) at opioid receptors. This makes the blockade produced potentially surmountable, but overcoming full naltrexone blockade by administration of very high doses of opiates has resulted in excessive symptoms of histamine release in experimental subjects.

The mechanism of action of naltrexone hydrochloride in the treatment of alcoholism is not understood; however, involvement of the endogenous opioid system is suggested by preclinical data. naltrexone hydrochloride, an opioid receptor antagonist, competitively binds to such receptors and may block the effects of endogenous opioids. Opioid antagonists have been shown to reduce alcohol consumption by animals, and naltrexone hydrochloride has been shown to reduce alcohol consumption in clinical studies.

Naltrexone hydrochloride is not aversive therapy and does not cause a disulfiram-like reaction either as a result of opiate use or ethanol ingestion.

The administration of naltrexone hydrochloride is not associated with the development of tolerance or dependence.

In subjects physically dependent on opioids, naltrexone hydrochloride will precipitate withdrawal symptomatology.

Clinical studies indicate that 50 mg of naltrexone hydrochloride will block the pharmacologic effects of 25 mg of intravenously administered heroin for periods as long as 24 hours. Other data suggest that

doubling the dose of naltrexone hydrochloride provides blockade for 48 hours, and tripling the dose of naltrexone hydrochloride provides blockade for about 72 hours.

Pharmacokinetics / Bioavailability

Following oral administration, naltrexone hydrochloride undergoes rapid and nearly complete absorption with approximately 96% of the dose absorbed from the gastrointestinal tract. Although well absorbed orally, naltrexone is subject to extensive "first-pass" hepatic metabolism with an oral bioavailability estimate ranging from 5 to 40%. The activity of naltrexone is believed to be due to both parent and the 6-β-naltrexol metabolite.

Following the administration of 50 mg Naltrexone Hydrochloride tablets to 24 healthy adult male volunteers, the C_{max} for Naltrexone and its major metabolite, 6-β-naltrexol were 8.6 ng/mL and 99.3 ng/ml, respectively. The maximum concentration (C_{max}) and area under the curve (AUG), for both naltrexone and 6-β-naltrexol are dose proportional over the range of 50 to 200 mg. The time to maximum concentration (T_{max}) is one hour for both naltrexone and 6-β-naltrexol. The mean elimination half-life ($T_{1/2}$) values for naltrexone and 6-β-naltrexol are 4 hours and 12.9 hours, respectively. The mean elimination half-life ($T_{1/2}$) and time to maximum concentration ($T_{max)}$ for Naltrexone and 6-β-naltrexol are independent of dose.

The volume of distribution for naltrexone hydrochloride following intravenous administration is estimated to be 1,350 litres. *In vitro* tests with human plasma show naltrexone to be 21% bound to plasma protein over the therapeutic dose range.

The systemic clearance (after intravenous administration) of naltrexone hydrochloride approximates 3.5 L/min, which exceeds liver blood flow (-1.35 L/min), and suggests that naltrexone hydrochloride is a highly extracted drug (>98% metabolized) and that extrahepatic sites of drug metabolism exist. The major metabolite of naltrexone is 6-β-naltrexol. Two other minor metabolites are 2-hydroxy-3-methoxy-6-β-naltrexol and 2-hydroxy-3-methyl-naltrexone. Naltrexone and its metabolites are also conjugated to form additional metabolic products. A renal clearance ranging from 30 to 127 mL/min for naltrexone suggests it is primarily cleared by glomerular filtration. A renal clearance of 230 to 369 mL/min for 6-β-naltrexol suggests an additional renal tubular secretory mechanism. Naltrexone hydrochloride and its metabolites are excreted primarily by the kidney (56% to 79% of the dose), with fecal excretion being a minor elimination pathway. The urinary excretion of unchanged naltrexone hydrochloride accounts for less than 2% of an oral dose; urinary excretion of unchanged and conjugated 6-β-naltrexol accounts for approximately 43% of an oral dose. The pharmacokinetic profile of naltrexone hydrochloride suggests that naltrexone hydrochloride and its metabolites undergo enterohepatic recycling.

Adequate studies of naltrexone in patients with severe hepatic or renal impairment have not been conducted; however, a recent preliminary communication stated that naltrexone bioavailability is increased in patients with liver cirrhosis as compared to healthy subjects. (See PRECAUTIONS: Special Risk Patients.)

Clinical Trials

A blinded, randomized, balanced, two treatments, two sequence, two period, cross-over, single oral dose (1 x 50 mg) bioequivalence study of Naltrexone Hydrochloride Tablet 50 mg (T) with REVIA™ (Naltrexone Hydrochloride) Tablets 50 mg (R) was carried out in normal healthy, adult male volunteers under fasting conditions.

Trial Design and study Demographics

Summary of patient demographics for clinical trials in (specific condition)

Study #	Study Design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
Study No.: S-21-634	A blinded, randomized, balanced two treatment, two sequence, two period, cross-over, single-dose oral bioequivalence study in 40 healthy, adult, human subjects under fasting conditions.	**Dosage**: Single dose of 50 mg Naltrexone hydrochloride tablet. **Route of administration:** Oral **Duration:** Clinical study was conducted over duration of 12 days. A wash out of 07 days between each consecutive dosing period was maintained.	No of subjects planned- 40 No of subjects enrolled- 40 No of subjects dosed in period I- 40 No of subjects dosed in period II-34 No of subject completed the study- 34 No of subject withdrawn- 01 No of subjects not reported- 05	Mean age of 40 subjects- 32.25 yrs Mean age of 34 subjects- 30 yrs	Male

Comparative bioavailability studies

Table for single dose studies

Analyte Name (Naltrexone 50 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test***	**Reference†**	**% Ratio of Geometric Means**	**Confidence Interval#**
AUC_T‡ (units)	28.4659 32.4728 (51.45 %)	29.0885 33.7779 (60.58 %)	97.86%	90.21% TO 106.16%
AUC_I (units)	12.728 14.606 (54.16 %)	11.326 13.027 (54.45 %)	112.37%	99.41% TO 127.03%
C_{max} (units)	30.6781 34.7026 (49.61 %)	31.1722 35.8116 (57.92 %)	Not applicable	Not applicable
T_{max}§ (h)	0.83 (0.33 - 2.50)	1.38 (0.50 - 2.00)	Not applicable	Not applicable
$T_{½}$€ (h)	3.15 (54.74 %)	2.76 (37.91 %)	Not applicable	Not applicable

Table for multiple dose studies

Analyte Name (Naltrexone 50 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test***	**Reference†**	**% Ratio of Geometric Means**	**Confidence Interval#**
AUC_{tau} (units)	28.4659 32.4728 (51.45 %)	29.0885 33.7779 (60.58 %)	97.86%	90.21% TO 106.16%
C_{max} (units)	12.728 14.606 (54.16 %)	11.326 13.027 (54.45 %)	112.37%	99.41% TO 127.03%
C_{min} (units)	30.6781 34.7026 (49.61 %)	31.1722 35.8116 (57.92 %)	Not applicable	Not applicable
T_{max}[10] (h)	0.83 (0.33 - 2.50)	1.38 (0.50 - 2.00)	Not applicable	Not applicable

Treatment of Opioid Addiction

Naltrexone hydrochloride has been shown to produce complete blockade of the euphoric effects of opioids in both volunteer and addict populations. When administered by means that enforce compliance, it will produce an effective opioid blockade, but has not been shown to affect the use of cocaine or other nonopioid drugs of abuse.

