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Naltrexone – Assisted Rapid Methadone Discontinuation : A Pilot Study

THESE

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SEVRAGE RAPIDE DE LA MÉTHADONE ASSISTÉ PAR LA NALTREXONE: UNE ÉTUDE PILOTE

Rapport de Synthèse

Un sevrage lent comme méthode élective pour l'interruption de la méthadone est coûteux en termes de temps, le plus souvent associé à un taux élevé d'abandon.
Bien que les méthodes ultrarapides de désintoxication des opiacés aient gagné en popularité récemment, elles sont chères et posent les problèmes spécifiques liés aux patients traités par la méthadone.

Méthodologie: ont été inclus dans l'étude dix patients en traitement de substitution avec de la méthadone. La dernière dose de méthadone a été administrée le matin même du jour de l'admission, en préalable à l'hospitalisation.

Les médicaments suivants ont été administrés le jour suivant l'admission:
ondansetron 36mg, ranitidine 40mg, loperamide 8m., clonazepam 4m., promazine 100mg, metoclopramide 70mg, naltrexone 50mg.

L'échelle objective de sevrage des opiacés (*Objective Opiate Withdrawal Scale*) a été appliquée au deuxième, troisième et quatrième jour d'hospitalisation, deux fois par jour, à 8h00 et 18h00. Un suivi a été réalisé sous la forme d'entretiens téléphoniques pendant une semaine, respectivement six mois après la date de sortie de l'hôpital, faisant suite à la désintoxication. Un autre entretient téléphonique a été réalisé dans les six mois suivant le "post-sevrage", avec pour objectif d'investiguer la continuité du traitement, une éventuelle rechute dans l'abus de drogues et une possible réintroduction de la méthadone.

Résultats: nous avons pu déterminer quatre groupes de symptômes, sur la base d'une observation de trois jours d'évolution: 1) Les signes typiques du syndrome de sevrage de retrait des opiacés, symptôme de froid et chaud, pilo-érection, anxiété caractérisée par une intensité initiale élevée et une disparition relativement continue. 2) Hyperactivité neurovégétative caractérisée par une intensité initiale élevée et une rapide disparition. 3) Phénomènes neurovégétatifs dont l'intensité s'est maintenue durant toute la période d'observation. 4) Contractions musculaires, insomnies et anorexie, manque d'appétit, réapparaissant chez certains patients au 2ème et au début du 3 ème jour.

Conclusions: une procédure courte de désintoxication utilisant une dose unique de naltrexone s'avère être une méthode alternative valable pour un sevrage de la méthadone. Cette méthode semble accélérer et écourter la symptomatologie associée au sevrage. Le cours des symptômes peut être interprété comme biphasique. Une première phase de retrait est éminemment caractérisée par tous les symptômes typiques eux-mêmes et probablement induits par la naltrexone. La seconde phase, pour un plus petit nombre de patients, peut être interprétée comme en corrélation avec une concentration de méthadone en diminution significative ultérieurement.

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Naltrexone-Assisted Rapid Methadone Discontinuation: A Pilot Study

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Methadone · Opiate withdrawal syndrome · Naltrexone · Dependence, opiate

Abstract
Slow downtitration as a methadone discontinuation method is time-consuming and associated to high dropout rates. Whereas ultra-rapid opiate detoxification methods have recently gained some popularity, they are expensive and may be associated with particular problems in methadone patients. In the present study, a 3-day detoxification procedure accelerated with a unique dose of naltrexone was used in 10 methadone-substituted patients. Whereas the treatment resulted in a shortened withdrawal syndrome, which was satisfactorily controlled by the drugs used, a two-phase course was observed, some symptoms reappearing between the end of day 2 and the beginning of day 3. The first phase of withdrawal symptoms was attributed to the antagonistic effect of naltrexone, which possibly also improved under the weakening of naltrexone. The second phase of withdrawal symptoms may be related to falling methadone plasma levels.

Introduction

The effectiveness of methadone maintenance treatment in reducing heroin use, criminal activity, risk of HIV, fatal and non-fatal heroin overdoses, and in improving health and social functioning can actually been considered as well validated [1, 2].

However, when it comes to the decision to stop methadone, many patients experience difficulty in ceasing methadone, with completion rates ranging from about 40 to 100% depending on factors such as staff approval, rate of reduction, psychosocial support and medication provided.

