CASE REPORT

Naltrexone: report of lack of hepatotoxicity in acute viral hepatitis, with a review of the literature

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Abstract
Many clinicians appear to be concerned about the potential hepatotoxicity of the opiate antagonist naltrexone (NTX) and this may be one reason why it is not used more widely in treating both heroin and alcohol abusers. Some much-quoted early studies noted abnormalities in liver function tests (LFTs) in very obese patients taking high doses, although there was no evidence of clinically significant liver dysfunction. These concerns may be reinforced by advice in the UK product information sheet to perform LFTs before and during treatment, by high infection rates with hepatitis C virus (HCV) among injecting heroin addicts and by the frequency of abnormal LFTs in alcohol abusers. We describe a heroin abuser in whom clinical and laboratory manifestations of acute hepatitis B and C appeared a few days after the insertion of a subcutaneous naltrexone implant. A decision was made not to remove the implant but the hepatitis resolved completely and uneventfully well within the normal time-scale. A review of the literature indicates that even when given at much higher doses than are needed for treating heroin or alcohol abusers, there is no evidence that NTX causes clinically significant liver disease or exacerbates, even at high doses, serious pre-existing liver disease. During the past decade, NTX has been shown to be safe and effective in the treatment of pruritus associated with severe jaundice caused by severe and sometimes life-threatening cirrhosis and other liver diseases. Its safety, even in these extreme conditions, is particularly reassuring. We suggest that it may be more appropriate and economical to advise patients to report promptly any suspected side effects than to perform regular LFTs, which may be misleading.

Introduction
When given under supervision as part of a relapse prevention programme, controlled studies show that naltrexone (NTX) can significantly reduce relapse to opiate use in detoxified opiate addicts1–3 and it is also helpful in alcoholism. It is clear that supervised administration is crucial to the effectiveness of oral NTX in opiate abuse4 as it is with disulfiram in alcoholism,5,6 and failure to appreciate the importance of supervision may be one reason why NTX is not used more widely. However, another explanation may be fear of hepatotoxicity. As well as advising caution in the presence of 'hepatic impairment', the product information sheet in Britain states that liver function tests (LFTs) should be performed before starting treatment and at regular intervals while treatment continues. This advice may have created a climate in which NTX is seen as an inherently hepatotoxic drug.
patient groups with a high incidence of liver disease from hepatitis B and C and alcohol toxicity, this could act as a disincentive to NTX prescribing, especially in an age of increasing litigation.

In reality, a search of Medline shows that the evidence for alleged NTX hepatotoxicity is limited to a small number of clinical reports, none of them relevant to the treatment of opiate or alcohol dependence. In one study, \(^7,^8\) 46 of 60 obese subjects were given up to 100 mg of NTX daily. The remaining 14 were a placebo control group. Such obese patients often have hepatic steatosis and 28 of the 60 in this study had pretreatment baseline LFT abnormalities. Some of them experienced elevations of alanine transferase (ALT), aspartate transferase (AST) and gamma glutamyltranspeptidase (GGT), but bilirubin levels were not affected and apart from the normal laboratory findings, none of the patients experienced any clinically obvious ill effects. Five of the placebo group also developed LFT abnormalities. In the other, \(^9\) NTX was administered at doses of up to 300 mg daily, which is to say six times the normal dose, for the treatment of opiate dependence but to test its anorexic potential in a group of very obese men. The authors state specifically that at doses 'recommended for [treating] opioid addiction', no LFT abnormalities occurred.

However, in the light of these findings, and after noting that 'many addicts with minor liver abnormalities have been treated with NTX during the past 11 years without developing clinical problems or worsening of hepatic function', Kleber\(^10\) felt that on the information then available (in 1985) 'it is prudent... to observe the following precautions'. These included:

Patients with acute liver failure or acute hepatitis should not be treated with NTX. All patients receiving NTX should have baseline liver function studies and then repeat tests once a month for the first 4 to 6 months. Do not start NTX if the SGOT [AST] is greater than approximately two times normal. Discontinue NTX if the SGOT rises to greater than three times normal unless some other cause is found. Patients with baseline liver abnormalities should be tested every two weeks up to six weeks before going to once a month frequency.

