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A pilot study to assess the impact of naltrexone implant on accidental opiate overdose in 'high-risk' adolescent heroin users

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Abstract

Morbidity and mortality rates for regular heroin users are much greater than those observed in the general population. In 'high-risk' heroin users implantable naltrexone has been used under Commonwealth Therapeutic Goods Administration Compassionate guidelines in Western Australia since August 2000. This pilot study compared the frequency of accidental opiate overdose and other morbidity resulting in hospital presentations in eight 'high-risk' dependent heroin using adolescents pre- and post-naltrexone implant treatment. We reviewed the hospital medical records retrospectively for the participants across the four public hospitals in Perth. The review period was September 1999 – October 2002. The eight adolescents (aged 15 – 19 years) initially underwent naltrexone implant treatment between September 2000 and September 2001. The data indicated a dramatic reduction in opiate overdose post-implantable naltrexone treatment, with a smaller reduction in opiate overdose during oral naltrexone treatment compared to the pre-oral/implant period. Implant treatment in the high-risk heroin user may provide an important prophylaxis against mortality associated with accidental opiate overdose. These encouraging findings now require validation using a larger cohort over an extended period.

Introduction

Heroin use is increasingly a habit of Australia's youth. Lynskey & Hall[1] examined two large studies involving a total of 1292 heroin users. The mean age of first heroin use among individuals born between 1940 – 49 and 1970 – 79 was 20.5 and 16.5 years, respectively. Among heroin users, non-fatal opiate overdoses represent a significant morbidity. A recent survey of 218 heroin users indicated that 48% had experienced at least one non-fatal overdose in their life-time (median was two overdoses) with 11% reporting an overdose in the last 6 months.[2]

Oral naltrexone maintenance as a treatment for heroin dependence has been available in Western Australia since mid-1997, and has subsequently gained increased acceptance in other States in Australia. Naltrexone is a long-acting opiate antagonist that can be taken orally as a single daily dose of 50 mg in people who have detoxified from heroin, and can completely block the effects of heroin,[3] therefore preventing accidental opiate overdose. Trials have, however, shown that while

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having some clinical value, naltrexone is often associated with non-compliance which may result in a patient's withdrawal from treatment and return to heroin use,[3–8] with a probable associated increased risk of accidental overdose. In 'high-risk' heroin users, implantable naltrexone has been used under Commonwealth Therapeutic Goods Administration Compassionate Guidelines in Western Australia since August 2000, with approximately 582 patients having now been treated via this method. This procedure removes the onus of daily compliance associated with oral naltrexone from the individual.

We have reported previously that in humans the use of a single (1.7 g naltrexone mass) or double (3.4 g naltrexone mass) GoMedical implant maintains blood naltrexone above 2 ng/ml for 80 and 165 + days, respectively.[9] This period of antagonist cover is greater than has been reported previously. Given this opiate antagonist coverage, it is anticipated that blood naltrexone levels associated with the implant will provide a prophylactic for accidental overdose for median to relatively high doses of heroin over these periods of coverage.[10–13]

This paper reports the results of a pilot study that compared the frequency of accidental opiate overdose and other morbidity resulting in hospital presentations in eight high-risk dependent heroin using adolescents pre- and post-naltrexone implant treatment.

Methods and materials

Participants

The study population consisted of adolescent substance users where ethics approval had already been received to audit hospital emergency department presentations as part of a larger study on adolescent alcohol and other drug use.[14] Only eight people among this larger cohort (n = 162) had received implants. They underwent initial naltrexone implant treatment at the Perth Naltrexone Clinic (The Australian Medical Research Procedures Foundation) between September 2000 and September 2001. The use of naltrexone implants has been described previously.[15] In brief, the implanted naltrexone is encapsulated in a microsphere form by loading poly-DL-lactide micro-spheres (Purac Biochem, the Netherlands) with naltrexone and compressing the formulation into pellets. This polymer is similar to that used in surgical sutures and screws, and is implanted in the subcutaneous tissues, usually on the right side of the lower abdomen.

