Myth exploded

Clinical safety of 1500 mg oral naltrexone overdose

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Summary

This case represents a clinical overdose of the largest known dose of oral naltrexone, equivalent to the taking of a whole bottle of the oral naltrexone preparation. The patient's intention was to control craving for alcohol and opiates. The patient quickly settled with expectant management. As such it demonstrates that earlier concerns that have been voiced in this area, particularly relating to naltrexone-related hepatotoxicity and depression, may have been overstated, at least in the experience of this patient. This patient's course was marked only by gastric irritation, of which she had some history. As such the present profile provides case report evidence consistent with more robust views of the patient safety of naltrexone itself, and opposing more cautious views. Her polydrug craving was suppressed for a period of 2 weeks, which raises the important question of the mechanism of action of naltrexone's generalised suppression of refractory hedonic consumptive addictive behaviours.

BACKGROUND

This case is important for four principal reasons. First, reports exist which cast strong doubt on the ability of oral naltrexone treatment to be a useful treatment for opiate addiction.^{1–5} The time course of this patient's progress, with suppression of her drug use and drug craving during her period of naltrexone use and for some weeks after, suggest strongly that in fact it is indeed a useful agent in this situation. Second, there is a significant literature relating to the safety of oral naltrexone in terms of its own side effects (largely insomnia, anorexia and nausea, depression and lethargy)^{6–8} and the propensity of patients to overdose with opiates after cessation of oral naltrexone administration.^{3 5 9 10} In line with earlier clinical series this patient's experience suggests that even very high doses of oral naltrexone are tolerated very well, and the side effects experienced in this case are amenable to treatments that are widely available in clinics experienced in its use. Third, it emphasises that the psychosocial milieu in which treatment occurs is critical to the success of oral naltrexone treatment, in terms of the supervision of oral dosing regimes, and for the purposes of the follow-up programme and social and employment reintegration of patients after detoxification and stabilisation on oral medication. Fourth, it strongly suggests that the activity of naltrexone to reduce drug craving may be related to its serum level with higher doses being more effective. The fact that her consumption of all drugs was completely suppressed during her toxic period suggests that naltrexone may be acting in ways other than as a classical opiate antagonist in the limbic system for which it is well known, or that its effects as a classical opioid antagonist are amplified beyond its immediate locus of action such as by stimulating the proopiomelanocortinergic system of the appetite regulatory centres in the hypothalamus.

CASE PRESENTATION

A 26-year-old woman presented requesting assistance with polydrug misuse and wanting to detoxify from methadone treatment at a dosing level of 20 mg daily. Her substance

misuse history included smoking a packet of 20 cigarettes daily, drinking 1–2 750 ml bottles of wine daily and varying amounts of spirits, smoking 2 g daily of cannabis, injecting 2 g of heroin daily and the use of various stimulants including ecstasy, amphetamines and cocaine. Her cannabis use had begun at age 12 years, and heroin use the following year. She had therefore been opiate dependent for 14 years at the time of presentation, and had spent 8 years on methadone maintenance treatment.

She also had an extensive history of psychosocial trauma and grief and loss, having been sexually abused from 5 years old, lost her 37-year-old boyfriend the year prior who had died from pancreatic cancer after a long history of tobacco, alcohol and cannabis use; and her baby had died at 8 months of age 6 weeks after its third open heart operation for congenital ventricular septal defect after a pregnancy in which she had used large amounts of cannabis and methadone. Both losses had occurred in the preceding year and both were still felt very acutely. Her drug use was financed by prostitution and drug dealing. She lived in motels. She had been raped many times. Her father, a policeman, had been violent towards her mother and herself. Her arm had been twisted behind her back until it broke. Her parents were presently divorced. She had left home at 13 years of age. She had been in the state sprinting team from ages 10 to 13 years. Her boyfriend had run over her in a car, fracturing her ribs, one arm and one leg. She had taken many overdoses, many of them in order to die to be with her deceased children and boyfriend. Her current boyfriend was imprisoned on drug trafficking charges.

Her medical history included anorexia nervosa, genital herpes, a termination of pregnancy and four spontaneous abortions. She worked as a youth worker part time. After appropriate liaison with her previous methadone clinic prescribers, relevant government authorities and the dispensing chemist, and 1 day without methadone, the patient was given a low dose of buprenorphine (2/0.5 mg, as the combined buprenorphine/naloxone sublingual tablet 'Suboxone') to introduce this partial agonist into her system 1 December 2008, together with symptomatic support

including 30 diazepam daily. By 9 December 2008 the dose was increased up to 10 mg buprenorphine. Acamprosate was added on 11 December 2008 to assist her with reduction of her alcohol misuse and varenicline on 12 December 2008 to assist with cessation of tobacco consumption.

