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Naltrexone Implants – Duration, Tolerability and Clinical Usefulness

A Pilot Study

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Opioid antagonist implants · Naltrexone · Opioid dependence

Abstract
Naltrexone blocks opioid effects effectively, but poor compliance limits the clinical usefulness in the treatment of opioid dependence. Long-acting implanted formulations might increase the clinical feasibility. Several implants have been produced, but few clinical reports have been published. This paper describes an open trial with an Australian implant. This implant is claimed to have duration of up to six months with double implants and acceptable levels of side effects. This was explored in the present pilot study with 13 opioid-dependent patients. By single implant of 1.8 g naltrexone the duration judged by naltrexone plasma levels above 1 ng/ml naltrexone was between 2 and 4 months. Double implants maintained such plasma levels for 5–6.5 months. Clinically, the implants appeared promising. Side effects were minimal. During the period with adequate plasma levels of naltrexone, use of opioids was absent and use of other psychoactive drugs reduced. At 1-year follow-up, the patients rated the implants highly positively.

Introduction

Naltrexone is a well known opioid antagonist [1]. During naltrexone treatment relapse rates to opioid use are minimal and overdose mortality for all practical purposes prevented. The clinical usefulness, however, is limited by high attrition [2]. Except for highly motivated patients such as probationers that might prevent their return to prison by complying with naltrexone treatment [2, 3] and physicians and other professionals at risk of loosing their licenses, the benefits of naltrexone seem to be marginal beyond a short post-treatment period [2].

Two strategies seem promising in order to secure long-term naltrexone treatment [4]. One is community reinforcement [5] and the other is use of sustained release formulations [6–13]. Several different implants have been produced, but all lack proper clinical trials and so far, none of the implant formulations have been registered for clinical use. Nevertheless, positive experiences have been published. In a previous study, the present authors investigated a US implant from Wedgewood pharmacy (N.J., USA) [12, 13]. Clinical impressions were favorable, but measurements demonstrated wide variations in naltrexone concentrations in plasma as well as with respect to time periods with sufficient drug concentrations. Judged by a plasma level naltrexone of 1 ng/ml,

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the duration of opioid blockage varied from approximately 30 to 80 days. Further, at re-implantation there was an increase in tissue reactions, sometimes necessitating surgical revision. There were no signs of hepatotoxic effects and side effects were insignificant [12, 13].

On this basis, we have investigated another implant, produced by Go Medical in Australia, as this implant has been claimed to have longer duration and infrequent tissue reactions. The study therefore aimed to determine naltrexone concentration in plasma and to measure side effects and possible unwanted clinical events. Further, as a negative influence by naltrexone on the motivational reward systems has been suspected [14], we investigated changes in well-being, depression and stress levels. As blocking of opioid receptors has been hypothesized to influence craving, the relationship between plasma concentration of naltrexone and drug-related cognition was examined. Finally, clinical usefulness and patient satisfaction were investigated.

Methods and Material

The investigated implant from Go Medical Industries (Pty Ltd., Australia) contained 1.8 g of naltrexone in a biodegradable polylactic-based polymer, reviewed in 1997 with a foreign body reaction incidence of 4.9% [15]. This implant contained less than 1% of magnesium stearate. The Wedgewood implant used in the earlier project [12] with magnesium stearate as containing medium had higher concentrations. The implant was also installed in double. A single implant is claimed to give relapse protection for at least 3 months and the double implant for at least 5 months [15, 16].

The implants were imported by special permission from the Norwegian Medical Agency. Patients who knew about the implants or had friends with implants from abroad and were actively interested in this type of treatment were recruited. Each patient had thorough information on the current status of implants and signed informed consent. The regional medical ethics board was notified and accepted the procedures.