Method

The study was a retrospective case series reviewing the hospital medical records of the participants across the four teaching hospitals in Perth, Western Australia. Medical notes were reviewed for the period from approximately September 1999 to October 2002. Presentations were classified as 'overdose' (OD) if the term was used in the triage summary or hospital notes. ODs were subdivided into those involving opiates and non-opiate ODs. All alcohol or other drug (AOD) presentations not involving ODs were classified as 'other AOD' and hospital presentations not involving AOD use were grouped as 'non-AOD'.

Data on naltrexone implants [date of implant, size, expected release rate (ERR)] were collected from patient records at the Perth Naltrexone Clinic, where written informed consent was obtained to review records. Information on oral naltrexone maintenance prior to naltrexone implant treatment was recorded and tabulated with information on Rapid Opiate Detoxification (ROD). This procedure has been described elsewhere.[16]

Results

The eight adolescents (four female) were aged 15–19 years (median 18 years) when first identified by the review. The mean length of follow-up for the cases was 1155 days (SD 12). Table 1 shows naltrexone treatments and the number of hospital presentations classified by type: OD (opiate or non-opiate), other AOD and non-AOD presentations. An event summary of opiate overdoses and their temporal relationship to treatment with ROD, oral naltrexone and naltrexone implants are shown in Fig. 1.

Figure 1 covers the time from baseline (approximately September 1999) to mid-October 2002. As each member of the cohort had a different start date, the figure includes a reference point for each person: 9 September 2000 was the date when the first member of the cohort received an implant. The period of blockade was estimated at 80 days for single implants (mass approximately 1.7 g) and 165 days for double implants (mass approximately 3.4 g). These times repre-

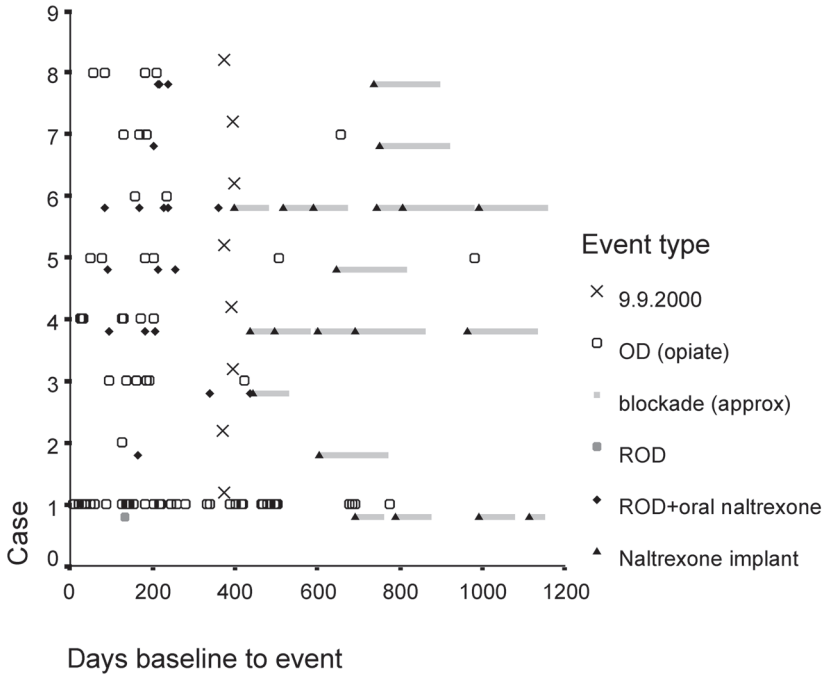

Figure 1. *Hospital opiate overdose presentations and pharmacotherapies.*

sent the lower boundary of the 95% confidence interval for the pharmacokinetic decay curve of blood naltrexone to reach 2 ng/ml.[9] As shown, there were two opiate overdoses post-implantation, but in both instances they fell outside the blockade period. Case 1 had an OD 83 days after a single implant and case 5 had an OD 333 after a double implant. There were also four non-opiate ODs post implantation (see Table 1), of which three occurred during the opiate blockade period.