The drug is reported to be of greatest use in good prognosis opioid addicts who take the drug as part of a comprehensive occupational rehabilitative program, behavioural contract, or other compliance enhancing protocols.

Alcoholism

The efficacy of naltrexone hydrochloride as an aid to the treatment of alcoholism was tested in placebo controlled, outpatient, double-blind trials. These studies used a dose of naltrexone hydrochloride once daily for 12 weeks as an adjunct to social and psychotherapeutic methods. Patients with psychosis, dementia, and secondary psychiatric diagnosis were excluded from these studies.

In one of these studies, 104 alcohol-dependent patients were randomized to receive either naltrexone hydrochloride once daily or placebo. In this study, naltrexone hydrochloride proved superior to placebo in measures of drinking including abstention rates (51% vs. 23%), number of drinking days, and relapse rates (31% vs. 60%). In a second study with 82 alcohol-dependent patients, the group of patients receiving naltrexone hydrochloride were shown to have lower relapse rates (21% vs. 41%), less alcohol craving, and fewer drinking days compared with patients who received placebo.

The clinical use of naltrexone hydrochloride as adjunctive pharmacotherapy for the treatment of alcoholism was also evaluated in a multi-center safety study. This study of 865 individuals with alcoholism included patients with comorbid psychiatric conditions, concomitant medications,

polysubstance abuse and HIV disease. Results of this study demonstrated that the side-effect profile of naltrexone hydrochloride appears to be similar in both alcoholic and opioid-dependent populations. Naltrexone hydrochloride was not uniformly helpful to all patients, and the expected effect of the drug is a modest improvement in the outcome of conventional treatment.

INDICATIONS AND CLINICAL USE

RPC-NALTREXONE (naltrexone hydrochloride) is indicated to provide blockade of the pharmacologic effects of exogenously administered opioids as an adjunct to the maintenance of the opioid-free state in detoxified, formerly opioid-dependent individuals. There are no data that demonstrate an unequivocally beneficial effect of naltrexone hydrochloride on the rates of recidivism among detoxified formerly opioid-dependent individuals, who self-administer the drug. Naltrexone hydrochloride is expected to have a therapeutic effect only when given under conditions that support continued use of the medication.

Naltrexone hydrochloride is indicated in the treatment of alcohol dependence, as a component of a comprehensive psychotherapeutic or psychological alcoholism counselling program to support abstinence, and reduce the risk of relapse. The efficacy of naltrexone hydrochloride beyond twelve weeks of treatment has not been established.

CONTRAINDICATIONS

RPC-NALTREXONE is contraindicated in:

1. Patients receiving opioid analgesics.
2. Patients currently dependent on opioids, including those currently maintained on opiate agonists [e.g., Methadone or LAAM (levo-alpha-acetyl-methadol)].
3. Patients in acute opioid withdrawal (see WARNINGS).
4. Any individual who has failed the NARCAN® challenge (see DOSAGE AND ADMINISTRATION Section).
5. Any individual who has a positive urine screen for opioids.
6. Any individual with a history of sensitivity to naltrexone hydrochloride or any other components of this product (see PHARMACEUTICAL INFORMATION: Composition). It is not known if there is any cross-sensitivity with naloxone or other phenanthrene containing opioids.
7. Any individual with acute hepatitis or liver failure.

WARNINGS

Unintended Precipitation of Withdrawal

To prevent occurrence of an acute withdrawal syndrome, or exacerbation of a pre-existing sub-clinical withdrawal syndrome, patients should remain opioid-free for a minimum of 7-10 days before starting RPC-NALTREXONE. Since the absence of an opioid drug in the urine often is not sufficient proof that the patient is opioid-free, a NARCAN® challenge may be required to minimize the possibility of precipitating a withdrawal reaction following administration of naltrexone hydrochloride. The NARCAN® challenge test is described in the DOSAGE AND ADMINISTRATION Section.

Hepatotoxicity

Naltrexone hydrochloride has the capacity to cause dose related hepatocellular injury. Prior to making a decision to initiate treatment with RPC-NALTREXONE, the physician should establish whether the patient has subclinical liver injury or disease (see PRECAUTIONS: Laboratory Tests). Naltrexone hydrochloride is contraindicated in acute hepatitis or liver failure, and its use even in patients with evidence of less severe liver disease or a history of recent liver disease must be carefully considered in light of its hepatotoxic potential.

The evidence that identified naltrexone hydrochloride as a hepatotoxin was not obtained in studies involving its use at the doses recommended for opiate blockade, or for treatment of alcohol dependence (50 mg/day). However, the margin of separation between the apparently safe and the hepatotoxic doses appears to be only five-fold or less.

Patients should be warned of the risk of hepatic injury and advised to stop the use of naltrexone hydrochloride and seek medical attention if they experience symptoms of acute hepatitis.

Evidence of the hepatotoxic potential of naltrexone hydrochloride is derived primarily from a placebo-controlled study in which naltrexone hydrochloride was administered to obese subjects at a dose approximately five-fold that recommended for the blockade of opiate receptors (300 mg/day). In the study, 5 of 26 naltrexone hydrochloride recipients developed elevations of serum transaminases (ie, peak ALT values ranging from a low of 121 to a high of 532, or 3 to 19 times their baseline values) after three to eight weeks of treatment. Although the patients involved were generally clinically asymptomatic and the transaminase levels of all patients on whom follow-up was obtained returned to (or toward) baseline values in a matter of weeks, the lack of any transaminase elevations of similar magnitude in any of the 24 placebo patients in the same study is persuasive evidence that naltrexone hydrochloride is a direct (ie, not an idiosyncratic) hepatotoxin. This conclusion is also supported by evidence from other placebo-controlled studies in which exposure to naltrexone hydrochloride at doses from one to two-fold the amount recommended for the treatment of alcoholism or opiate blockade (50 mg/day) consistently produced more numerous and more significant elevations of serum transaminase than did placebo, and reports of transaminase elevations in 3 of 9 patients with Alzheimer's Disease who received naltrexone hydrochloride (up to 300 mg/day) for 5 to 8 weeks in an open clinical trial have been reported.

Although no cases of hepatic failure due to naltrexone hydrochloride administration have ever been reported, physicians are advised to consider this as a possible risk of treatment and to use the same care in prescribing naltrexone hydrochloride as they would other drugs with the potential for causing hepatic injury.