She also made approaches to an inpatient detoxification unit for assistance, but was not successful in gaining admission. Similarly she applied to several rehab centres of inpatient accommodation, but was also unsuccessful. She did experience significant support through a community recovery programme called the Hope Foundation, which specialises in assisting women who have been victims of sexual abuse, drug addiction or the sex industry to find more constructive pathways to rehabilitate their lives. In particular this group was able to offer her a supportive accommodation environment in which to facilitate her recovery. She maintained and used a useful therapeutic relationship with a community counsellor with whom she had been in contact over a long period. She also had some links, albeit tenuous, with various community faith-based organisations, with usually positive interactions.

Over the following year, and at the patient's vehement request, her dose of buprenorphine was reduced three times in an attempt to reduce her gradually to become completely opiate free. However whenever she got below 2–4 mg she became unstable and relapsed into dependent drug use. At one point her dose of buprenorphine had to be increased to 24 mg.

Eventually the patient decided to opt for a different mode of treatment and chose the naltrexone implant as a putative way to control her opiate and alcohol use. Her buprenorphine dose was therefore gradually reduced again, with the support of extra benzodiazepine sedation and some caring friends from the Hope Foundation with whom she was able to live. On 3 November 2009 a single 3.1 g Perth 'Go Medical' naltrexone implant was inserted in the subcutaneous tissue of the patient's left iliac fossa by techniques previously described.¹¹

Her main difficulty after naltrexone implant insertion was insomnia. This required alprazolam (4 mg daily, dispensed from the pharmacy as single daily doses) and quetiapine (200 mg daily from sample stocks) for control.

Some local irritation at the implant site manifesting as pain and swelling and local discomfort with movement was noted, which required the injection of local steroids (as celestone chronodose 1 ml on three occasions) or short courses of oral prednisone treatment (on two occasions from 4 to 16 weeks after the implant), and temporally associated with drinking binges. Interestingly after one of these doses of oral steroids she became very ill with a severe vomiting attack over 4 days, which responded only temporarily to treatment in the local Emergency Department with parenteral metoclopramide and intravenous fluids. On a plain abdominal film gross distension of her stomach was evident. Acute gastritis was therefore diagnosed, and the patient responded promptly and definitively to oral treatment with pantoprazole ('Somac') and antacids ('Mylanta'). Oral steroid administration on both occasions was also complicated by recurrence of genital herpes outbreaks, which were managed in the usual manner with valaciclovir.

The Christmas/New Year holiday period was difficult for this patient in view of the social isolation she experienced,

including some significant painful anniversaries of various losses. The usual support structures she used were not available at this period. Some binge drinking occurred over this time. The craving for drugs and alcohol had increased to the point where on 27 January 2010 oral naltrexone was given in addition to the implant naltrexone she already had placed. In view of the local difficulties she had experienced at the implant site it was felt that this route of administration was safer in terms of less local tissue irritation, and would also achieve higher levels of naltrexone in her serum to challenge the alcohol craving. Unfortunately no carer was available to supervise her dosing in this way as she had become increasingly socially isolated.

On 15 March 2010 the patient again reported intense opiate craving after another alcoholic binge. She also had a stinging sensation locally in the implant site, although there was almost imperceptible local swelling to see on inspection and palpation. As treatment for her implant site irritation she was prescribed 50 mg oral prednisone. As she was being non-compliant with her oral naltrexone, she was encouraged to take this medication again. The next day she presented and described that in her frustration and torment at the continued drug and alcohol craving, she had in fact taken a whole bottle of oral naltrexone (=1500 mg). She had been vomiting all night. An ambulance and police had attended her, but she had declined hospital admission. On examination she was hypertensive (blood pressure (BP) 165/90) and tachycardic P 116 with no change in BP with posture. Abdominal examination was unremarkable. Upon discussion with the local poisons centre, little information was available on such large overdoses. Pathology tests were taken including blood count (white cell count (WCC)= $11.9 \times 10^9/l$, neutrophils= $10.5 \times 10^9/l$), biochemical profile (alanine transaminase (ALT)=13 u/l, bilirubin=6 mmol/l, albumin=49g/l) and prothrombin time (international normalised ratio (INR)=1.2 (1.0 to 1.5)) and inflammatory markers (erythrocyte sedimentation rate=8 mm/hr, high sensitivity C reactive protein (CRP)=0.1 mg/l), which were all essentially normal excepting her low-level neutrophilia. Semiquantitative mass spectrometry analysis of her urine drug screen confirmed that massive amounts of naltrexone were present requiring dilution for meaningful analysis (urinary creatinine 12.7 mmol/l consistent with a moderately concentrated sample).