Different methadone discontinuation strategies have been proposed and studied, and all have their pros and cons. One of the most usual methods is the progressive downtitration of methadone until reaching 0 mg. This has sometimes been supported by concomitant symptomatic treatment of withdrawal symptoms with α_2-adrenergic agonists [3, 4]. Another method is to substitute methadone with buprenorphine, and progressively discontinue buprenorphine [5–7]. The feasibility of using buprenorphine to assist methadone withdrawal may particularly be complicated by difficulties in transferring from methadone to buprenorphine, as this can precipitate withdrawal symptoms.

The major disadvantage of all slow downtitration methods are their time-consuming aspect, and their high dropout rates [5]. Reducing the duration of detoxification treatment has, on the other hand, recently become of major interest as shortening of withdrawal by different means has increasingly been found to be possible without important increases in the severity of withdrawal symptoms. One of the strategies developed with the aim of shortening the opiate withdrawal syndrome uses opiate antagonists such as naloxone hydrochloride or naltrex-

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Table 1. Treatment protocol

Time, h	Administered drug	Dose, mg
10:00[a]	Ondansetron	36
	Ranitidine	40
	Loperamide	8
	Clonidine	0.3
	Clonazepam	4
	Promazine	100
11:00	Metoclopramide	20
	Naltrexone	50
11:40	Metoclopramide	50
	Clonidine	0.3

[a] All drugs administered simultaneously.

one to precipitate withdrawal [8]. A particular method using an opiate receptor antagonist for opiate detoxification is the so-called ultra-rapid opiate detoxification, which is usually performed under conditions of general anesthesia [9, 10] or profound sedation [11, 12]. Different modifications of the techniques have been developed and introduced into practice [13, 14]. One major drawback to these methods is the need of expensive critical care. Furthermore, safety is also a major issue for these procedures, since cases of death have been reported following this procedure [15].

Furthermore, many of the anesthesia procedures used in heroin-dependent patients have been found to have higher complication rates in methadone patients [16]. Moreover methadone patients seem to experience more severe withdrawal symptoms, which may be due to the lipophilicity, large distribution volume and long half-life of methadone. These particularities often make it necessary to modify and complicate the detoxification procedure [16].

The majority of trials studying opiate detoxification treatments, and especially those examining rapid methods, did not specifically select for methadone-substituted patients, while many patients included were withdrawing from methadone [4, 12, 17–19]. Furthermore, several studies describing methadone detoxification used methadone mainly to stabilize the opiate dose prior to withdrawal and not as substitution treatment [9, 20, 21].

With regard to antagonist-assisted detoxification, the antagonist has usually been maintained over the detoxification period [10, 11, 22, 23], and there is no documented clinical experience on the temporary administration of antagonists to accelerate the withdrawal process without continuing the administration of the antagonist. However, the administration of small doses of antagonists may be an interesting approach not only to accelerate withdrawal but possibly also to modify the symptom spectrum, and even to reduce symptom intensity as suggested by recent reports [18, 22].

The present study was aimed to assess the efficacy and tolerability of a 3-day detoxification procedure accelerated with a unique dose of naltrexone in a selected sample of methadone-substituted patients for whom the indication of an urgent detoxification was given.

Methods

Setting

The study was carried out at the Psychiatric Hospital of the Canton Neuchâtel, Perreux, Switzerland, which covers a catchment area of 200,000 inhabitants. As a rule drug-dependent patients are admitted on a voluntary basis.

The usual method for methadone discontinuation in the canton of Neuchâtel consists of slow downtitration over several weeks on an outpatient basis. For many patients, a several-week program in abstinence-centered therapeutic communities is often recommended by treating professionals following the withdrawal of methadone. However, one admission criterion of these centers is abstinence already at entry into the program, and places are often only available at short term. Hence there is a necessity for a rapid, simple and short treatment protocol for these patients as a means of methadone discontinuation allowing them to enter the therapeutic community within a few days.

Treatment Protocol

The treatment protocol outlined in table 1 was developed by shortening the usual clinical protocol by adding a single dose of naltrexone. All medication was administered orally.

The last methadone dose was administered the morning of the admission day before admission itself in all patients. Patients entered the unit between 10:00 and 11:00 a.m. During the whole 1st day of hospitalization no pharmacological treatment was applied. On the 2nd day of hospitalization, the treatments were administered as indicated in table 1. On the 3rd day no further drugs were administered.