<u>Attempt to overcome blockade</u>

While naltrexone hydrochloride is a potent antagonist with a prolonged pharmacologic effect (24 to 72 hours), the blockade produced by naltrexone hydrochloride is surmountable. This is useful in patients who may require analgesia, but poses a potential risk to individuals who attempt, on their own, to overcome the blockade by administering large amounts of exogenous opioids. Indeed, any attempt by a patient to overcome the antagonism by taking opioids is very dangerous and may lead to a fatal overdose. Injury may arise because the plasma concentration of exogenous opioids attained immediately following their acute administration may be sufficient to overcome the competitive receptor blockade. As a consequence, the patient may be in immediate danger of suffering life endangering opioid intoxication (e.g., respiratory arrest, circulatory collapse). **Patients should be told of the serious consequences of surmounting the opiate blockade. (See INFORMATION FOR THE CONSUMER.)**

There is also the possibility that a patient who had been treated with naltrexone will respond to lower doses of opioids than previously used, particularly if taken in such a manner that high plasma concentrations remain in the body beyond the time that naltrexone exerts its therapeutic effects. This could result in potentially life-threatening opioid intoxication (respiratory compromise or arrest, circulatory collapse, etc.).

Patients should be aware that they may be more sensitive to lower doses of opioids after naltrexone treatment is discontinued.

PRECAUTIONS

General

Emergency Pain Management in Patients Receiving Fully Blocking Doses of RPC-NALTREXONE

In an emergency situation in patients receiving fully blocking doses of naltrexone hydrochloride, a suggested plan of management is regional analgesia, conscious sedation with a benzodiazepine, use of nonopioid analgesics or general anesthesia. In a situation requiring analgesia which can only be achieved with opioids, the amount of opioid required may be greater than usual, and the resulting respiratory depression may be deeper and more prolonged. In such circumstances, a rapidly acting opioid analgesic which minimizes the duration of respiratory depression is preferred. The amount of analgesic administered should be titrated to the needs of the patient. No methods to reverse opioid overdose in patients receiving naltrexone have been established by clinical trials. However, the use of the opioid antagonist naloxone, should be considered when attempting reversal.

Additionally, non-receptor mediated actions may occur (e.g., facial swelling, itching, generalized erythema, presumably due to histamine release). Irrespective of the drug chosen to reverse naltrexone hydrochloride blockade, the patient should be monitored closely by appropriately trained personnel in a hospital setting equipped and staffed for cardiopulmonary resuscitation.

Interference with the Action of Opioid Containing Drug Product

Patients taking naltrexone hydrochloride may not benefit from opioid-containing medicines, such as cough and cold preparations, antidiarrheal preparations, and opioid analgesics. Where a non-opioid containing alternative is available, it should be used.

Accidentally Precipitated Withdrawal

Severe opioid withdrawal syndromes precipitated by the accidental ingestion of naltrexone hydrochloride have been reported in opioid-dependent individuals. Symptoms of withdrawal have usually appeared within five minutes of ingestion of naltrexone hydrochloride and have lasted for up to 48 hours. Mental status changes including confusion, somnolence and visual hallucinations have occurred. Significant fluid losses from vomiting and diarrhea have required intravenous fluid administration. In all cases patients were closely monitored and therapy tailored to meet individual requirements.

Use of naltrexone hydrochloride does not eliminate or diminish withdrawal symptoms. If naltrexone hydrochloride is initiated early in the abstinence process, it will not preclude the patients' experience of the full range of signs and symptoms that would be experienced if naltrexone hydrochloride had not been started. Numerous adverse events are known to be associated with withdrawal.

Special Risk Patients

Renal Impairment: Naltrexone hydrochloride and its primary metabolite are excreted primarily in the urine, and caution is recommended in administering the drug to patients with renal impairment.

Hepatic Impairment: Caution should be exercised when naltrexone hydrochloride is administered to patients with liver disease. An increase in naltrexone AUG of approximately 5- and 10-fold in patients with compensated and decompensated liver cirrhosis, respectively, compared with subjects with normal liver function has been reported. These data also suggest that alterations in naltrexone bioavailability are related to liver disease severity.

Drug Interactions

Studies to evaluate possible interactions between naltrexone hydrochloride and drugs other than opiates have not been performed. Consequently, caution is advised if the concomitant administration of naltrexone hydrochloride and other drugs is required.

The safety and efficacy of concomitant use of naltrexone hydrochloride and disulfiram is unknown, and the concomitant use of two potentially hepatotoxic medications is not ordinarily recommended unless the probable benefits outweigh the known risks.

Lethargy and somnolence have been reported following doses of naltrexone hydrochloride and thioridazine.

Suicide

The risk of suicide is known to be increased in patients with substance abuse with or without concomitant depression. The risk is not abated by treatment with naltrexone hydrochloride (see ADVERSE REACTIONS).

Laboratory test

Tests designed to detect hepatic injury should be obtained prior to initiation of naltrexone hydrochloride therapy and periodically thereafter (see WARNINGS Section on Hepatotoxicity).

Periodic testing of all patients after initiation of treatment is critical if the occurrence of naltrexone hydrochloride induced liver damage is to be detected at the earliest possible time. Evaluations, using appropriate batteries of tests to detect liver injury are recommended on a monthly basis during the first six months of use; thereafter, clinical judgement about the frequency of monitoring must be relied upon.

Laboratory tests which may be used for the separation and detection of morphine, methadone, or quinine in the urine and with which naltrexone hydrochloride does not interfere include thin-layer, gas-liquid, and high-pressure liquid chromatographic methods.

Impairment of Fertility

Naltrexone Hydrochloride (100 mg/kg, approximately 100 times the human therapeutic dose) caused a significant increase in pseudopregnancy in the rat. A decrease in the pregnancy rate of mated female rats also occurred. The relevance of these observations to human fertility is not known.

Use in Pregnancy

There are no adequate and well-controlled studies in pregnant women. Naltrexone hydrochloride should be used in pregnancy only when the potential benefits justify the potential risk to the fetus. Naltrexone hydrochloride has been shown to have embryocidal and fetotoxic effects in rats and rabbits when given in dosages 30 and 60 times, respectively, the human dose.

Labour and Delivery

It is not known whether naltrexone hydrochloride affects the duration of labour and delivery.

Nursing mother

It is not known whether naltrexone hydrochloride is excreted in human milk. Because many drugs are excreted in human milk, naltrexone hydrochloride should be administered to a nursing mother only when the potential benefits justify the potential risk to the infant.

Pediatric Use

The safe use of naltrexone hydrochloride in subjects younger than 18 years of age has not been established.

