The Study of the Demographic and Clinical and Laboratory Findings in Naltrexone Poisoning Patients Admitted to Razi Hospital, Rasht, During 2007-08

Morteza Rahbar Taromsar[1], Ali Reza Badsar[1], Choubineh Mah Manzar[2], Morteza Fallah Karkan[2]*

Received: 05.03.2012 *Accepted:15.04.2012*

ABSTRACT

Background: Naltrexone is a competitive opioid receptor antagonist blocking the euphoric effects of exogenous opioids. When used concomitantly with opioids, naltrexone causes severe withdrawal symptoms.The main aim of the study is to determine the symptomatology and outcome of patients who consumed naltrexone in conjunction with an opioid substance.

Methods: This cross-sectional study was performed on the patients hospitalized with history of naltrexone usage coincided with opioid substances at Razi Hospital, Rasht, Iran. The collected data were demographic information, abuse information, clinical signs and symptoms, laboratory findings, and therapeutic measures taken. Data analysis was performed by descriptive tests using SPSS software version 16.

Results: The mean age of the patients was 33.7±10.2. The majority of the cases were male (95.6%) and urban (96.7%). The main cause of withdrawal symptoms in 91.1% of the patients was inappropriate naltrexone usage.The main poisoning agent in 80% of the cases was consumed naltrexone alone. The route of consumption in 90.1% of the cases was oral and in 9.9% the cases was IV injection. The major clinical features were nausea, vomiting, and agitation.The main therapeutic measures were supportive intravenous fluids (94.8%) and opioid administration in the form of methadone. The mean hospitalization period was 21.8±18 hours.

Conclusion: Severity, clinical course, and outcome of opioid withdrawal by accidental or intentional naltrexone abuse varies greatly among patients and is unpredictable. Common findings upon presentation were gastrointestinal symptoms and agitation and the main therapeutic measures for these patients were support with intravenous fluids and anti-nausea drugs administration as plasil and opioid administration as methadone.

Keywords: Naltrexone, Opioid Substance, Poisoning.

IJT 2012; 649-654

INTRODUCTION

Treatment for opioid-dependent criminal justice clients has largely been abstinence oriented even though drug-free counseling for these individuals has failed to demonstrate efficacy. Despite the success rate of agonist treatments such as methadone and buprenorphine, relatively few probationers/parolees receive these medications (1). The criminal justice system generally has not been favorable to these treatments because they produce opioid effects similar to heroin and they have the potential for abuse and diversion (2). Moreover, many clients encounter barriers to methadone therapy, including their strictions of daily dosing regimens and the fear of detoxification from

1. Department of Forensic Medicine, Guilan University of Medical Sciences, Rasht, Iran.
2. Guilan University of Medical Sciences, Rasht, Iran.
*Corresponding Author Email: Badsar@Gums.ac.ir

methadone (3). An alternative treatment is antagonist maintenance with naltrexone (4,5).

The opioid antagonist naltrexone has been used for 20 years as an adjunct pharmacotherapy for the treatment of opioid dependence. Offenders with a history of opioid dependence are a particularly difficult group to treat and large proportions of them usually relapse shortly after release from prison, commit drug-related crimes and then are arrested and eventually re-incarcerated (4).

Naltrexone, a mu, kappa, and delta-opiate receptor antagonist with greatest affinity for the mu receptor, can be prescribed for treating opiate dependence. However, to date, naltrexone has been under-utilized as a maintenance treatment for opioid dependence, in part because of poor retention and compliance with the oral formulation (5). Naltrexone blocks the intoxicating and reinforcing effects of opioids, yet it has virtually no psychotropicor euphoric effects and is not an addictive drug. When taken regularly, naltrexone extinguishes opioid-taking behavior. Among non-offenders, clinical trials have shown the beneficial effects of naltrexone while patients remain in treatment. However, patients are often reluctant to initiate the medication and, once prescribed, compliance with naltrexone turn into a problem (4).

The first report on accelerated withdrawal syndrome due to the concomitant use of naltrexone and opioids was released in 1974 (6). The purpose of this study was to determine clinical findings and patients outcome in concomitant use of naltrexone and opioids**.**

MATERIALS AND METHODS

This cross-sectional study was performed on the hospitalized patients with the history of naltrexone usage coincided with opioid substances that referred to Razi Hospital, Rasht, Iran, during 2007-8. Patients who had referred to other health care centers before Razi Hospital or had incomplete records were excluded from the study. Data on demographic information, abuse information, clinical signs and symptoms, laboratory findings, and therapeutic measures were collected and analyzed by descriptive tests using SPSS software version 16.