Thirteen patients, 11 males and 2 females, received one or more implants. Eight patients had one single, three had one double and two had one single followed by one double implant. Thus, the 13 patients had 15 implant periods. The mean age was 26.9 years (SD = 4.9). At implantation, the patients had a history of mean 4.8 years (SD = 3.3) of heroin dependency with intravenous use as the typical pattern of drug use. Most had drug use careers from their mid-teens and extensive experience with several other psychoactive substances except cocaine, in particular amphetamines, cannabis and benzodiazepines. Their earlier treatment experiences varied considerably. At entry one came directly from an earlier trial of implants and had been abstinent for close to 1 year. Five had been detoxified from a project with time-limited use of Subutex with a follow-up period between 2 and 6 weeks. One remained abstinent supported by oral naltrexone, 1 had one relapse to heroin and had strong cravings, 2 had increasing use of heroin with use 2–4 times a week, and 2 had daily use. One of these needed institutional detoxification and the others had outpatient treatment with minimum abstinence of 4 days controlled with trial of oral naltrexone. Two were in prison. One of these used heroin in jail albeit not regularly. Four had failed in abstinence-oriented treatment and had a pattern of daily heroin use. Three of these needed institutional detoxification. One came without earlier treatment experience and was detoxified from a pattern of regular use on an outpatient basis.

Before treatment, the patients had routine somatic check-up with blood samples drawn for control of liver enzymes and indicators of infections. A standard psychiatric interview was performed in order to diagnose possible psychiatric disorders. As patients sought treatment with a non-registered medical drug, they were strongly encouraged to come for regular testing of plasma concentrations, for clinical examination and psychometric testing, daily the first week, then weekly and finally monthly. They also consented to a 1-year follow-up after the last implant.

At control consultations, a checklist for side effects, the Hopkins symptom checklist (SCL 25) [17], the Beck depression rating scale [18] and the Likert scales for evaluative judgments were administered.

The side effects checklist was developed with separate scores for cephalagia, nausea, diarrhea, muscule and articular pain or discomfort, anxiety and irritability, each area scored with 0 as 'not at all', 1 as small/insignificant, 2 as obvious/troublesome, and 3 as severe problems. SCL 25 was used in the four-step version with 1 as 'no problem' and 4 as maximum problem. The mean score was used as a general indicator of anxiety/stress. With this version of SCL, scores of 1.75 and above are typical levels found in outpatients psychiatric units [19]. Drug related cognition, for convenience here coined 'craving', was measured by 7-point Likert scales responding to the questions 'To what degree do you experience: (1) longing for drug intake, (2) wish to stop treatment, (3) longing for your drug friends, (4) fantasies about taking drugs.' The Likert scales had 'not at all' as score 1 while 'very strong' scored 7. The evaluating questions posed at final follow-up were: (1) Are you satisfied with the use of implants? (2) Would you recommend the implant to a friend with opioid dependence? (3) Are you satisfied with your life situation in general? They were also asked whether they wanted a new implant if available. Maximum positive response on these Likert scales (absolutely) was 1 and maximum negative response (not at all) was 7.

The concentration of naltrexone and the metabolite 6-β-naltrexol in plasma were determined using liquid chromatography/mass spectrometry (LC/MS) operated in the electrospray ionization mode, combined with a reversed-phase column and acetonitrile/ammonium acetate buffer at pH 5 as mobile phase. Solid phase extraction was used as sample pretreatment as described earlier [12]. The limits of detection (LOD) and quantification (LOQ) were 0.3 and 0.9 ng/ml, respectively, for both compounds. The coefficient of variation was approximately 5% for both low and high concentration levels of naltrexone (1 and 16 ng/ml).

The implants were installed under local anesthesia subcutaneously in the left or right lower abdominal quadrant. Blood samples collected for naltrexone and 6-β-naltrexol analyses were centrifuged and plasma stored at –20°C until analyses. Totally, 110 samples were collected from the 10 patients receiving a single implant (ranging from 4 to 14 samples per patients). Fifty-five samples were collected from the 5 patients receiving double implant (from 8 to 17 samples per patients; for some patients, only capillary blood was

collected due to obliterated veins). The concentration ratio between venous and capillary plasma was determined to be 0.9 ± 23% [20].

The patients filled out the side effects checklist before implantation and then every day first week and then at control sessions. SCL 25, Beck and the Likert scales for craving were filled out before implantation, after 1 week, thereafter monthly.

The patients were followed up at a mean of 11 months (SD = 1.6) post-implantation with a semistructured interview. The interview investigated self-reports on drug use measured in number of day's use of each substance during the last month, their present life situation and their evaluation of the implant measured by Likert scales.