However, Kleber recognized that alcohol abuse was a common 'other cause' and might require the addition of disulfram to the treatment programme. Since 1985, physicians in many countries have accumulated and reported a great deal more experience of NTX.

In an extensive review, Verebey & Mule\(^11\) noted that there was much evidence that opiate agonists (including morphine) could cause elevations in hepatic enzymes—sometimes quite considerable. These might be related to the well-known tonic effect of agonists on the sphincter of Oddi, thus temporarily raising intrahepatic biliary pressure. However, they concluded that these elevations did not appear to have any clinical significance, often disappeared despite continued medication and were never accompanied by elevated bilirubin levels. In some cases, apparent enzyme elevations were due to interference with analytical methods by opiate metabolites and they comment on the frequency of hepatic abnormalities among very obese populations. Their most startling suggestion is that the transaminase elevations seen in some patients treated with NTX could be due to the biotransformation of NTX in the liver to metabolites, which can include small amounts of opiate agonists. Marrazzi \textit{et al.}\(^12\) reviewed the literature partially up to 1997, particularly studies involving high doses and eating disorders, and found no evidence of clinically significant hepatotoxicity. They also noted that increases in hepatic enzymes were often transient and reverted to normal despite maintaining or increasing the dose of NTX.

In contrast to alarmist early reports, Brahen \textit{et al.}\(^13\) noted no differences in LFTs between patients receiving NTX and a placebo control group. A study by Pini \textit{et al.}\(^14\) in patients receiving NTX at doses averaging 50 mg daily also failed to find significant liver function changes. Both these studies involved patients who had abused opiates. In a randomized Dutch study of over 200 opiate-dependent patients treated with oral NTX after rapid opiate detoxification, no clinically significant changes were seen in hepatic (or renal, or thyroid) function after 1 month. (M. Bosman, C. de Jong, personal communication). Sax \textit{et al.}\(^15\) reported no significant or persistent LFT abnormalities in 10 patients with Huntington's disease receiving 50–300 mg of NTX daily for 10–36 months. Given that many patients do not take oral NTX for more than a few weeks, this long exposure to high
doses is particularly reassuring. In any case, the misleading sensitivity of liver function tests to a number of ordinary environmental toxins was shown in a case report by Salvato et al.\(^{16}\) of a patient receiving the closely related opiate antagonist nalmefene (6-deoxy-6-methylene-naltrexone). During an experimental study, this patient developed significant but transient abnormalities of LFTs which disappeared spontaneously, despite the continuation of nalmefene. They were subsequently thought most likely to have been a response to chillies in oriental food and it is clear that other incidental and non-pharmacological factors can cause transient LFT abnormalities. For example, Mitchell et al.\(^{9}\) noted a short-lived increase in AST in one of their patients 2 days after she had taken part in a marathon.

The realization that NTX could be helpful in the management of alcohol abuse naturally raised questions about its safety in a group of patients whose livers might already be compromised by alcoholic hepatitis. From the first reported studies onwards\(^17\) these anxieties have been consistently allayed. Although patients with very elevated hepatic enzymes were excluded from some trials, all studies so far of NTX in alcoholism have failed to reveal any clinically significant adverse hepatic effects. In placebo-controlled studies, the usual finding is that previously elevated LFTs fall in the NTX group and to a greater extent than in the placebo group, presumably because most placebo groups also reduce their alcohol consumption, but not as much as the naltrexone groups.

The multi-centre COMBINE research group\(^18\) studied 108 patients at 11 sites randomized to placebo, NTX or NTX plus acamprosate. Again, no adverse hepatic effects were seen although NTX was withdrawn in a hepatitis C-positive patient after a relapse associated with significant LFT elevations. Balldin et al.\(^{19}\) randomized 118 alcoholic patients to NTX or placebo. ‘NTX was well tolerated and no patients discontinued the study due to side effects’. Croop et al.\(^{20}\) examined the safety profile of NTX in a sample of 570 alcoholic patients. ‘The results of liver function tests in the naltrexone group were similar to those in the reference group’. In a large multi-centre placebo-controlled trial of oral NTX in 171 alcoholic patients (of whom over 80% were at least 80% compliant with medication) Gastpar et al.\(^{21}\) found that ‘the median reduction in γ-GT for the NTX group was greater than for the placebo group at all timepoints’.