RESULTS

Overall, 127 patients with naltrexone usage coincided with opioid substances referred to Razi Hospital, Rasht, Iran, during 2006-7. Of them, 24 cases were excluded because they had referred to other health care centers and received effective treatment on their clinical symptoms and laboratory results before admission to Razi Hospital, and 13 cases were excluded because of their incomplete records. Eventually, 90 cases were studied.

The mean age of the patients was 33.7±10.2 which ranged in age from 19 to 58 years. The majority of the cases were male (95.6%) and urban (96.7%) (Table 1) and the highest and lowest frequencies of occurrence of disease were in summer (31.1%) and winter (18.9%) seasons, respectively.

Table 1: Frequency distribution of demographic information in the patients

Demographic Information	Frequency (%)
Age	
< 20 yrs.	3 (3.3)
21-30	41 (45.6)
31-40	24 (26.7)
41-50	14 (15.5)
> 50 yrs.	8 (8.9)
Gender	
Male	86 (95.6)
Female	4 (4.4)
Residence	
Urban	87 (96.7)
Rural	3 (3.3)

The main poisoning agent in 80% of the cases was consumed naltrexone alone, in 14.4% of the cases was consumed naltrexone in conjunction with an opioid substance, and in 5.5% of the cases was consumed naltrexone in conjunction with the sedative hypnotic drugs such as

clonazepam, diazepam, and fluoxetine (Table 2). The main cause of withdrawal symptoms in 91.1% patients was inappropriate naltrexone usage and in 8.9% of the cases was suicide.

The route of consumption in 90.1% of the cases was oral and in 9.9% cases was injection. In one case, naltrexone injection was with cristal, and another with rice tablet, but none of them had suicidal intentions.

The major clinical features included nausea (39%), vomiting (37%), agitation (20.3%), abdominal cramps (18.6%), tremor (16.9%), and weakness (10%). In one case, hyperemesis was reported coffee ground.

Laboratory data were recorded in 36 cases. Leukocytosis was seen in 44.4% and elevated liver enzymes including AST, ALT, and ALP were reported in 16.7%, 25%, and 11.1% of the cases, respectively.

The main therapeutic measures were supportive with intravenous fluids (94.8%), opioid administration as methadone, IV and antiemetic as plasil (72.9%), and IV (37.3%). There was none mortality during the hospitalization period. The mean hospitalization period was 21.8±18 hours (range: 1 hour to 5 days).

Table 2: Frequency distribution of poisoning causes in the patients

Poisoning cause	Frequency (%)
Incorrect use of naltrexone alone	72 (80)
Concomitant use of naltrexone with opioid	13 (14.4)
Concomitant use of naltrexone with other drugs	5 (5.5)

DISCUSSION

Naltrexone is an opioid receptor antagonist used primarily in the management of opioid dependence. Naltrexone should not be started prior to several (typically 7-10) days of abstinence from opioids. This is due to the risk of acute opioid withdrawal if naltrexone is taken, as naltrexone will displace most opioids from their receptors.

In the current study, the main cause of withdrawal symptoms in 91.1% of the patients was inappropriate naltrexone usage and in 8.9% of the cases was suicide. This finding is consistent with Hassanian Moghadam *et al*.'s study showed 75.8% of the cases, personally, or following the prescription have used naltrexone to management of opioid dependence, and 6.8% of them have used it with the poisoning deliberate intention (7). These results indicate that general population has easy access to naltrexone, while the consumers have at least information on pharmacology, appropriate usage, and side effects of the substance.

In our study, the main poisoning agent in 80% cases was naltrexone alone, in 14.4% cases was naltrexone in conjunction with an opioid substance, and in 5.5% cases was naltrexone in conjunction with the sedative hypnotic drugs such as clonazepam, diazepam, and fluoxetine. This is consistent with Hassanian Moghadam *et al*.'s study which reported that 78% of the cases consumed naltrexone alone. There are some case-report studies indicating the incidental usage of benzodiazepine, cannabis, and amphetamine with opioids based on urine toxicology tests (8, 9).