For measurements of side effects on implantation and duration of implants, all 15 implantation periods were investigated. For evaluation of naltrexone tolerability and for evaluation of clinical effects the number of different patients was 13.

Statistical Package for Social Sciences (SPSS) 10.0 for Windows was used for analyses. In view of the small number in the trial, only frequencies with mean and standard deviation were calculated. Absolute numbers were preferred to percentages.

Results

There were no observations of complications in relation to the implantation. After the first week, compliance with the evaluation procedures varied considerably both in regard to regular blood sampling and psychometric measurements. Two of the 13 patients in the trial went on a period of intensive use of amphetamines and were largely unavailable for psychometric testing. The attendance at follow-up sessions varied. Four were present at all interviews, two missed one, four missed two and one missed three appointments. Except for the two in active drug use, the reasons given for absence differed by types of inconvenience. None explained nonattendance by side effects, mental or somatic disturbances.

Eleven met for follow-up interview on schedule. The remaining two were known from contact with relatives, and have later been interviewed with retrospective data.

Side Effects

Side effects were recorded for all 13 patients at 15 implantations. One patient had mild local irritation that responded to antihistamines. Systematic registration of side effects gave higher scores before than after implantation. Diarrhea, muscule pain and irritability were those most frequently mentioned before implantation while muscule pain, irritability and anxiety was mentioned for the first week after. In the day-by-day registration, days one through three were slightly more troubled. The mean value of the side effect scores was found in the range of 0–1 ('not at all' to 'slightly') for all the different types of symptoms already in the first week after implantation and thereafter throughout the study. Side effects were few and mild except that one patient, who had had four earlier implants with the Wedgewood implant in the first pilot project [12], developed a tissue reaction with necrosis that necessitated revision.

Naltrexone Levels

Naltrexone was detected in some of the samples collected shortly before implantation. The reason was that some of the patients had been on oral naltrexone or had measurable plasma levels from previous implants. In 1 patient, the result was maximum level 25 ng/ml, without subjective discomfort. The typical plasma concentration curve after single implant for those without measurable naltrexone before implantation was a concentration increase to 3–5 ng during the first day with very slow decrease over the following weeks. Plasma levels between 1 and 2 ng/ml were reached between approximately 1 and 3 months after a single implant. A level between 1 and 2 ng/ml was reached between 3 and 5 months after a double implant. The naltrexone plasma concentrations decreased slowly from day 2 or 3 (fig. 1, 2) until the end of the implant period. The 6-β-naltrexol concentrations (not included in the figures) were higher compared to naltrexone during the whole implant period (approximately 1–2.5 times), similar to what has been documented earlier [12].

Psychometric Measurements

Table 1 gives an overview of findings. As can be seen from the SCL 25 score, mean findings indicated a level of anxiety before implantation corresponding to that found in psychiatric outpatients. There was a slight tendency to decrease in scores during the first 2 weeks, but scores seemed relatively stable. This corresponded with clinical impression. Several patients mentioned that they felt more relaxed when they did not need to fight the relapse impulses.

The Beck Depression Inventory gave a mean score of 16.8 (SD 13.8) before implantation, which is a sign of moderate depression. After implantation we observed a general tendency to decrease in depression score. Examination of individual scores showed that none had increase from pre-implantation scores. Table 1 indicates, however, a tendency to increase in depression scores at the end of the period.

Mean findings for the four Likert scales examining drug-related cognition are presented in table 2. We can