Participants

Methadone patients who were interested in withdrawal from methadone maintenance treatment were considered for the study. In order to be included in the protocol, patients had to be at least 18 years old, give informed consent, be under methadone substitution for at least 12 months, and without concomitant illegal drug consumption for at least 6 months as established by regular urine drug screenings. Furthermore, the decision to discontinue methadone had to be made jointly by the patient, his treating physician as well as the responsible physician of the detoxification

unit, on the basis of a pre-hospitalization interview which took place 2–4 weeks before hospitalization, and during which social, professional and familial stability was evaluated.

The main non-inclusion criteria were serious medical or psychiatric conditions, pregnancy, and known intolerances to the substances used in the present protocol. Finally, patients who were also dependent on benzodiazepines, alcohol or cocaine according to ICD-10 were excluded. Patients in whom urine screening revealed recent benzodiazepine use, but for whom no benzodiazepine dependence could be diagnosed, were included.

Assessment

All patients underwent medical assessment on admission and a urine drug screening was done in order to assess potential other drug consumptions. Furthermore, standard laboratory measurements (full blood count, clinical chemistry profile) were performed, and results were available before application of the first dose of treatment. Patients with samples positive for opiates (other than methadone) were excluded from the study. Diagnoses were determined according to ICD-10.

The Objective Opiate Withdrawal Scale (OOWS) [24] was applied on the 2nd, 3rd and 4th day of hospitalization, twice a day, at 8:00 a.m. and at 6:00 p.m. Blood pressure and pulse rate were also measured. The OOWS is an objective scale with 13 observable physical signs of withdrawal. A clinician rates the symptoms as being absent (0) or present (1). The maximum score is therefore 13.

In addition the following three items were attached to the standard OOWS scale: craving, insomnia, and lack of appetite.

Blood pressure, heart frequency and temperature were assessed twice daily (8:00 a.m. and 6:00 p.m.). As all values remained within normal ranges during the whole observation period, they will not be specifically reported in the results section.

Follow-Up

A follow-up was performed by telephone interview 1 week and 6 months after discharge. As all patients were transferred to a therapeutic community after methadone detoxification, a nurse from the corresponding therapeutic community was contacted after 1 week to assess possible persistent withdrawal symptoms. A further telephone interview at 6 months after withdrawal was done which aimed to investigate retention in treatment, relapse in drug abuse, and possible reintroduction of methadone.

Results

Characterization of the Patients

The patient sample consisted of 3 women and 7 men. The mean age was 30.0 ± 3.7 (range 25–35) years. Besides the ICD-10 diagnosis of opiate dependence and methadone substitution, 3 patients were also diagnosed as having borderline personality disorder (ICD-10: F60.31), 1 patient had a diagnosis of impulsive personality disorder (ICD-10: F60.30), and 1 patient had a history of obsessive-compulsive disorder (ICD-10: F42.2) and generalized anxiety disorder (ICD-10: F41.1).

Two patients were treated on admission to the hospital with quetiapine, and 1 patient received paroxetine. The mean methadone dose at entry was 44.5 ± 38.4 (range 10–140) mg/day.

The initial urine drug screening revealed recent amphetamine consumption in 1 patient, benzodiazepine intake in 5 patients, cannabis consumption in 5 patients, and 1 subject had recently consumed cocaine.

Efficacy

The efficacy data are shown in table 2. The symptoms are arranged in 4 groups (A–D) according to their evolution over the 3 days of observation. As only 1 patient presented with mydriasis during the whole observation period, serious doubts about the accuracy of the ratings for this item must be raised, and therefore it is not shown in table 2.

Group A symptoms, which contains some of the most typical signs of the opiate withdrawal syndrome (craving, hot and cold flashes, piloerection and anxiety), are characterized by a high initial prevalence with most of the patients presenting with these symptoms which continuously disappear over the following 3 days.

Group B symptoms are mainly related to neurovegetative hyperactivation and are characterized by a high initial prevalence and rapid disappearance in most patients.

Group C symptoms are also linked to neurovegetative phenomena, however their prevalence remains low over the whole observation period.

Group D symptoms, such as muscle twitches, insomnia and lack of appetite, reappeared in some patients at the end of day 2 and the beginning of day 3. Four of the 5 patients who complained of muscle twitches and pain on the morning of day 3 were among the patients who presented insomnia the nights before.