ADVERSE REACTIONS

While extensive clinical studies evaluating the use of naltrexone hydrochloride in detoxified, formerly opioid dependent individuals failed to identify any single, serious untoward risk of naltrexone hydrochloride use, placebo controlled studies employing up to five-fold higher doses of naltrexone hydrochloride (up to 300 mg/day) than that recommended for use in opiate receptor blockade have shown that naltrexone hydrochloride caused hepatocellular injury in 5 of 26 patients exposed at this higher dose (see WARNINGS and PRECAUTIONS: Laboratory Tests).

Aside from this finding, however, available evidence does not incriminate naltrexone hydrochloride, used at any dose, as a cause of any other serious untoward event for the patient who is "opioid free". It is critical to recognize that naltrexone hydrochloride can precipitate or exacerbate withdrawal signs and symptoms in any individual who is not completely free of exogenous opioids. (see CONTRAINDICATIONS, WARNINGS, DOSAGE AND ADMINISTRATION).

Opioid Withdrawal like symptoms

Studies in alcoholic populations and in volunteers in clinical pharmacology studies have suggested that a small fraction of patients may experience an opioid withdrawal-like symptom complex consisting of tearfulness, mild nausea, abdominal cramps, restlessness, bone or joint pain, myalgia, and nasal symptoms. This may represent the unmasking of occult opioid use, or it may represent symptoms attributable to naltrexone. A number of alternative dosing patterns have been recommended to try to reduce the frequency of these complaints. (see Individualization of Dosage).

Opioid Addiction

Events Other than Hepatocellular Injury Reported During Clinical Testing:

The following adverse reactions have been reported both at baseline and during the naltrexone hydrochloride clinical trials in opioid addiction at an incidence rate of more than 10%: Difficulty sleeping, anxiety, nervousness, abdominal pain/cramps, nausea and/or vomiting, low energy, joint and muscle pain, and headache.

The incidence was less than 10% for: Loss of appetite, constipation, increased thirst, increased energy, feeling down, irritability, dizziness, skin rash, delayed ejaculation, decreased potency, and chills.

The following events occurred in less than 1% of subjects:

Respiratory: nasal congestion, itching, rhinorrhea, sneezing, sore throat, excess mucus or phlegm, sinus trouble, heavy breathing, hoarseness, cough, shortness of breath.

Cardiovascular: nose bleeds, phlebitis, edema, increased blood pressure, non-specific EGG changes, palpitations, tachycardia.

Gastrointestinal: excessive gas, haemorrhoids, diarrhea, ulcer.

Musculoskeletal: painful shoulders, legs or knees, tremors, twitching.

Genitourinary: increased frequency of, or discomfort during urination, increased or decreased sexual interest.

Dermatologic: oily skin, pruritus, acne, athlete's foot, cold sore, alopecia. Psychiatric: depression, paranoia, fatigue, restlessness, confusion, disorientation, hallucinations, nightmares, bad dreams.

Special Senses: eyes- blurred, burning, light sensitive, swollen, aching, strained; ears “clogged", aching, tinnitus.

General: increased appetite, weight loss, weight gain, yawning, somnolence, fever, dry mouth, head "pounding", inguinal pain, swollen glands, "side" pains, cold feet, "hot spells".

Post-marketing Experience

Data collected from post-marketing use of naltrexone hydrochloride show that most events usually occur early in the course of drug therapy and are transient. It is not always possible to distinguish these occurrences from those signs and symptoms that may result from a withdrawal syndrome. Events that have been reported include anorexia, asthenia, chest pain, fatigue, headache, hot flushes, malaise, changes in blood pressure, agitation, dizziness, hyperkinesia, nausea, vomiting, tremor, abdominal pain, diarrhea, elevations in liver enzymes or bilirubin, hepatic function abnormalities or hepatitis, palpitations, myalgia, anxiety, confusion, euphoria, hallucinations, insomnia, nervousness, somnolence, abnormal thinking, dyspnea, rash, increased sweating, and vision abnormalities.

Depression, suicide, attempted suicide and suicidal ideation have been reported in the post-marketing experience with naltrexone hydrochloride used in the treatment of opioid dependence. No causal relationship has been demonstrated. In the literature, endogenous opioids have been theorized to contribute to a variety of conditions. In some individuals the use of opioid antagonists has been associated with a change in baseline levels of some hypothalamic, pituitary, or gonadal hormones. The clinical significance of such changes is not fully understood.

Laboratory Test

With the exception of liver test abnormalities in investigator studies (see WARNINGS, PRECAUTIONS), results of laboratory tests, like adverse reports, have not shown consistent patterns of abnormalities that can be attributed to treatment with naltrexone hydrochloride.

In the trials evaluating naltrexone hydrochloride for the blockade of opiate receptors, abnormal liver function tests and lymphocytosis were the two most common categories of abnormalities reported. These abnormalities are common among populations of parenteral opioid users and alcoholics. As is the case with the untoward events described above, a large proportion of patients had abnormal tests

at baseline, further supporting the conclusion that the abnormalities observed are not attributable to naltrexone hydrochloride.

Idiopathic thrombocytopenic purpura was reported in one patient who may have been sensitized to naltrexone hydrochloride in a previous course of treatment with naltrexone hydrochloride. The condition cleared without sequelae after discontinuation of naltrexone hydrochloride and corticosteroid treatment.

Alcoholism

In two randomized, double-blind placebo-controlled 12-week trials to evaluate the efficacy of naltrexone hydrochloride as adjunctive treatment of alcohol dependence, a total of 93 patients received naltrexone hydrochloride at a dose of 50 mg once daily. The most common (incidence greater than 10%) adverse events associated with the use of naltrexone hydrochloride in these trials (incidence at least 5% greater than in patients receiving placebo} were: somnolence, nervousness, vomiting, weight decrease, dry mouth and decreased libido. The incidences of adverse events leading to discontinuation of naltrexone hydrochloride in these trials were: vomiting (5%); agitation (2%); insomnia (2%); nervousness (1%); drowsiness (1%); and malaise (1%). Discontinuation rate for headache was 1% for patients on naltrexone and 2% for patients on placebo. No serious adverse events were reported during these two trials.

In an open label safety study with approximately 570 individuals with alcoholism receiving naltrexone, the following new onset adverse reactions occurred in 2% or more of the patients:

Adverse Reaction	Percent (%)
Nausea	10%
Headache	7%
Dizziness	4%
Nervousness	4%
Fatigue	4%
Insomnia	3%
Vomiting	3%
Anxiety	2%
Somnolence	2%
Dry Mouth	2%
Dyspepsia	2%

In an open label safety study with approximately 570 individuals with alcoholism receiving naltrexone, the following adverse events were responsible for discontinuation in ≥ 1% of patients:

Adverse Reaction	Incidence of Discontinuation
Nausea	6%
Headache	3%
Dizziness	3%
Anxiety	2%
Nervousness	2%
Fatigue	1%
Vomiting	1%
Depression	1%
Euphoria	1%
Mouth Dry	1%
Insomnia	1%

Depression, suicidal ideation, and suicidal attempts have been reported in all groups when comparing naltrexone, placebo, or controls undergoing treatment for alcoholism.