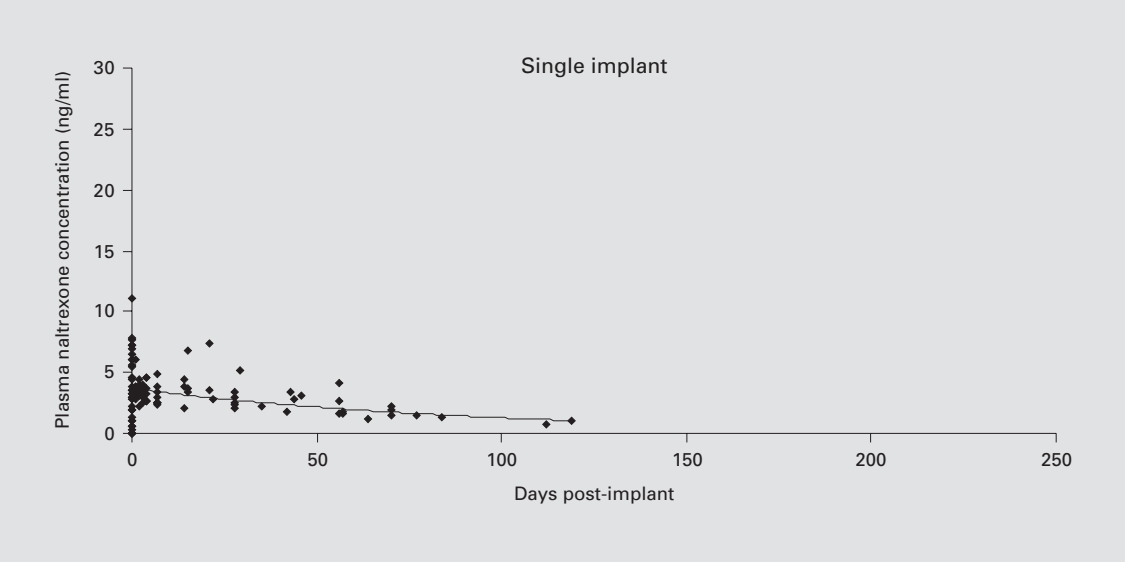

Fig. 1. The relation between naltrexone plasma concentrations (ng/ml) and time (days) after implantation of 10 patients receiving single implants (1.8 g naltrexone). n = 110 samples, 4–14 samples/patient.

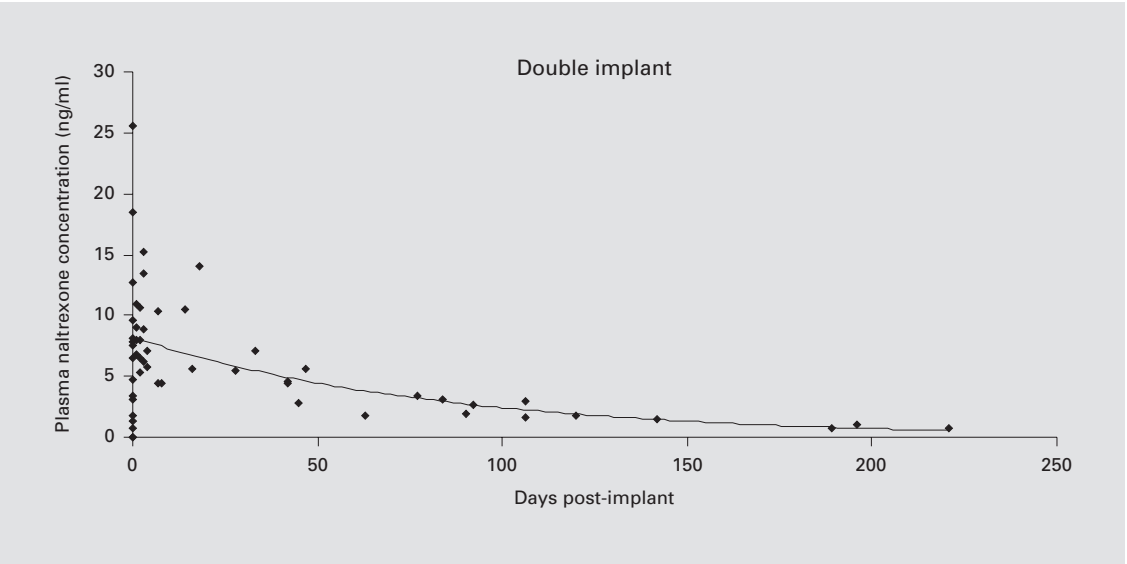

Fig. 2. The relation between naltrexone plasma concentrations (ng/ml) and time (days) after implantation of 5 patients receiving double implants (3.6 g naltrexone). n = 55 samples, 8–17 samples/patient.