Follow-Up

One week after dismissal from the unit, i.e. 10 days after the beginning of treatment, the responsible nurse of the therapeutic community was contacted by telephone and interviewed with regard to possible persistent withdrawal symptoms. Among the 10 patients, 5 presented further episodes of aches and 6 had 1 or more nights with sleep problems (initial or midnight insomnia). No evident other withdrawal symptoms were reported. Craving seemed to be absent in all patients during the 1st week after dismissal from our unit, as reported by the nurse.

With regard to the follow-up at 6 months, 8 of 10 patients completed the therapeutic program as planned or

Table 2. Evolution of symptoms

	Day 1		Day 2		Day 3	
	8:00 h	18:00 h	8:00 h	18:00 h	8:00 h	18:00 h
Group A						
Craving	7	7	5	3	4	2
Anxiety	6	6	4	4	3	1
Hot and cold flashes	9	6	5	4	5	3
Piloerection	6	7	4	7	4	2
Group B						
Tremors	7	3	3	2	1	0
Restlessness	7	3	5	3	2	1
Abdominal cramps	8	2	1	2	1	0
Vomiting	4	1	2	1	0	0
Perspiration	4	0	0	1	1	1
Group C						
Yawning	2	3	3	2	0	0
Lacrimation	2	2	2	0	0	0
Rhinorrhea	3	2	0	2	2	1
Group D						
Muscle twitches	3	3	2	4	5	3
Insomnia	4		3		5	
Lack of appetite	4	3	2	4	2	1

Items of the Objective Opiate Withdrawal Scale (OOWS) are given in italics. The item mydriasis is not given due to doubts about accuracy of ratings.

were still in the therapeutic community. Of these 8 patients, 2 had had at least one consumption episode, 1 patient abusing alcohol and 1 patient relapsing to heroin. Of the 2 patients who did not complete the therapeutic program, 1 patient of foreign nationality was expelled from Switzerland and therefore the program was interrupted, and the other patient dropped out due to a relapse to cannabis and alcohol consumption. This last patient has subsequently received buprenorphine substitution treatment.

Discussion

In this pilot study on 10 patients undergoing rapid methadone detoxification using a single dose of naltrexone, we found the present treatment procedure to shorten and satisfactorily control the withdrawal syndrome. The typical signs of opiate withdrawal, craving, hot and cold flashes, piloerection and anxiety, improved continuously over the 3 days of observation.

The course of the symptoms can be interpreted as biphasic. A first withdrawal phase, which is mainly characterized by all typical withdrawal symptoms, is probably naltrexone-induced and can be seen in most patients as group A symptoms during the whole day 1, and as group B symptoms on the morning of day 1. In a second phase, concerning fewer patients and extending between the end of day 2 and the morning of day 3, aches, insomnia, and loss of appetite worsened, which can be interpreted as being related to the further significantly declining methadone concentrations.

Group B symptoms, mainly related to neurovegetative hyperactivation and characterized by a high initial prevalence and rapid disappearance, could be related to the antagonistic effects of naltrexone which disappeared from day 2 onwards due to the short half-life of naltrexone and the reappearing effect of the remaining methadone concentrations.

Group D symptoms, muscle twitches, insomnia and lack of appetite, which reappeared in some patients at the end of day 2 and the beginning of day 3, could be interpreted as being related to the falling methadone plasma levels, as their beginning coincides with the habitually expected beginning of most of the methadone withdrawal symptoms. In those patients who complained about

muscle twitches and pain, insomnia the night before seemed to be a premonitory sign.

Therefore, the present treatment procedure seems to shorten the course of some typical opiate withdrawal symptoms, to move forward and at the same time shorten the neurovegetative hyperactivation associated with withdrawal, and therefore represents a promising alternative as a methadone detoxification method. A significant problem remains the reappearance of some distressing symptoms on day 3, which can be counteracted with adequate analgesic co-medications in future treatment protocols, for instance with ibuprofen.

The results of this study need to be viewed against their methodological limitations. The recorded differences between the symptom groups could have been due to observation biases, as the group B symptoms such as tremor are easily recognizable phenomena or likely to be reported by the patient such as nausea, whereas group C symptoms such as yawning, lacrimation, and rhinorrhea rely completely on the observation skills of the monitoring nurse. Further evident limitations of this pilot study are the open treatment conditions, the limited sample size, the limited observation duration, and the non-standardized follow-up, and the lack of biological validation (e.g. urinanalysis) of drug use during the follow-up period.

In conclusion, a short detoxification procedure using a single naltrexone dose appears to be a feasible alternative method for methadone detoxification, and seems to accelerate and shorten the withdrawal-associated symptomatology.

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