A rate of hospital events by the four categories (opiate overdose, non-opiate overdose, 'other AOD' presentations and 'non-AOD' admissions) was calculated for the period pre- and post-naltrexone implant. Where oral naltrexone was prescribed prior to implant, the rate of hospital events during the period on oral naltrexone was calculated. It should be noted that there are only seven cases for the periods 'pre-treatment' (oral or implant naltrexone) and 'oral naltrexone'. Case 1 did not complete ROD or commence oral naltrexone, so all her presentations prior to implantation are included in the pre-treatment period. Case 6 had already commenced oral naltrexone prior to the start of the review: all his hospital presentations up to implantation were included in the 'oral naltrexone' period. To allow for varying lengths of follow-up, individual rates of presentation were standardized as presentations per year and the overall rate per year tabulated in Table 2. The rates of all forms of hospital presentation were lower after naltrexone implantation compared to pre-treatment levels. The pattern of change between pre-treatment and post ROD/oral naltrexone was less consistent with only the rate of opiate ODs declining.

Discussion

These preliminary data indicate a dramatic reduction in opiate overdose associated with implantable naltrexone treatment, with a smaller reduction in opiate overdose associated with the period of oral naltrexone treatment compared to the pre-oral/implant period. Assuming that ED treatment for accidental overdose is a marker for the relative risk of fatal overdose, implant treatment in the high-risk heroin user may provide an important prophylaxis against mortality associated with accidental opiate overdose.

Non-compliance with the use of oral naltrexone and return to heroin use was a major feature of most adolescents, with five of the six cases treated with oral naltrexone undergoing at least

Table 1. *Naltrexone treatments and types of hospital presentation for each case*

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case7	Case 8	Total *n* (%)
Gender: age	female: 16	female: 19	male: 18	female: 18	female: 15	male: 17	male: 18	male: 19	–
Length of follow-up (days)	1144	1143	1167	1162	1146	1169	1166	1146	9243
Rapid opiate detoxification (*n*)	1§	1	2	3	3	5*	1	3	19*
Oral naltrexone prior to implant	no	yes	yes	yes	yes	yes	yes	yes	
Naltrexone implant mass g (ERR)	1.74 (0.4) 1.64 (0.4) 1.51 (0.4) 4.71 (0.4)	3.48 (0.4)	1.42 (0.2)	1.41 (0.2) 1.65 (0.6) 3.48 (0.4) 3.48 (0.4) 3.02 (0.4)	3.48 (0.4)	1.0 (0.46) 1.65 (0.6) 1.75 (0.4) 1.61 3.28 (0.4) 3.12 (0.4)	3.22 (0.4)	3.22 (0.4)	20
Hospital department									
ED	59	3	13	33	12	10	6	6	142 (90)
Other	1†	4	3	5	1	2	–	–	16 (10)
Presentation type									
Opiate OD	43 (+1‡)	1	6	8	5 (+1‡)	2	4	4	75 (48)
Non-AOD related									
Non-opiate OD	5	0 (+1‡)	–	12 (+1‡)	1	0 (+2‡)	1	–	23 (14)
Other AOD related	5	1	3	4	–	4	–	–	17 (11)
Non-AOD related	6	4	7	13	6	4	1	2	43 (27)
Total	60	7	16	38	13	12	6	56	158 (100)

§Procedure not completed: *Plus one ROD prior to the study period; †prison medical centre; ‡overdose post-implant. ERR = expected release rate %/day: AOD = Alcohol or other drugs: ED = emergency department: OD = overdose.