NTX is also being used for compulsive disorders such as pathological gambling, compulsive sexual behaviour\(^{22}\) and kleptomania, as well as eating disorders, but at doses much higher than those that are customary for treating opiate or alcohol abuse. Marrazzi et al.\(^{12}\) administered doses up to 200 mg/day in patients with eating disorders but found ‘no adverse clinical or laboratory changes in liver function’. Kim et al.\(^{23}\) conducted a randomized placebo-controlled trial of doses up to 250 mg/day in compulsive gamblers \((n = 45)\). They found elevated LFTs in five patients, four of whom were taking non-steroidal analgesics as well as NTX, but the patients had ‘no subjective symptoms’ of illness and LFTs normalized quickly after stopping medication. Grant & Kim\(^{24}\) used NTX in doses of up to 200 mg/day in kleptomania \((n = 10)\). They reported no elevations in LFTs. NTX also appears to reduce the compulsive and repetitive self-injurious behaviour, which is common in severe learning disability,\(^{25,26}\) This typically involves long-term treatment in a well-supervised setting with high compliance rates. Although individual case reports indicate no hepatotoxic effects of NTX even in patients with chronic hepatitis,\(^{27}\) larger studies rarely look specifically at liver functions. However, there appear to be no reports of adverse NTX effects on LFTs in this group.

For more than 20 years the problem of poor compliance with oral NTX programmes has led to studies of depot preparations. Kranzler et al.\(^{28}\) closely monitored a group of alcoholic patients receiving either a placebo injection or an experimental injectable depot preparation of NTX. Their hepatic enzyme levels decreased during NTX treatment. Recently, Comer et al.\(^{29}\) reported on a group of 12 heroin addicts with normal LFTs receiving a low or a higher dose of the same preparation. Some average increases in liver enzymes were noted in the low-dose group but ‘Although these [increases] were statistically significant, it is important to note that they were not clinically significant’. In any case, there were no such LFT increases in the higher-dose group. They state: ‘Therefore, it appears that the formulation of NTX used in the present study has minimal effects on liver functioning’ and note that ‘this is consistent with several studies demonstrating a lack of effect of NTX on liver
functioning, even after daily administration of high doses of NTX’. A Norwegian study of 10 detoxified heroin addicts having NTX implants also found no evidence of hepatotoxicity, even though several patients had chronic hepatitis C. In most studies, therefore, including some large ones, NTX had no adverse effects on LFTs. A few studies noted LFT abnormalities that were usually mild and often normalized despite continuing NTX at the same or higher doses. In the small number of cases where it was thought prudent to discontinue NTX because of increases in LFTs enzyme levels quickly fell, although clearly they might have fallen anyway in some cases.

The increasing number of studies involving NTX and the growing range of new clinical indications for NTX treatment would be reason enough for another review of the hepatotoxicity literature. However, even if clinicians are reassured by the essentially negative findings, they might still be concerned about initiating or continuing NTX treatment for patients with acute or chronic viral or alcoholic hepatitis showing not just elevated LFTs or other biochemical abnormalities but obvious clinical and/or histological evidence of serious liver disease as well. One of these new indications for NTX is therefore particularly relevant. In the past few years, it has become clear that NTX and nalmefene are very effective for relieving the pruritus associated with jaundice due to intrahepatic cholestasis in conditions such as cirrhosis. By definition, such patients must have severe acute or chronic liver disease, although NTX is also effective when jaundice is due to extrahepatic obstruction. Wolfhagen et al. conducted a placebo-controlled trial of NTX in 16 patients with cholestatic jaundice. Thirteen had primary biliary cirrhosis (PBC) and the others had definite or probable primary sclerosing cholangitis. ALT was up to 10 times the upper limit of normal (ULN). Bilirubin levels were up to 30 times the ULN and bile salts up to 42 times the ULN. NTX was highly effective and there were no adverse effects on LFTs.