There are two forms of pharmaceutical naltrexone; tablets or depot. However, our results showed that the consumption method of naltrexone was injecting or oral tablet. In the 4 prior reports, the cause of injection was reported intentional and accidental, rather than heroin (9). In the current study, the main clinical manifestations were gastrointestinal problems. The withdrawal syndrome (the frequency is more than 10%) included nausea (39%), vomiting (37%), agitation (20.3%), abdominal cramps (18.6%), tremor (16.9%), and weakness (10%). Also, 3.3% of our cases had decreased alertness which was similar to the classic signs of acute withdrawal

syndrome. Although the symptoms observed have the same diversity as the previous reports and findings, there are plenty of obvious differences compared with Hassanian Moghadam *et al.*'s study that reported the most clinical manifestations as CNS including agitation (96.2%) and decreased alertness (38.6%) (7, 10, 11). Armstrong's report in Department of Emergency Medicine, Australia, showed the gastrointestinal manifestations in 50%, CNS problems in 50%, respiratory disorders in 19% and tachypnea in 33% of the cases. This is different from the results obtained in our study (12). In fact, the withdrawal signs and symptoms caused by hepatic metabolism of naltrexone were widely diverse and unpredictable in intensity and duration.

The result of laboratory variables (CBC, BS, BUN, Cr, serum electrolytes, and liver function test), were normal in most cases. All of the case report studies had also normal laboratory findings.

In the present study, therapeutic procedures were carried out in accordance with patients' complaints and clinical symptoms, including vital measures. Gastrointestinal symptoms were treated by serum therapy and anti-nausea drugs such as metoclopramide and hyoscine for abdominal cramping. Benzodiazepines and IV haloperidol were used for CNS disorders such as agitations and anxiety. Use of methadone and morphine opioid antagonist for suppression of withdrawal symptoms, clonidine for adrenergic syndrome, and analgesics, such as diclofenac, acetaminophen, and codeine, for decreasing myalgia were in accordance to the guide treatment of withdrawal syndrome, except in sedative drugs. In the guide treatment of withdrawal syndrome, non-opioid analgesics such as NSAID and paracetamol should be prescribed (13,14).

Gastric intubation (NGT) was taken for 10% of the patients and one patient underwent oxygen therapy.

There is contradictory evidence on prescription of opioid agonists, such as methadone and morphine, for suppression of withdrawal syndrome. Since naltrexone is a competitor for the receptor antagonists, venous injection of opioids could be helpful in suppression of withdrawal symptoms. Although use of opioid agonists is authorized by the guide treatment of withdrawal syndrome, the studies have announced that prescription of opioid agonists in terms of naltrexone consumption is useless and even dangerous (15-17). The main problem is a risk of overdose and over-sedation of patient in order to decrease naltrexone effects. Hence, if required in such cases, prescription of a short-acting agonist at a low dose is recommended (17). Administration of opioids should be under monitoring since not enough studies have been done in this regard (15). In our study, intravenous methadone and morphine were prescribed for 72.9% and 16.9% of the cases, respectively. In Bristow's study, intravenous methadone was prescribed for both presented cases at first, which was ineffective (18). Thus, both patients received intravenous methadone again, although the result was not clinically significant.

In Armstrong's study, 4 patients have died in emergency room within 12 days, 1 months, 4 months, and 9 months of detoxification during the study period (12). The cause of death, according to forensic medicine report was opioid drugs overdose. There was no mortality during the hospitalization in our study, but such patients should be aware of the dangers of arbitrary use of naltrexone, especially risks of high dose opioid consumption for overcoming the antagonistic effect of naltrexone, because it is likely that besides decreasing of the naltrexone effects, patients experience overdose with less than usual opioid consumption (19).

Average hospital stay was 21.8 ± 18 hours in the patients admitted and 32.2% of the patients had less than 24 hours of

hospitalization while 57.8% of the cases were discharged during 24 hours, and 10% of cases within 5 days after admission. In Armstrong's study, 40% of the cases were discharged in less than 24 hours, clinical manifestation of most of them was CNS problems (12). In addition, 33.3% of the cases were discharged 1-2 days after admission that most of them had GI disorders, and 11.9% of the cases were hospitalized for more than 7 days.