Rate Ranges of New Onset Events

New Onset Event	Naltrexone	Placebo
Depression	0-15%	0-17%
Suicide Attempt/ Ideation	0-1%	0-3%

Although no causal relationship with naltrexone hydrochloride is suspected, physicians should be aware that treatment with naltrexone hydrochloride does not reduce the risk of suicide in these patients (see PRECAUTIONS).

DRUG ABUSE AND DEPENDENCE

Naltrexone hydrochloride is a pure opioid antagonist. It does not lead to physical or psychological dependence. Tolerance to the opioid antagonist effect is not known to occur.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms
There is limited clinical experience with naltrexone hydrochloride overdosage in humans. In one study, subjects who received 800 mg daily naltrexone hydrochloride for up to one week showed no evidence of toxicity.

Treatment
Consideration should be given to contacting a poison control center for the most up-to-date information. In view of the lack of actual experience in the treatment of naltrexone hydrochloride overdose, patients should be treated symptomatically in a closely supervised environment.

DOSAGE AND ADMINISTRATION

Initiation of RPC-NALTREXONE (Naltrexone Hydrochloride) Therapy

DO NOT ATTEMPT TREATMENT WITH NALTREXONE HYDROCHLORIDE UNLESS, IN THE MEDICAL JUDGEMENT OF THE PRESCRIBING PHYSICIAN, THERE IS NO REASONABLE POSSIBILITY OF OPIOID USE WITHIN THE PAST 7-10 DAYS. IF THERE IS ANY QUESTION OF OCCULT OPIOID DEPENDENCE, PERFORM A NARCAN® CHALLENGE TEST AND DO NOT ATTEMPT TO INITIATE NALTREXONE HYDROCHLORIDE THERAPY UNTIL NARCAN® CHALLENGE IS NEGATIVE (see below).

Treatment of Opioid Dependence
Initiate treatment with naltrexone hydrochloride using the following guidelines:

1. Treatment should not be attempted until the patient has remained opioid-free for 7-10 days. Self-reporting of abstinence from opioids should be verified by analysis of the patient's urine for absence of opioids. The patient should not be manifesting withdrawal signs or reporting withdrawal symptoms.

2. If there is any question of occult opioid dependence perform a NARCAN® challenge test (see below). If signs of opioid withdrawal are still observed following NARCAN® challenge, treatment with naltrexone hydrochloride should not be attempted. The NARCAN® challenge can be repeated in 24 hours.

3. Treatment should be initiated carefully, slowly increasing the dose of naltrexone hydrochloride administered. This can be accomplished by administration of 25 mg of naltrexone hydrochloride initially. The patient should be observed for 1 hour. If no withdrawal signs occur, the patient may be given the rest of the daily dose.

Once the patient has been started on naltrexone hydrochloride, 50 mg every 24 hours will produce adequate clinical blockade of the actions of parenterally administered opioids (i.e., this dose will block the effects of a 25 mg intravenous heroin challenge). A flexible approach to a dosing regimen may be employed in cases of supervised administration. Thus, patients may receive 50 mg of naltrexone hydrochloride every weekday with a 100 mg dose on Saturday or patients may receive 100 mg every other day, or 150 mg every third day. While the degree of opioid blockade may be somewhat reduced by using higher doses at longer dosing intervals, improved patient compliance may result from dosing every 48-72 hours.

Several of the clinical studies reported in the literature have employed the following dosing regimen: 100 mg on Monday, 100 mg on Wednesday, and 150 mg on Friday. This dosing schedule appeared to be acceptable to many naltrexone patients successfully maintaining their opioid free state.

Treatment of Alcoholism

A dose of 50 mg once daily is recommended.

The placebo-controlled studies that demonstrated the efficacy of naltrexone hydrochloride as an adjunctive treatment of alcoholism used a dose regimen of naltrexone hydrochloride 50 mg once daily for up to 12 weeks. Other dose regimens or durations of therapy were not evaluated in these trials.

A patient is a candidate for treatment with naltrexone hydrochloride if:

- the patient is willing to take a medicine to help with alcohol dependence;
- the patient is opioid free for 7 - 10 days;
- the patient does not have severe or active liver or kidney problems (typical guidelines suggest liver function tests no greater than three times the upper limits of normal, and bilirubin normal); and
- the patient is not allergic to naltrexone hydrochloride, and no other contraindications are present.

Refer to CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS for additional information.

Naltrexone hydrochloride should be used as part of a comprehensive treatment program for alcohol dependence. Factors associated with a good outcome include: appropriate management of comorbid conditions; use of community-based support groups; and good medication compliance. To achieve the best possible treatment outcome, appropriate compliance enhancing techniques should be implemented for all components of the treatment program, especially medication compliance.

The efficacy of naltrexone hydrochloride beyond twelve weeks of treatment has not been established.

NARCAN® CHALLENGE TEST

The NARCAN® challenge test should not be performed in a patient showing clinical signs or symptoms of opioid withdrawal, or in a patient whose urine contains opioids. The NARCAN® challenge test may be administered by either the intravenous or subcutaneous routes.

Intravenous: Inject 0.5 mL (0.2 mg) NARCAN® (0.4 mg/mL). Observe patient for 30 seconds for signs or symptoms of withdrawal. If there is no evidence of withdrawal, inject another 1.5 mL (0.6 mg) of NARCAN®. Observe patient for an additional 20 minutes.
Subcutaneous: Administer 2 mL (0.8 mg) NARCAN® (0.4 mg/mL). Observe patient for 20 minutes for signs or symptoms of withdrawal.

Note: Individual patients, especially those with opioid dependence, may respond to lower doses of NARCAN®. In some cases, 0.25 mL (0.1 mg) intravenous NARCAN® (0.4 mg/mL) has produced a diagnostic response.

Interpretation of the Challenge: Monitor vital signs and observe the patient for signs and symptoms of opioid withdrawal. These may include, but are not limited to: nausea, vomiting, dysphoria, yawning, sweating, tearing, rhinorrhea, stuffy nose, craving for opioids, poor appetite, abdominal cramps, sense of fear, skin erythema, disrupted sleep patterns, fidgeting, uneasiness, poor ability to focus, mental lapses, muscle aches or cramps, pupillary dilation, piloerection, fever, changes in blood pressure, pulse or temperature, anxiety, depression, irritability, back ache, bone or joint pains, tremors, sensations of skin crawling or fasciculations. If signs or symptoms of withdrawal appear, the test is positive and no additional NARCAN® should be administered.