see that wanting reactions (do you long for the drug effects) and drug fantasies (do you have fantasies of drug intake) scored highest before implantation with a decrease after. Ambivalence (wish to stop treatment) scored low from the start and remained low while 'drug friends' (thoughts on meeting drug-using friends) had a relatively low score level throughout the study period. As the attendance at interviews varied, we have done a separate analysis not presented in the paper comparing the group compliant at all interview sessions with the noncompliant

Table 1. Mental status before and after naltrexone implantations measured by SCL 25 and Beck depression inventory

	Before (n = 13)	+1 week (n = 12)	+2 weeks (n = 8)	+4 weeks (n = 8)	+8 weeks (n = 9)	+12 weeks (n = 7)
Anxiety/stress SCL 25*	1.9 ± 0.69	1.5 ± 0.66	1.3 ± 0.32	1.7 ± 0.58	1.5 ± 0.57	1.6 ± 0.55
Depression (Beck)	16.8 ± 13.6	12.0 ± 12.1	7.6 ± 7.2	10.8 ± 9.0	10.1 ± 11.9	14.7 ± 10.4

Mean values in 13 patients at 12 weeks' follow-up.
* SCL version with 1–4 scale.

Table 2. Craving and drug-related cognition during the follow-up period measured by subscales, mean values

	Week –1 (n = 13)	Week 1 (n = 11)	Week 2 (n = 8)	Week 4 (n = 8)	Week 8 (n = 8)	Week 12 (n = 7)
Wanting	3.9 ± 2.0	3.5 ± 1.8	3.0 ± 1.4	3.8 ± 2.0	2.9 ± 1.9	3.7 ± 2.3
Ambivalence	1.8 ± 1.2	1.4 ± 0.7	1.4 ± 0.7	1.6 ± 1.8	1.6 ± 1.1	2.1 ± 2.3
Drug friends	2.5 ± 2.0	1.5 ± 0.5	2.0 ± 1.3	1.8 ± 0.9	2.1 ± 2.1	2.9 ± 2.3
Drug fantasy	4.8 ± 2.0	3.8 ± 2.4	4.0 ± 1.9	3.8 ± 1.8	2.9 ± 2.3	3.6 ± 2.1
Sum score	3.3 ± 1.4	2.6 ± 1.1	2.6 ± 1.1	2.7 ± 1.4	2.4 ± 1.6	3.1 ± 2.1

Likert scales: 1 is none, 7 is maximal.

group excluding the two on an amphetamine binge. The finding was that mean values did not differ. The patients had the same pattern with high motivation (low score on ambivalence) throughout the 3-month period. They did not seem to change in their reactions towards the drug-taking milieu. Both groups showed a tendency to increase in drug use fantasies and wanting at the end of the period with known relapse protection. We used the sum score as an indicator of craving. As can be seen from table 2, the sum score indicated a decrease in drug-associated cognition after implantation with a tendency to increase when the possibility to relapse came closer.

Follow-Up

The 13 patients were followed up at an average of 11.3 months (SD 1.6) after the last implant. At this point, 2 were in active drug use and difficult to locate. These were therefore not interviewed, but their status regarding drug use and life situation were known and included. One patient was at that time in methadone maintenance therapy. Eleven were interviewed by personal follow-up.

Eight patients reported no use of heroin during the last 30 days, two had 1 and one had 2 days of use. Accordingly, in total 8 of 13 patients (62%) were abstinent from illegal opioids and 3 (23%) had had minimal intake. Six (46%) had no use of benzodiazepines; two had regular prescriptions and three had between 3 and 12 days of use. Five patients (38%) had not touched cannabis while four had from 1–5 days of use. One reported 10 days of cannabis use. Accordingly, 9 (69%) of 13 patients reported no or no regular use during the last month. Problems with use of amphetamine were insignificant except for the two in active use. Nine had not used amphetamine at all while one reported 1 day and one 4 days of use. Alcohol problems were not recorded systematically even though seven told of more or less regular use. The two in active use were known with frequent injections but of the others, only four had used drugs by injections; three once and one four times.

The life situation was mostly good or acceptable. Six (46%) had their own apartments and five (38%) lived with their parents. One was homeless and one in treatment institution. Six (46%) of 13 were employed and one studied at university level. Six were without employment. Of these, three were in rehabilitation or in treatment for somatic diseases such as HCV. Ten (80%) had their main income from earned income, fellowship or rehabilitation benefits.