Table 2. *Overdose and other hospital presentations associated with periods of pre-naltrexone, oral naltrexone and implantable naltrexone*

Type of presentation	Number of presentations per year: grand mean (standard error)		
	Pre-naltrexone (cases = 7, events = 82, days observation = 1794)	Oral naltrexone Post ROD + (cases = 7, events = 55, days observation = 2908)	Post-implantable naltrexone (cases = 8, events = 21, days observation = 4494)
Opiate OD	8.9 (2.6)	1.9 (0.74)	0.19 (0.13)
Non-opiate OD	0.38 (0.38)	2.0 (1.8)	0.27 (0.14)
Other AOD	0.76 (0.51)	1.1 (0.64)	0.16 (0.11)
Non-AOD	2.1 (1.1)	4.2 (2.1)	1.1 (0.36)

OD = overdose: AOD = alcohol or other drugs.

two ROD inductions onto oral naltrexone during the review period. This is consistent with 6-month review data published previously on 300 oral naltrexone patients from this clinic, showing that 65% ceased naltrexone and used heroin before returning to naltrexone maintenance.[17] Importantly in these five cases, accidental opiate overdose was observed during this oral naltrexone period. Frequent naltrexone maintenance re-treatment and accidental opiate overdose may therefore be clinical markers identifying the need for implantable naltrexone.

Given the high relapse potential associated with heroin dependence it is anticipated that patients may test periodically the opiate blocking effects of their implant. There is, however, no knowing the exact level of blood naltrexone to opiate dose that will be required to fully antagonize the effects of any opiate dose used or to prevent overdose. Recently, however, Brewer provided data that serum naltrexone levels of 2.8 ng/ml achieved using the GoMedical implant was sufficient to block doses of pure diamorphine as high as 500 mg.[11] Given pharmacokinetic data that the single or double GoMedical implant maintains blood naltrexone above 2 ng/ml for 80 and 165 + days, respectively,[19] it is reasonable to expect that the implant will provide a prophylaxis for accidental overdose for median to relatively high doses of heroin over this period. Only two opiate overdose were noted in this study group following implant treatment (cases 1 and 5). In case 1, the adolescent insisted that the implant procedure be terminated when only a single 1.7 g implant had been inserted. The overdose occurred at 83 days post-implant when naltrexone blood levels would have been depleted considerably.[9] Furthermore, given the significant history of overdose in this patient (43 in the period prior to implant) it is likely that the level of heroin used was significant. In case 5 the overdose was 333 days post-implant, when no blockade would be anticipated.

A number of limitations should be considered in the interpretation of the data. The study design (pre–post without a control group) does not allow causality to be imputed. This problem was exacerbated by selection biases: these adolescents are probably not representative of young heroin users, as implantable naltrexone was only available to those considered at high-risk. Changes in OD patterns may therefore be due to regression towards the mean, collateral aspects of the implantation procedure (i.e. physical presence of an implant that is clearly palpable, increased commitment to cease heroin use), treatments received from other (unidentified) sources, or fluctuations in the availability or purity of heroin.

Given the history of frequent relapse back to heroin use by these dependent heroin users, the former explanations of increased motivation or other unidentified treatments seem unlikely. Similarly, the latter explanation of fluctuations in availability or heroin purity is unlikely because the 1100-plus-days time scale for each case was across the same time period with cases exposed to oral naltrexone and naltrexone implant at different stages. From Fig. 1 it can be seen that after the first implant in the cohort (9 September 2000) other members of the group continued to have opiate overdoses, thus the decline in opiate overdoses post-implantation cannot be attributed solely to the (un)availability of heroin. Regardless of the timing of implant, accidental opiate over-

dose declined following implant treatment. The authors would also make reference to the sudden cessation of accidental overdose associated with case 1 and suggest that, short of supervised residential incarceration, no other currently available treatment would arrest, to the degree observed, the significant level of opiate overdose observed prior to implant for this young woman (three overdoses in the 15 days prior to implant; 40 in the preceding 675-day period).

Where the effect of opiates is blocked it may be argued that other drug use, especially polydrug use, may replace opiate use, posing a new overdose risk situation. These preliminary data suggests that an increase in non-opiate overdose was not associated with implant treatment; in fact, non-opiate overdoses also declined post-implant (see Table 2).

In conclusion, the extremely encouraging findings of this pilot study now require validation using a larger cohort over an extended period of time. In particular, a more detailed investigation is required to establish the relationship between implant mass, ERR, time since insertion and overdoses.

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