CONCLUSION

Intentional or accidental abuse of naltrexone by addicts can lead to acute opioid withdrawal symptoms and the intensity, duration and outcome vary greatly and are unpredictable. Since the most common clinical symptoms in these patients are GI problems and agitation, serum therapy and using prescribed anti-nausea drugs, such as plasil (metoclopramide), and opioid agonists, such as methadone, are the main therapeutic measures taken for these patients.

Due to the ease of preparation of the drug and the increased likelihood of such cases due to the incorrect use of naltrexone, it is necessary to inform consumers about the risks of arbitrary consumption of drugs, in particular, and the risks of high doses of drugs to overcome the antagonistic effects of naltrexone.

ACKNOWLEDGEMENT

The authors are grateful to experts who helped to provide this project.

REFERENCES

1. Cropsey KL, Villalobos GC, St. Clair CL. Pharmacotherapy treatment in substance-dependent correctional populations: A review. Substance use & misuse. 2005;40(13-14):1983-99.
2. Prendergast ML. Interventions to promote successful re-entry among drug-abusing parolees. Addiction science & clinical practice. 2009;5(1):4-13.
3. Coviello DM, Zanis DA, Wesnoski SA, Alterman AI. The effectiveness of outreach case management in re-enrolling discharged methadone patients. Drug and alcohol dependence. 2006;85(1):56-65.
4. Coviello DM, Cornish JW, Lynch KG, Alterman AI, O'Brien CP. A Randomized Trial of Oral Naltrexone for Treating Opioid-Dependent Offenders. The American Journal on Addictions. 2010;19(5):422-32.
5. Mysels DJ, Cheng WY, Nunes EV, Sullivan MA. The association between naltrexone treatment and symptoms of depression in opioid dependent patients. The American journal of drug and alcohol abuse. 2011;37(1):22-6.
6. Gonzalez J, Brogden R. Naltrexone. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy in the management of opioid dependence. Drugs. 1988;35(3):192-213.
7. Hassanian-Moghaddam H, Afzali S. Naltrexone induced withdrawal in opioid abusers. APAMT Scientific Congress 2007. Available from:http://www.asiatox.org/6th%20APAMT%20pdf.
8. Boyce S, Armstrong P, Stevenson J. Effect of innappropriate naltrexone use in a heroin misuser. Emergency medicine journal. 2003;20(4):381-2.
9. Mannelli P, Risio SD, Pozzi G, Janiri L, Giacomo MD. Serendipitous rapid detoxification from opiates: the importance of time-dependent processes. Addiction. 1999;94(4):589-91.
10. Anonymous. Naltrexon: Drug information. 2008. Available at: http://www.Uptodate.com.
11. Gray A. Systematic review of the safety of buprenorphine, methadone and naltrexone. WHO "guidelines for phychosocially assisted pharmacotherapy of opioid dependence.Geneva, Switzerland.2007. Available from: http://www.who.int/substance_abuse/activities/buprenorphine_methadone_naltrexone.pd.
12. Armstrong J, Little M, Murray L. Emergency Department Presentations of Naltrexone-accelerated Detoxification. Academic emergency medicine. 2003;10(8):860-6.

13. Norouzi M, Naderi Sh, et al. Comprehensive Guide to Drug Treatment. 2 ed. Tehran: Pishgaman Tose'e; 2005.
14. Bell J, Kimber J, Lintzeris N, White J, Monheit B, Henry-Edwards S, et al. Clinical guidelines and procedures for the use of naltrexone in the management of opioid dependence. Canberra: Australian Government Department of Health and Ageing. 2003.
15. Stolbach A, hoffman RS. Opiod withdrawal in the emergency setting. 2008. Available at: http://www.Uptodate.com.
16. Quigley M, Boyce S. Unintentional rapid opioid detoxification. Emergency medicine journal. 2001;18(6):494-5.
17. drugs.com [homepage on the Internet]. Naltrexone: Product monograph. [cited 2001]. Available from: http://www.drugs.com/monograph/naltrexone.html.
18. Bristow K, Meek R, Clark N. Acute opioid withdrawal in the emergency department: Inadvertent naltrexone abuse? Emergency Medicine. 2001;13(3):359-63.
19. Bell JR, Young MR, Masterman SC, Morris A, Mattick RP, Bammer G. A pilot study of naltrexone-accelerated detoxification in opioid dependence. Medical Journal of Australia. 1999;171:26-30.