When seen the following day she was clinically normal and able to eat and drink well. On the next day she was not well and stated that she was only able to eat and drink a little. As her implant was again uncomfortable, another dose of prednisone (50 mg) was again prescribed, together with Mylanta to protect her stomach. On 19 March 2010 she phoned in again after experiencing vomiting and was sent to the local emergency department for treatment and rehydration. As they refused to see her, she re-presented to this clinic. Abdominal examination in the clinic revealed a hyper-resonant, greatly distended stomach. Parenteral octreotide (0.1 mg subcutaneous injection) and ondansetron (4 mg intramuscular injection) were administered, and the patient quickly began to feel a little better. The following day she was back to normal. Laboratory studies and urine drug screen were again performed on 22 March 2010, and were normal. In particular the urine drug screen showed only nicotine and quetiapine, ALT=15 u/l, bilirubin=

5 mmol/l, albumin=46g/l, WCC= 9.8×10^9 /l, neutrophils= 6.4×10^9 /l, INR=1.1(1.0 to 1.5) and high sensitivity CRP <0.1 mg/l.

The patient's drug craving remained controlled for 2 weeks, after which time it returned once again. It is now controlled with oral naltrexone dispensed on a weekly basis from the chemist. The patient reports that she has no intention of ever repeating this overdose episode again. She is now working about 30 h weekly, is becoming ever better integrated into the community and her social isolation is gradually reducing. She is very much enjoying being drug free. She is abstinent from alcohol and is planning to work on her tobacco addiction in the near future.

DISCUSSION

Naltrexone is a synthetic opiate antagonist with an *N*-methylcyclopropyl ring substituted onto the morphinan nucleus.¹² First synthesised at Endo laboratories as long ago as 1963, it was originally chosen for clinical development because it was found to be relatively non-toxic in early pre-clinical and clinical trials.^{7 13–16} Naltrexone has therefore been called the 'ideal' narcotic antagonist¹⁷ and indeed in toxicological terms has been described as a 'non-drug'.¹⁶ In a large multicentred National Institute of Drug Abuse study¹⁸ naltrexone only had to be stopped because of side effects in 5.3% of 1005 patients to whom it was administered, and in about half of these patients the principal issue was gastrointestinal irritation.¹⁹ When naltrexone is given to patients who are opiate dependent, the resulting side-effect profile is felt in large measure to be related to symptoms of residual detoxification and generally settles rapidly with continued treatment.^{7 20}

Some early studies raised hepatotoxicity as a leading cause of concern and indeed such cautions appear on the product insert on the basis of such concerns. Because of the high prevalence of elevated serum liver enzymes in the opiate dependent population such issues if real would pose a serious limitation on its applicability in this group and might potentially lead to its underuse.²¹ These authors went on to give 300 mg daily, a dose many times higher than that usually recommended (50–100 mg daily) without noting any untoward elevation of serum hepatic transaminases. Indeed, while like many drugs naltrexone is contraindicated in patients with acute liver failure, in most patients we see with solely biochemical evidence of chronic liver disease their serum transaminases tend to normalise on oral naltrexone treatment.⁸ Indeed, in two studies patients in whom elevation of serum transaminases was noted had pre-existing obesity and fatty liver disease and the naltrexone dose was much higher than usual.¹⁸ Formal tests of hepatic function by antipyrine clearance failed to show any deficit attributable to naltrexone.²² More recent reviews of this subject have not confirmed that hepatotoxicity is a clinically important issue with naltrexone.²³

Depression and mood disturbance has also been noted to be a significant issue with naltrexone with some authors noting positive^{24–27} and some negative^{5 9} changes. Such negative affective changes are not entirely unexpected in patients who are undergoing a frequently difficult opiate detoxification procedure, particularly with minimal social support or completely alone. Indeed implant naltrexone has been associated with very positive changes in mental health

which include reduced rates of depression and mental illness and reduced rates of heroin overdose presentation^{28 29} and reduced mortality compared to currently accepted pharmacotherapeutic modalities.^{30 31}

The leading concern associated with oral naltrexone treatment relates to the possibility of heroin overdose after premature naltrexone cessation.^{3 5 10} Notwithstanding this limitation very high rates of compliance with oral naltrexone for prolonged periods have been described where oral treatment is supervised as with parolees, professionals,^{7 32–35} and in various culturally defined international settings.^{11 36–38} Indeed, it has been noted that the very widely disparate rates of compliance with oral naltrexone treatment (see McGregor *et al*³⁹ and Naderi-Heiden *et al*⁶ for comparison) are largely explained by the degree of social support of the patients and the degree of supervision of tablet taking⁴⁰ and this has been formally demonstrated at high levels of statistical significance.¹¹