The patients gave generally a positive evaluation even though nine still could feel their implant on palpation of

Table 3. Patients opinions on the implant measured by Likert scales at follow-up (1 = completely satisfied/positive, 7 = completely dissatisfied/negative)

	Mean	SD
What are your evaluations of the use of the implant	1.6	0.5
Would you have one more implant if possible	3.1	1.9
Would recommend implant to a friend with opioid addiction	1.2	0.4
Satisfied with my situation	2.5	1.4

the implant area and six felt some anxiety or discomfort by the lump. Table 3 presents the scores on Likert scales for satisfaction with one as the maximum positive and seven as the maximum negative evaluation. As can be seen the eleven interviewed had a positive evaluation of the implant (mean 1.6). They would strongly recommend the implants to friends who wanted to stop heroin use (mean 1.2), and all except three would have another implant if available (mean 3.1). Two thought it unnecessary and one had adverse reaction. Life satisfaction was scored with a mean of 2.5.

Discussion

The main findings in this study were high patient satisfaction with a naltrexone implant of long duration and a high level of opioid abstinence at follow-up. Single implants gave on average a time period with naltrexone plasma level above 1 ng/ml for approximately 3 months and the double implant for nearly half a year. During the implantation period, the plasma naltrexone concentration declined gradually. The inter-individual variation in plasma levels measured at approximately the same time after implantation was small. These findings contrast positively with the findings in the study of the Wedgewood implant [12, 13].

At present there is insufficient evidence to establish a plasma level of naltrexone necessary to block the effect of administration of common user doses of heroin. Chiang et al. [21] have suggested the critical plasma level to be about 1 ng/ml. If this holds true, the implants tested in the present study may secure protection from effects of heroin use for a clinically important time period.

At 1-year follow-up the patients reported long periods without relapse to heroin use, and even other types of drug use seemed clearly reduced. As this was an open clinical small group study no conclusions can be drawn except that the treatment approach seemed promising.

It is also of interest that side effects appeared insignificant except for the patient with several earlier Wedgwood implants. This patient was the only one with clinically important local tissue reaction. One of the others had a milder form effectively treated with antihistamines. This gives some warning on repeat implants. However, compared to findings with other implants, the problem level seems acceptable [7, 12, 13].

None of the patients developed increased mental problems and depression, anxiety and anhedonia did not seem typical. The two who went on an amphetamine binge were not investigated by psychometric evaluation, but have later given interview data on unchanged well-being. The 11 in the group participating showed, on the SCL measurements, a relatively stable anxiety/stress level (GSI index). The impression and the likely inference was a tendency that the patient felt more secure and less stressed after implantation when they did not need to fight impulses to drug taking. Neither did the study give any indications for depression as measured by the Beck depression inventory. This confirms the findings of Malcolm et al. [22] in a placebo-controlled 2-month study and is in line with conclusions from two review studies [23, 24]. The tendency was that the patients were less depressed while on implants with scores indicating worsening as the end of the period with active implants came close. This might indicate reactions towards prospects of renewed problems and might also represent a warning against post-naltrexone overdoses judged to be a problem in an Australian overdose study [25].

Another aspect was the effect on drug-related cognition. Several studies have indicated that a reduction in craving is experienced after the introduction of naltrexone therapy [26, 27]. Traditional craving measuring instruments were not used in this study as the focus was set on cognition on drug-related behavior. The findings indicate in particular that longing for drugs and fantasies of drug taking are diminished by naltrexone implantation, but as these results were marked almost immediately at implantation and seemed to diminish with knowledge that heroin use again might be effective, the cause might be psychological rather than caused by the naltrexone.

It is noteworthy that the implants seem very slowly absorbable, and even though the storage medium is judged to be harmless, this might be a problem.

Conclusion

The naltrexone implants studied are promising for further clinical trials. All patients evaluated implantation positively and reported drug use to be diminished and heroin use to be almost absent. Periods where psychosocial improvements are possible, seemed secured, at repeat double implants, for up to 1 year. Side effects were minimal. However, only large-scale trials might reveal more infrequent side effects and unwanted events.

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