In a study of nalmefene in a similar patient group (n = 11) Bergasa et al. recorded ‘no serious adverse events’, although in two patients the drug was withdrawn as a precaution because of symptoms such as chest tightness, fever and eosinophilia that seem rather unlikely to have been due to the antagonist. Neuberger & Jones report a patient in whom pruritus was so severe that liver transplantation was being seriously considered. Alkaline phosphatase (ALP) was 1634 (ULN = 330) and AST was 114 (ULN = 43). After 3 months of treatment, she remained pruritus-free on 150 mg/day of NTX. In an even more persuasive report, Nunes et al. describe a man who became seriously ill with prolonged drug-induced cholestasis. His bilirubin rose to 40 times the ULN and his albumen level fell to barely half the lower level of normal. He needed parenteral nutrition and renal dialysis, yet NTX relieved his pruritus without causing any worsening of LFTs or clinical status.

In the most recent randomized placebo-controlled trial, Terg et al. administered naltrexone 50 mg daily to 20 patients for up to 2 months. All had chronic intrahepatic cholestasis and their diagnoses included chronic HCV infection (one with hepatocellular carcinoma as well), primary sclerosing cholangiitis, autoimmune hepatitis and autoimmune cholangiopathy. Patients with drug-induced or extrahepatic cholestasis were excluded. ‘No significant changes in hepatic biochemistry were observed with NTX treatment. Thus current data suggest that NTX can be safely administered to patients with chronic liver disease’ [our italics]. In a study of particular relevance to NTX treatment of opiate abuse, Lozano et al. monitored transaminases in 116 patients infected with HCV (including some with HIV as well) receiving either methadone maintenance or NTX. Neither drug caused any transaminase increases compared with a control group receiving no pharmacological treatment.

Patients with severe liver disease may still need all the help they can get, including NTX, if they are to avoid relapse to injecting heroin, not forgetting the public health implications of continued injecting. It is in this context that we report the case of a patient treated with NTX who acquired hepatitis B & C during a brief relapse to opiate use and became jaundiced with severe LFT disturbance 1 week after the insertion of a subcutaneous NTX implant.

Case report

In November 1998 the patient, then aged 23 years with a history of injecting heroin since the age of 20, was admitted to a general medical ward after developing hepatitis A. Investigations at that time showed him to be negative for hepatitis B &
C. He made a rapid and uncomplicated recovery and was discharged after 1 week. However, the hospital admission enabled him to withdraw from opiates and he then came to the Stapleford Centre to have a NTX implant inserted. The implant (Wedgewood Pharmacy, Sewell, NJ, USA) contained 1 g of naltrexone. Before his admission to hospital, he had been on a methadone programme. Although his methadone counsellor was supportive of his efforts to remain opiate-free, she was very much opposed to the use of NTX in any form to help him avoid relapse and advised him not to have another implant, even though he had never managed to remain opiate-free for more than 2 months in the ordinary community, despite 3 months of ‘Twelve-Step’ (i.e. AA/NA-based) residential treatment.

In February 1999, he relapsed but he managed to stay opiate-free for 4 days and was able to resume oral NTX followed by a second implant on 6 March. On 9 March, he telephoned from work to say that he was experiencing some sweating. This was thought to reflect a residual withdrawal syndrome and a small dose of clonidine was prescribed. On 10 March, he came to the Stapleford Centre because his urine was dark and he felt unwell. He was slightly icteric and LFTs on that day (normal range in brackets) were: bilirubin 32 μmol/l (2–22); ALT 1885 IU/l (8–45); AST 942 IU/l (10–35); and GGT 502 IU/l (5–50). He was transferred to a medical ward under the care of V. S. W. On subsequent questioning, he denied sharing needles or syringes but admitted that he had shared a spoon with another addict for ‘heat sterilizing’ the heroin solution prior to injection. Like many addicts, he was unaware that simple boiling leaves many viruses unaffected.

