

## PRECIPITATED WITHDRAWAL REACTION TO OPIATES IN CASES OF IMPROPER USE OF NALTREXONE

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### SUMMARY:

Lately Naltrexone is often used as a part of the complex overall drug rehabilitation program as an adjunct to maintenance of an opioid-free state in detoxified former opioid-dependent patients. However when the medicine is not applied properly according to the treatment safety protocol, different adverse effects can occur. The most important and dangerous of them is the occurrence of a strong precipitated withdrawal reaction to opiates. The authors describe 16 cases of Naltrexone precipitated withdrawal- 5 hospitalized and 11 ambulatory. Only 6 patients started Naltrexone treatment after a psychiatrist consultation. All the patients did not keep the necessary safety protocol of the medicine. 4 cases had a severe clinical presentation, 1 of them ended lethally. The treatment of the withdrawal is discussed and the necessity of strict clinical observation during the first days of Naltrexone use.

**Key words:** naltrexon, opioid, withdrawal, addiction.

### INTRODUCTIN:

Naltrexone / trade names Re Via; Nalorex, etc. / is a pure opiate antagonist, a synthetic derivate of oxymorphone. Naltrexone and its main active metabolite, 6-beta- naltrexol, are competitive antagonists at mu- and ka-opioid receptors and less at delta-opioid receptors. They reversibly block or significantly attenuate the subjective effects of opioids / classic morphine-like opiates and analgesics with agonist and antagonist activity/. Naltrexone does not lead to development of tolerance or dependence. It is not aversive therapy and therefore it does not cause disulfiram-like reactions. Naltrexone has low toxicity by itself – DL 50 mouse 1,1- 1,5 mg / kg. Its

bioavailability is 5 to 40%. It is well absorbed in GIT and has a first-pass hepatic metabolism. Plasma protein binding is 21%. The half-life of Naltrexone is 4 hours and of the main metabolite 6-beta –Naltrexol- 16 hours. In cases of developed physical dependency Naltrexone will cause a dramatic withdrawal symptomatology if the therapeutic protocol has been not strictly kept. The aim of Naltrexone treatment is to block the pharmacologic, mainly euphoric effects of the exogenously administered opioids as an adjunct to the maintenance of an opioid-free state in detoxified, former opioid-dependent patients. The usual dosage is 50 mg/ 24 hr. when blockade is adequate this dose blocks 25 mg Heroine IV. The usual duration of the treatment is 3 months. It is important to emphasize that Naltrexone treatment is only a part of the complex overall drug rehabilitation therapy. Different adverse effects of Naltrexone treatment have been described: 1. Unintended early and severe precipitation of opiate withdrawal when opiates have been taken 7-10 days prior to the beginning of Naltrexon application. 2. Hepatotoxicity- a dose related hepatocellular injury. 3. A fatal opiate overdose is still possible if attempts to overcome the competitive receptor blockade are made with a very high opiate dose during abuse or in case of general anesthesia. 4. After the end of Naltrexone treatment an increased sensitivity of the receptors to opiates exists, so lower doses opiates can cause fatal overdoses. 5. Some milder and rarer side effects have been described.

All the cases we describe are from the first group- accidental precipitation of withdrawal because of serious failure to observe the treatment protocol. According to it the patient should be opioid-free at least 7 to 10 days prior the first dose Naltrexone. If this safety instruction has not been followed a severe

acute withdrawal syndrome occurs or a pre-existing sub clinical withdrawal syndrome is exacerbated. Verification of an opioid-free state is made by anamnesis / not very reliable /, urine drug opiate test and, most important, a special Naloxone challenge test, recommended and described in details by the pharmaceutical firms. If Naloxone challenge test of a patient is positive the treatment with Naltrexone should not be started.

During the period 2001-2005 16 patients have been treated at the Department of Toxicology, Naval Hospital-Varna, with Naltrexone precipitated opiate withdrawal. 5 of them were in-patients and 11, who refused hospitalization, ambulatory out-patients. All of them admitted taking ReVia or Nalorex before 10-opiate-free days had passed.

#### **DESCRIPTION OF HOSPITAL CASES:**

**Case 1.** I.K.P., 23 years old, male, HR№1375 from 08.05.2001. Last dose Heroin IV –on 06.05.01; Codeine-7 tablets taken on 08.05.01 early morning. First dose Naltrexone / Nalorex/ 50 mg- on 08.05.2001. 50-60 minutes after that the patient got severe withdrawal symptoms- excessive vomiting, abdominal cramps, profuse diarrhea, muscle cramping, pains all over the body, seizures, uncontrolled psychomotor excitation, fever, raised temperature to 38.2 degrees C. He was admitted in Toxicology Department 3 hours later in a very impaired condition, in delirium, with seizures, with continuous severe vomiting and diarrhea and hypovolemia . Next 3 days severe GI, cerebral neurological and dysmetabolic abstinence syndrome with great intensity had been observed ; after that 2 days with milder symptoms. The patient has been discharged from hospital on 13.05.200. in a good condition.