Warning: If the test is positive, do NOT initiate naltrexone hydrochloride therapy. Repeat the challenge in 24 hours (see Confirmatory rechallenge). If the test is negative, naltrexone hydrochloride therapy may be started if no other contraindications are present. If there is any doubt about the result of the test, withhold naltrexone hydrochloride and repeat the challenge in 24 hours (see Confirmatory rechallenge).
Confirmatorv rechallenge (if necessarv): Four (4) mL (1.6 mg) of NARCAN® (0.4 mg/mL) should be injected intravenously and the patient again observed for signs and symptoms of withdrawal. If none are present, naltrexone hydrochloride may be administered. **If signs and symptoms of withdrawal are present, administration of naltrexone hydrochloride should be delayed until repeated NARCAN® challenge indicates the patient is no longer at risk.**

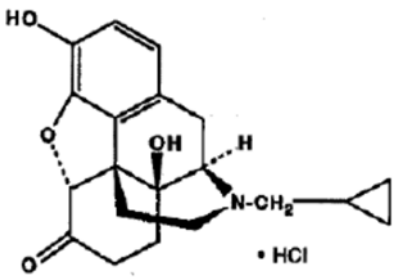
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Naltrexone Hydrochloride

Chemical Names:
1) Morphinan-6-one,17-(cyclopropylmethyl)-4,5-epoxy-3,14- dihydroxy,(5α)-
2) 17-(Cyclopropylmethyl)-4,5a-epoxy-3,14-dihydroxymorphinan-6-one

Structural Formula:



Molecular Formula: $C_{20}H_{23}NO_4$ HCl

Molecular Weight: 377.87
Description: Naltrexone hydrochloride is a white, crystalline compound which is highly soluble in water to the extent of about 100 mg/mL.

pKa_1: 8.73

pKa_2: 9.89

pH: 5.17 of a 1% solution in water 14

Melting Point by DSC: 270°C followed by decomposition

Partition co-efficient: 1.6 between n-octanol and 0.1 M phosphate buffer at pH 6.97± 0.02.

Composition

RPC-NALTREXONE (naltrexone hydrochloride) tablets contain 50 mg naltrexone hydrochloride. Nonmedicinal ingredients colloidal silicon dioxide, crospovidone, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and Sheff Coat Yellow.

Stability and Storage Recommendations
Store at controlled room temperature (15°-30°C). Dispense in a tight container as defined in the USP.

AVAILABILITY OF DOSAGE FORMS

RPC-NALTREXONE (naltrexone hydrochloride) is available as 50 mg, light yellow, capsule-shaped, biconvex, film coated tablets. Debossed with “5” &”0” on either side of score line on one side and "R P" on the other side. Bottles of 30 & 50 and blisters of 10 tablets.

INFORMATION FOR THE CONSUMER

Patient Information Leaflet

RPC-NALTREXONE (Naltrexone Hydrochloride) 50 mg Tablets

Please read this leaflet carefully before you start to take RPC-NALTREXONE. If you have any questions or are not sure about anything just ask your doctor or pharmacist.

USE

RPC-NALTREXONE is used together with your other forms of treatment such as counselling to help you to remain free from your dependence on alcohol, heroin, methadone or other similar opiate drugs of addiction.

HOW IT WORKS

Opiate drugs affect certain parts of the brain known as opiate receptors, producing euphoria (or "a high") and other effects. Naltrexone hydrochloride is an opiate receptor blocker. Naltrexone

hydrochloride blocks onto these receptor sites and blocks the effects of opiate drugs as well as the body's own opioids. The body's own opioids which occur naturally in the brain may be involved in alcoholism. While it is not completely understood how naltrexone hydrochloride works, in the treatment of alcoholism, in patients who have stopped drinking, naltrexone hydrochloride may help to prevent a return to heavy alcohol use. RPC-NALTREXONE will not make you sick as a result of drinking alcohol. It is not addictive.

HOW TO TAKE IT

For the treatment of alcoholism, the recommended daily dose is 50 mg.
If you are being treated for opioid dependence, you must have stopped taking opiate drugs for at least 7-10 days. Your physician will carry out a test which will show that you are free from these drugs before starting treatment. You will be given a starting dose of 25 mg and then one tablet (50 mg) daily, or it may be more convenient to take two tablets (100 mg) on Monday and Wednesday, and three tablets (150 mg) on Friday. Your doctor will decide which is best for you.

WHAT HAPPENS IF YOU MISS A DOSE

It is important to continue taking RPC-NALTREXONE as it only remains effective against alcohol and opiate drugs as long as you continue to take the tablets.

If you forget one dose it would have no long term consequences as the effect of RPC-NALTREXONE lasts for up to two days, but take the tablet as soon as possible. However, do not double-up on your dose. Do not take more than your prescribed dose.

If you stop taking RPC-NALTREXONE and re-start the use of opiate drugs or alcohol, there is a danger that you will relapse and become dependent on these drugs or alcohol again.

If you have restarted opiate drugs you must not take RPC-NALTREXONE until you have seen your doctor, who will make sure you are opiate free.

If you take RPC-NALTREXONE right after taking an opiate you will suffer withdrawal symptoms (cold turkey) (such as nausea, vomiting, shakiness, sweating and anxiety) which may be severe.

DURATION OF TREATMENT

You should continue to take RPC-NALTREXONE for as long as it is prescribed by your doctor. This could be for three months or longer. RPC-NALTREXONE does not produce "a high" and you cannot become addicted to it.

WHAT HAPPENS IF YOU DRINK ALCOHOL WHILE TAKING RPC-NALTREXONE (naltrexone hydrochloride)

You should not experience any unpleasant reaction if you drink alcohol while taking RPC-NALTREXONE. However, your blood alcohol level will still increase and you will become physically and mentally impaired if you do drink alcohol while taking RPC-NALTREXONE.

WARNINGS

Do not take opiates [including methadone or LAAM (levo-alpha-acetyl-methadol)] in an attempt to overcome the blocking effects of naltrexone hydrochloride. If you do, then you could be in trouble. Large doses of opiates can lead to difficulty in breathing and even to death.

Do not give your tablets to other people particularly those who are known to be dependent on opiate drugs because a withdrawal syndrome "cold turkey" may be precipitated. Signs and symptoms (such as nausea, vomiting, shakiness, sweating and anxiety) which may be severe, may develop within five minutes. If this happens call a doctor.

You should not take RPC-NALTREXONE if you are allergic to this product, or if you have acute hepatitis or liver failure. However, your doctor will advise you on these matters when the possibility of naltrexone hydrochloride treatment is first discussed.

Your doctor will request that a blood sample is taken before you start treatment and at various times during treatment. This is necessary because RPC-NALTREXONE is processed by the liver and these tests indicate if your liver is working well.

Do not drink alcohol during the time you are taking RPC-NALTREXONE as this could cause damage to your liver. If you develop abdominal pain lasting more than a few days, white bowel movements, dark urine, or yellowing of your eyes, you should stop taking RPC-NALTREXONE immediately and see your doctor as soon as possible.