Because he was obviously at high risk of relapse to heroin use, and bearing in mind the lack of evidence for significant NTX hepatotoxicity, a decision was made to leave the implant in situ while waiting to see whether the hepatitis resolved in the normal way. By this stage, serological and virological testing showed that he had become infected with both hepatitis B & C, presumably on the same occasion. His LFT abnormalities peaked on 14 March (bilirubin 113; ALT 2414; AST 1066; GGT 555) and declined rapidly. He was discharged from hospital on 22 March. Fortunately, he tested negative for HIV infection. On 4 May, LFT results were: bilirubin 9; ALT 21; GGT 57. He was cleared of HBsAg and HBcAg but was HCV-RNA-positive.

Although advised to continue on oral NTX under family supervision, he was not fully compliant and had further relapses and two further implants. However, when last seen in February 2002, he was taking NTX under family supervision 5 days a week and working regularly. A hair sample taken at that time showed that he had used no opiates during the preceding month. LFTs have been within normal limits since May 1999 and although he remains under regular review, viral testing for HCV is only intermittently positive.

Discussion

The Wedgewood implant used in this case normally produces NTX levels which can reach 25 ng/ml, but do not usually fall below 1 ng/ml until at least 6 or 7 weeks after insertion. These lower levels are similar to or greater than the trough levels recorded 24 hours after the oral administration of 50 mg of NTX, which are still sufficient to block large amounts of intranasal or intravenous diamorphine. However, the peak levels are generally higher than those in the heroin addicts receiving the type of depot NTX injection reported by Comer et al. and by Kranzler et al. Patients with the Wedgewood NTX implant therefore have blood levels that on average are not very different from those recorded in patients taking regular oral NTX. However, compliance with implants is virtually 100% for the first month or two at least rather than the rapidly declining rates which are common with unsupervised oral programmes. This case does not prove that NTX could never exacerbate the hepatic disturbances which are found in acute and—perhaps more relevantly—chronic hepatitis. However, it adds to the persuasive evidence—particularly the studies of NTX in patients with severe liver disease—that there is no absolute contraindication to using NTX when it is an appropriate intervention, even when the level of liver dysfunction is very marked. One of the patients reported by Waal et al. also developed acute hepatitis C during treatment with implanted NTX, his AST peaking at 859 μ/l. They too decided that there was no need to remove the implant. NTX treatment did not appear to exacerbate the illness or interfere with the effectiveness of the interferon treatment that was eventually prescribed.
Secondly, since its introduction in the early 1970s, no case appears to have been reported in which NTX treatment has caused, or has been suspected of causing, serious or even clinically significant liver disease. Furthermore, CB has treated well over 1000 patients with naltrexone implants—some of which can provide effective NTX levels for up to 12 months—and he has not encountered even one case where an implant had to be removed because of any actual or suspected toxic effect apart from local tissue reactions and one allergic rash. It is not even certain that the generally minor LFT abnormalities detected in atypical groups of obese patients taking NTX were due to NTX. The equally minor abnormalities noted by Sax et al. resolved spontaneously despite continued treatment. Many commonly prescribed drugs can cause minor LFT elevations at normal doses and some, such as paracetamol, can cause massive rises (AST values typically > 5000) in susceptible patients, notably alcohol abusers.39,40 Kaplowitz et al.41 note that ‘One to two percent of patients treated with chlorpromazine will develop jaundice, with 90% of the cases developing during the first five weeks of therapy’ and that ‘...considerable evidence suggests that this drug is intrinsically toxic with subclinical cholestasis occurring in most patients’; yet pre-treatment screening and regular LFTs are not usually regarded as essential before prescribing either of these drugs. We therefore question whether the advice to perform such tests routinely before and during NTX treatment is soundly based. As has been said of similar guidelines for monitoring disulfiram hepatitis and other rare complications of medical treatment, it is usually more important to educate patients about reporting promptly any apparent side effects than to engage in repeated testing which may not even detect the complication in question.42

References