Since such side effects are well known with oral treatment their occurrence is often mentioned as being of possible concern with the depot implantable forms of naltrexone delivery particularly by units who are not widely experienced in the use of the long acting preparations.^{3 10} However, the oral formulation of the drug is associated with achievement of serum naltrexone levels of above 40 ng/ml while typical peak serum levels for naltrexone implants patients are in the range 10–15 ng/ml.^{6 41–43} Furthermore in the major randomised clinical trials of implant and depot naltrexone none of the above discussed issues have been notable, beyond the well known and generally readily manageable symptomatology of the opiate withdrawal syndrome itself.^{38 44 45} The largest dose previously known to be administered is 800 mg daily, which was given without untoward effect.^{19 46}

A further note of importance and interest is that as a result of her overdose the present patient experienced a major and abrupt reduction in her craving for all substances, which from the time course described above was inversely related to the expected level of the serum naltrexone. Naltrexone is well known to block the effects of exogenous administered opiates and this is predictable from its effects as an antagonist of classical opiate receptors. It is also highly effective in the management of chronic alcoholism especially where its administration is supervised by a significant other.^{47–51} It has also been described as having useful activity in a variety of other addictions including cannabis, amphetamine, cocaine, self-mutilation, overeating/obesity and gambling.^{52–65} As such the apparent inverse relationship between the probable serum naltrexone levels and the time course of her polydrug craving raises again the question of the likely mechanism for this effect. While there is some speculation in the literature there appears to be little agreement on the mechanism that may account for such an effect. It is said not infrequently that this may be related to the non-specific effects of the opiate signalling system on hedonic behaviours. The appetite regulation centres of the hypothalamus would appear to have been largely overlooked from such discussion. A well described antagonism exists between endogenous opioidergic and melanocortinergic signalling in many sites.^{66–68} α -melanocyte stimulating hormone (α -MSH) accounts for

most of the endogenous melanocortinergic tone in the hypothalamus and elsewhere.⁶⁸ The melanocortins are responsible for the anorexic drive to appetite which typically signal satiety to the appetite centre, and thereby an end to hedonic consumption. Just as administration of exogenous opiate agonists is associated with a fall in endogenous melanocortinergic tone and a thoroughly documented rise in appetitive behaviours, the converse applies to the administration to xenobiotic opiate antagonists, which are associated with a rise in endogenous melanocortins and a decline in pan-appetitive hedonic behaviours. As such, phenomena such as the time dependent craving profile of the present patient would appear to suggest that more detailed behavioural and molecular dissection of the role of the hypothalamic appetitive centre may be indicated to better understand the control mechanisms of refractory addictive hedonic behaviours and their integration with the known neurocircuitry of addiction in the ventral tegmental system, amygdala, cingulate gyrus, prefrontal cortex and other centres of the extended limbic system.^{69 70}

Discussion of the various diverse aspects of this case has been included for a number of reasons. It is important to underscore in the treatment of such patients that their drug dependency syndrome does not occur in strict isolation from the remainder of their lives, and it is important for the effective overall management of their problems, that it be viewed appropriately within the overall context of their total life situation. The substantial contribution of grief and loss to this patient's continued episodic drug consumption is an important stimulus to relapse and dependent drug use that clearly needs to be carefully factored into any long-term management plan of her overall psychological situation. The extreme social isolation of this patient made effective support of her at many points challenging, and this needs to be carefully considered in models of treatment requiring close therapeutic liaison and alliance with patients, their carers and their families. The described features note in particular that this patient had experienced serious difficulties with oral naltrexone treatment as well as with methadone and buprenorphine. The presumed fetal toxicity of agents such as cannabis and methadone during gestation is of particular interest. Our clinical experience with depot implantable naltrexone has shown definitively that using these technologies it is possible to completely separate the substance dependency from the other sources of dysfunction in patients' lives. The features of this case are also consistent with this important feature. This behaviour tends to suggest that overly reductionist views of substance dependency are likely to be, perhaps albeit unsurprisingly, overly simplistic.

Learning points

- This report describes the relatively benign course of a massive oral naltrexone overdose associated only with mild hypertension and tachycardia.
- The importance of psychosocial support for the success of oral naltrexone treatment, for disciplined tablet administration and for post-treatment psychosocial support, is underlined.
- Polydrug craving can be controlled by elevated serum levels of naltrexone.
- There are several readily available treatments for the common causes of acute gastritis (alcohol, oral steroids, naltrexone) including antacids, proton pump inhibitors, 5-hydroxytryptamine 3 antagonists, octreotide and parenteral rehydration.

Competing interests None.

Patient consent Obtained.

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