Tell your doctor if you are pregnant or breast-feeding as the effects of naltrexone hydrochloride on the baby are not known.

If you experience any unusual sensations or feel unwell after starting RPC-NALTREXONE tell your doctor.

Some medicines may contain opiates, for example certain cough medicines, antidiarrheals (such as kaolin with morphine) and analgesics (pain killers). RPC-NALTREXONE may block the effects of these medicines. If you are ill and require treatment you must tell the doctor or pharmacists that you are taking RPC-NALTREXONE. They can then recommend a medicine which will be effective.

OVERDOSE

In the event of an accidental overdose go to your nearest hospital emergency department or tell your doctor immediately, even though you may not feel sick.

STORING YOUR MEDICINE

Keep your tablets in a safe place where children cannot reach them. These tablets could harm them.

If your doctor decides to stop the treatment, return any leftover tablets to the pharmacist.

PHARMACOLOGY

Naltrexone hydrochloride, an opioid antagonist, is a synthetic congener of oxymorphone, and differs in structure from oxymorphone in that the methyl group on the nitrogen atom is replaced by a cyclopropylmethyl group. Naltrexone is also related to the potent opioid antagonist, naloxone, or n-allylnoroxymorphone (NARCAN®), and is, technically, a thebaine derivative. However, it has no opioid agonist properties.

Naltrexone has been shown to be a potent orally effective and safe antagonist of a variety of opioid responses in rodents.

Naltrexone was 16 times more potent than naloxone in preventing etonitazene-induced Straub tail in female mice when administered p.o., but was only 1.6 times as potent when administered s.c.. In male mice, naltrexone was 11 times as potent as naloxone p.o., but was only 1.5 times as potent as naloxone s.c.. The greater relative oral potency suggests that in mice, naltrexone may be better absorbed orally than naloxone. Naltrexone was also shown to be a potent antagonist of:

1. oxycodone-induced Straub tail in mice (p.o.)

2. oxycodone blockade of phenylquinone-induced writhing in mice (p.o.)

3. morphine-induced catalepsy in rats (p.o., s.c.)

4. oxymorphone-induced loss of righting reflex in rats (s.c., i.v.)

Naltrexone competitively inhibited ^{3}H-naloxone and ^{3}H-dihydromorphine binding to the μ-receptor in rat brain membranes, and had a 5 times greater affinity for the μ-receptor than did naloxone.

Naltrexone has no selective anti-writhing activity in the phenylquinone-induced writhing test in mice (p.o., s.c.). The naltrexone antiphenylquinone effects were seen only at doses close to the toxic level, which suggests that they were not due to analgesia. Naltrexone had no analgesic activity in rats, and was virtually inactive in the rat phenylquinone-induced writhing test.
Naltrexone had an anesthetic effect 1.4 times as potent as naloxone and 0.27 times as potent as lidocaine on the sciatic nerve in rats when injected perineurally. In a study on the behavioral and autonomic effects and acute toxicity of naltrexone orally in mice and rats, naltrexone showed a low order of toxicity. Naltrexone caused only ataxia and loss of auditory pinna reflex in mice and no behavioral effect up to and including 324 mg/kg in rats.

Preclinical studies have demonstrated interactions between alcohol and opioid receptor activity. Morphine suppresses alcohol withdrawal in mice and alcohol suppresses morphine withdrawal in rats, indicating pharmacological cross-tolerance. In addition, opioid antagonists (i.e., naltrexone) have been shown to block some of the effects of alcohol, including behavioural symptoms of alcohol withdrawal in mice and rats. Naloxone also blocks alcohol-elicited increases in motor activity in mice. Preclinical evidence suggests that opiate antagonists can decrease alcohol consumption. For example, rats increase alcohol intake following inescapable but not escapable shock. Injections of naltrexone were found to block this increase in drinking following inescapable shock, when compared with rats given placebo injections.

Volpicelli (1987) and Volpicelli et al. (1986) studied a model of alcohol drinking in rats based on the observation that alcohol drinking often occurs following uncontrollable events. He referred to human studies supporting the notion that alcohol drinking increases following, but not during arousing situations. Alcohol-drinking rats increased their consumption of alcohol following the receipt of an inescapable electric shock. The large increases in alcohol consumption did not occur on days in which shock was administered but increased on the day after inescapable shock. Naltrexone, 10 mg/kg subcutaneously, blocked post-shock alcohol consumption whereas placebo-treated post-shock rats increased their consumption of alcohol.

The effects of naltrexone and naloxone were studied on the ability to train rats to consume various concentrations of alcohol. Sprague-Dawley rats were treated with either naltrexone or naloxone administered intraperitoneally (i.p.) 15 minutes prior to a 30-minute alcohol drinking access period.

Both naltrexone and naloxone dose-dependently decreased the voluntary consumption of a 20% weight/volume solution of alcohol ($p<0.01$).

The effects of naltrexone in decreasing alcohol intake has also been demonstrated in rhesus monkeys. Eight drug-naive rhesus monkeys were trained to self-administer at least 1.0 g/kg/day intravenous alcohol during a 4-hour daily session. Intramuscular administration of either saline or naltrexone (1, 3, or 5 mg/kg) was given 30 minutes before each daily session. Saline pretreatment periods were 10 days in duration and were alternated with 15 days of naltrexone treatment. Naltrexone decreased the self-administration of alcohol in a dose-dependent manner. Altshuler et al. (1980) suggested that the blockade of opioid receptors by naltrexone was responsible for the attenuation of the reinforcing effects of alcohol.

Naltrexone also decreased the consumption of alcohol in another experimental model in rhesus monkeys. Monkeys were trained to drink an alcohol solution under experimental conditions where they had free access to a continuous supply of water and alcohol. The effect of intramuscularly-administered naltrexone was studied (a) during the continuous supply of alcohol, and (b) after a two-day period of imposed abstinence from alcohol. Naltrexone significantly decreased the voluntary consumption of alcohol compared to placebo during both the continuous supply condition and after the two-day abstinence from alcohol. The decrease of drinking was selective since water drinking was not significantly affected by naltrexone.

The pharmacokinetics, tissue distribution and metabolism of naltrexone have been studied in male New Zealand White rabbits. After an intravenous bolus, the plasma half-life of naltrexone between 30 minutes and 3 hours was 55 ± 5 minutes and 53 ± 3 minutes for 1 and 5 mg/kg doses of naltrexone HCl, respectively. The drug concentration in the semen reached a maximum value between 15 and 30 minutes after the injection. At 120 minutes, the semen/plasma drug concentration ratio was 14 and 11 for the 1 and 5 mg/kg doses, respectively. Three minutes after injection 95% of the drug had left the plasma. After 5 minutes the conjugate levels exceeded the free drug levels in the plasma, suggesting rapid glucuronidation of the drug. Ninety minutes after injection, most of the tissues had concentrations of naltrexone and 6-β-naltrexol which exceeded the concurrent plasma concentration. Highest concentrations were observed in the submaxillary gland. Relatively high amounts of 6-β-naltrexol were found in the brain, fat, spleen, heart, testis, kidney and urine. The principal urinary metabolite was the glucuronide of naltrexone with 6-β-naltrexol and N-dealkylated naltrexone as minor metabolites.