**Case 2.** G.K.P., 23 years old, female, HR№1088 from 16.04.2001. Inhalation addiction to Heroine. Co morbidity- Anorexia nervosa. Last dose Heroine on 12.04.2001. First doses Nalorex- on 13, 14 and 15.04.01, j tablet- 12.5 mg daily. On 14.04.01q after the second Naltrexon dose-moderate withdrawal symptoms: gastrointestinal symptoms, tachycardia, abdominal cramps. Treated with benzodiazepines. On 15.04.01, after the third dose- worse abstinence with dominating excessive vomiting. On 16.04. 01 the patient was admitted in Toxicology Department with vomiting, hematemesis and .in a state of severe hypovolemic and hemorrhagic shock In spite of the intensive

treatment 7 hours later a lethal exit was registered. Pathoanatomic diagnosis: Heavy diffuse erosive gastritis. Atrophy of the stomach wall. Shock kidneys. Shock lungs. A lot of dark pigment in both lungs. Kachexia II stage.

**Case 3.** O.A.T., 20 years old, male. HR№4770 from 24.10.2002. On 23.10.02 he did urine opiate test and Naloxone challenge test as he prepared to start Naltrexon therapy. Both tests were negative and he was approved to start Nalorex the next day. On 23.10.02 in the evening he decided to have one last dose Heroin. On 24.10.02 in the morning he took the first 50 mg Naltrexon. 15 minutes later a strong withdrawal syndrome appeared: nausea, vomiting, diarrhea, abdominal and muscle cramps, fever, excitation, one big tonic-clonic seizure. Transported immediately to hospital. The withdrawal symptoms lasted 36 hours intensively in spite of the treatment. 3 days later he was discharged from the hospital in good health.

**Case 4.** V.D.I., 22 years old, male. HR№2838 from 19.07.2004. Last dose heroin on 18.07.04. Following the advice of a friend, started treatment with “a good pill to stop the addiction” on 19.07.04 . 15 minutes after the ingestion he had a strong headache, flush, sweating, nausea, vomited twice, became tense and frightened. HR 100/min., RR 180/90. Ambulatory diagnosis- “Antabus reaction”. Later information: the name of the pill was Nalorex. The withdrawal syndrome continued 24 hours with moderate severe mainly CNS expression. Two days later the patient was discharged.

**Case 5.** A.V.N., 24 years old, female.10.10.2005. Addiction to Heroin and benzodiazepines. Continuous ambulatory treatment with neuroleptics. Last dose Heroin- 5 days before the first dose naltrexon. 30 minutes after the first S tabl. ReVia the patient got moderate withdrawal: “unusual feelings”, chills, fever, headache, nausea, muscle stiffness and cramps of the arms. She took immediately 5 tablets Diazepam 0,010; 20 minutes started vomiting and had stomach cramps. She was admitted in a moderate severe abstinent state. 16 hours later she was discharged on her own demand in a better condition, with some minor withdrawal symptoms from CNS.

Description of the ambulatory cases. 11 patients had been treated as outpatients because of their refusal to be admitted in the hospital. In all cases they had declared a formal wish to stop their abuse. Only 2

patients started their treatment after a consultation with a psychiatrist. None of them kept the necessary opiate-free period. 4 patients had stopped heroin 4-6 days before the first dose Naltrexon; 5 patients- 2-4 days before that and 2 patients had smoked heroin the same day. All the 11 patients took continuously benzodiazepines and 3 of them- BZP and neuroleptics. The clinical expression of the withdrawal syndrome was severe in 1 case, moderate severe- in 8 cases and light- in 2 cases.

All the patients, including out-patients have been treated in the Intensive Care Unit of the Toxicology Department. Vital signs were monitored from 16 to 72 hours. Treatment was carried out with benzodiazepines by scheme IM and IV, cerebroprotectors- nootropics, vitamins, glucose and electrolyte infusions, correction of water and salts disturbances, protectors of the stomach mucosa, spasmolytics, antiemetics, antidiarrhea, hepatoprotectors, in some cases- carbamazepine, clonidine, etc

#### DISCUSSION:

The described cases illustrate the well known fact that naltrexon treatment of opiate addiction can be dangerous if the treatment safety protocol has not been kept properly. All the patients had some information about the predictable precipitation of withdrawal in case of improper treatment with this

medicine in advance. However they did not realize the seriousness of the safety advices or did not believe them. All the patients had taken the first dose naltrexon ambulatory. 4 of the hospitalized patients and 2 of the out-patients had started the treatment under the observation of a psychiatrist and with the agreement of their relatives. However they managed to break the safety rules. 5 of the out-patients had started the treatment after an advice of a medical specialist. One of the hospitalized and 4 of the out-patients had started the naltrexon treatment following the advice of non medics- relatives, friends, other addicts, etc. This fact arises some important questions. 1 How many patients treated recently for severe abstinence opiate syndrome have not declared their secret attempt for non official treatment with naltrexon or some similar medicine? 2. How many opioid addicts are currently treated with different medicines "prescribed "by non specialists and even non medics? 3. Does every patient who starts Naltrexon treatment sign an informed consent about it?

#### CONCLUSION:

As other strong acting treatments, the naltrexon treatment of opioid addiction should start either in a hospital for 3-4 days or ambulatory under a very close observation from medics and relatives until a successful opioid receptor blockade takes place.

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