The serum kinetics of 5 mg/kg intravenous naltrexone were studied in the dog. Serum samples were obtained from 2 minutes to 2 hours after injection and drug concentrations determined by radioimmunoassay. Serum levels of naltrexone fell rapidly; serum half-life during the elimination phase was 85.1 ± 9.0 minutes (mean ± SE).

Plasma level-time data for intravenous naltrexone at two dose levels in monkeys yielded no evidence of dose-dependent kinetics. A total body clearance of 51-55 mL/min/kg was demonstrated in two dogs. Urine (0-24 hours) contained 36% of the dose as naltrexone conjugates with less than 1% as unchanged naltrexone. Plasma level-time data for intravenous naltrexone in six monkeys yielded an average terminal half-life of 7.8 hours and a total body clearance of 64 mL/min/kg. The total body clearance for naltrexone was greater than the hepatic plasma or blood flow in both dogs and monkeys suggests, together with the extremely low renal excretion of naltrexone, the existence of elimination mechanisms besides liver metabolism and renal excretion.

In rabbits, monkeys and rats, naltrexone is reduced primarily to β-naltrexol. Monkeys receiving a daily oral dose of 12 mg/kg chronically, excreted very little free β-naltrexol and exhibited an

apparent sex-related difference in excretion patterns, with females excreting more than twice as much total base as males. Rabbits given an intraperitoneal dose of 30 mg/kg for 4 days excreted conjugated naltrexone as the predominant urinary metabolite, accounting for 80% of total base recovered in 24 hours. In rats receiving 100 mg/kg orally, less than 1% of the administered dose could be accounted for in the 24-hour urine, indicating that although the β-naltrexol is produced as a urinary metabolite, other means of disposition of the drug must exist. Thus, in man and the monkey, β-naltrexol is the predominant and persistent urinary metabolite.

The extent of binding of (15,16-^{3}H)-naltrexone is independent of naltrexone concentration over the concentration range of 1-500 ng/mL for dog plasma and of 0.1 - 500 ng/mL for human, monkey, guinea pig, rat and mouse plasma, ranging from 20% bound in rat plasma to 26% in plasma from beagle and mongrel dogs. This is consistent with previous findings of a large apparent volume of distribution in the dog. Determination of the tissue levels of radioactivity in mice at 1, 5, and 15 minutes after intravenous administration of (8-^{3}H)-naltrexone showed that naltrexone was rapidly distributed from plasma to tissues, with less than 4% of the dose present in plasma at one minute after injection.

The elimination of radioactivity after (15,16-^{3}H)-naltrexone administration i.v. was studied in rats and guinea pigs. An average of 42% of the dose was eliminated in urine and 55% in feces. Radioactivity levels in the excreta of one rat dosed i.m. yielded similar results. Guinea pigs which received 1 mg/kg i.v. excreted only 14% of the dose in feces and 84% in urine. Similar results were obtained following i.m. administration to guinea pigs. In guinea pig excreta, an average of 64% of the dose corresponded to naltrexone and conjugates, 19% to β-naltrexol and conjugates, and 2% to a-naltrexol and conjugates. In urine, the radioactivity corresponding to α-naltrexol and naltrexone was present mainly in conjugated form, whereas apparent β-naltrexol was mainly unconjugated. The radioactivity in feces corresponded principally to unconjugated naltrexone and β-naltrexol.

After subcutaneous injection of (15,16-^{3}H)-naltrexone (10 mg/kg) in male Wistar rats, peak concentrations of drug occurred in brain and plasma within 0.5 hours. Levels of naltrexone were sustained in brain between 2 and 24 hours and were barely detectable at 48 hours. The half-lives of naltrexone in brain and plasma were approximately 8.0 and 11.4 hours, respectively. The brain/plasma ratios of naltrexone at earlier times (0.5-1 hours) were higher than those at later times. The binding of naltrexone in vitro with rat plasma proteins in concentrations of 1-10 µg/mL ranged between 41% and 59%. 6-β-Naltrexol was present in very small amounts in brain but not in plasma. In addition to 7,8-dihydro-14-hydroxynormorphinone and 7,8-dihydro-14 hydroxynormorphine, tentative evidence was obtained for three other metabolites of naltrexone in brain. These metabolites were also present in plasma in addition to free and conjugated naltrexone and its N-dealkylated metabolites.

TOXICOLOGY

Test parameters and drug-related findings of toxicology studies carried out with naltrexone are summarized in the following table:

Acute Toxicity	Dose (mg / kg)	Drug-Related Findings LD_{50} (mg/kg)			
Species		p.o.	s.c.	i.v.	i.p.
Mouse	Various	1100	570	95,180*	332
Rat	Various	1450	1930	117	---
Guinea Pig	Various	1490	301	--	--
Dog	Various	>130	200	117	--

In the acute toxicity studies in the mouse, rat, and dog, cause of death was due to clonic-tonic convulsions and/or respiratory failure.

Species	Duration	Dose (mg/kg/day)	Observations
Sub chronic Toxicity Studies			
Rat	90 day	35,70,560 p.o.	No significant findings.
Rat	30 day	3,15,300 S.C.	No significant findings.
Dog	90 day	20,40,100 p.o.	Emesis at 100 mg/kg/d; no other significant findings
Dog	3 week	0.8,4,20 i.v.	Emesis, salivation, urination and other signs; decreased adrenal weights in females.
Dog	28 day	2,10,50 S.C.	Emesis, salivation, mild Tremors and muscular weakness at 50 mg/kg/d; no other significant findings.
Chronic Toxicity Studies			
Monkey	1 year	1,5,10,20 p.o.	No significant findings
Carcinogenicity Studies			
Mouse	24 months	30, 100 p.o.	No significant findings
Rat	24 months	30, 100 p.o.	No significant findings

In the two-year carcinogenicity study in rats, there were small increases in the numbers of mesotheliomas in males, and tumours of vascular origin in both sexes. The number of tumours were within the range seen in historical control groups, except for the vascular tumours in females, where the 4% incidence exceeded the historical maximum of 2%.

Mutagenesis: A total of twenty-two distinct tests were performed using bacterial, mammalian, and tissue culture systems. All tests were negative except for weakly positive findings in the Drosophila recessive lethal assay and non-specific DNA repair tests with *E. coli*. The significance of these findings is undetermined.

Reproduction Studies: Naltrexone Hydrochloride has been shown to have embryocidal and fetotoxic effects in rats and rabbits when given in dosages 30 and 60 times, respectively, the human dose.

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