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A Randomized Double-Blind Placebo Controlled Study of Methadone and Diazepam with or without Carbamazepine for Combined Opioid and Benzodiazepine Detoxification

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Abstract

Background: Evidence for detoxification from concurrent opiate and benzodiazepine use are scarce. Some schemes include benzodiazepines and opiates, while others add carbamazepine to avoid exacerbation of opiate withdrawal and seizures. This study was undertaken to test clinical outcome and safety in a benzodiazepine / opiate / carbamazepine versus a benzodiazepine/opiate only protocol.

Methods: We included patients with a diagnosis of opiate and benzodiazepine dependence, admitted for detoxification of both substances, in this randomized, double-blind, placebo controlled trial. Patients were randomized to either one of the treatment protocols methadone, diazepam, and carbamazepine (group 1) versus methadone, diazepam, and placebo (group 2). Treatment retention and adverse events (AE) served as primary endpoints.

Results: Each 50 patients were randomized to either group. 27 patients of the group 1 and 31 of the group 2 completed the treatment regularly (n.s.). No serious AE arose, while 87 AEs occurred, including elevated liver enzymes (n=51), elevation of p-amylase (n=25), ataxia (n=5), skin rash (n=3), increased heart beat rate / blood pressure (n=2), and one seizure. On the single item level elevation of p-amylase was more frequent in group 1 (49 versus 36; p<.05). Furthermore the sum of all AEs was also higher in group 1 compared to the group 2 (49 versus 36; p<.05).

Conclusion: Effectiveness of the detoxification protocols methadone, diazepam, and carbamazepine or methadone and diazepam alone in patients with opioid and benzodiazepine dependency are comparable, but treatment safety is better with the methadone / diazepam protocol.

Keywords: Opiates; Benzodiazepines; Dependence; Detoxification; Effectiveness; Safety

Introduction

Addiction is regarded as a chronic relapsing brain disease, which requires situation-adapted treatment approaches [1]. Treatment options for opioid dependence comprise crisis intervention, substitution treatment, detoxification, relapse prevention and other harm reduction measures [2]. Detoxification aims to avoid opioid withdrawal symptoms such as anxiety, chills, myalgia and weakness, lethargy and drowsiness. Various pharmacologic substances can be used to achieve this purpose, with methadone as the agent most widely applied. The pharmacological detoxification concept is characterized by the replacement of a short-acting illegal opioid by a long-acting legal agonist (e.g. methadone), which is subsequently tapered and ultimately discontinued [3]. Opioid dependent subjects often show a poly-drug use pattern, in which benzodiazepines play a central role [4]. A gradual taper in benzodiazepine detoxification is - like in opioid detoxification- preferable to abrupt discontinuation, and carbamazepine is thought to be an effective intervention for benzodiazepine gradual taper discontinuation [5]. Despite frequent co-dependence from opiates and benzodiazepines, studies focusing on polydrug detoxification are scarce [6].

Kristensen and co-workers favored a combined buprenorphine / valproate protocol to detoxify poly-drug users with at least opioid and benzodiazepine dependence [7]. De Wet and co-workers detoxified patients with concurrent opioid and benzodiazepine dependence by a simultaneous linear dose reduction. They reported an increased number of severe withdrawal symptoms in patients detoxified concurrently from opioids and benzodiazepines compared to those detoxified from opioids alone, with concurrent benzodiazepine withdrawal exacerbating the opioid withdrawal syndrome [8]. Adding carbamazepine to the opioid and benzodiazepine may help to avoid an exacerbating withdrawal syndrome in concurrent opiate and benzodiazepine detoxification [9]. On the other hand, every fifth patient treated with carbamazepine suffers from adverse events, including hepatotoxicity [10-11]. Especially against the background of frequent hepatitis virus infections in opioid dependent intravenous drug users, it is desirable to reduce the risk of (hepatic) adverse events to the inevitable minimum [12]. Moreover, carbamazepine is a cyp 3A4 inducer that interacts with methadone, and may lead to decreased methadone plasma levels [13].

Therefore the question was raised whether a concurrent opioid and benzodiazepine detoxification can safely be administered by tapering methadone and diazepam without additional use of carbamazepine. We expected less adverse events in the methadone / diazepam group, except for an increased risk for seizures.

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Method

The study was conducted in an opioid detoxification unit at a tertiary care hospital in Munich, Germany. Inclusion criteria comprised (a) ICD-10 criteria for opioid and benzodiazepine dependence, (b) age between 18 and 50 years, and (c) provision of written informed consent. Patients were excluded from the study in case of alcohol or barbiturate dependency, history of seizures, schizophrenic psychosis, severe depression or mania, pregnancy or breast-feeding, and contraindications for either one or more of the study medications.

Patients were continuously randomized in a double blind manner to either the group 1 (protocol: methadone, diazepam, and carbamazepine) or the group 2 (protocol: methadone, diazepam, and placebo). The methadone and diazepam protocol were alike in both groups; in case the patient was on methadone maintenance treatment when entering the study, the methadone maintenance dose was equivalent to the methadone study starting dose. In case the patient was admitted from the open drug scene, each gram of reported heroin consumption was assumed to be equivalent to 25 mg methadone. Methadone was reduced by 5 mg per day from day 2 onwards. Benzodiazepine-intake was transformed into diazepam equivalents; initially 50% of the reported daily diazepam equivalent was applied with a maximum of 30 mg/day. Diazepam then was reduced by 5 mg per week. The group 1 received 400 mg carbamazepine t.i.d.; carbamazepine reduction was initiated the day after the last diazepam application. Carbamazepine was then reduced by 200 mg every second day. Therefore, the group 1 with carbamazepine is assumed to be treated one week longer. Intake of medication was directly observed. The length of treatment depends on the starting dose of methadone or diazepam. The study was closed upon inclusion of 50 patients in each treatment group.

Patients were examined clinically, including vital parameters (blood pressure, heart beat rate) on a daily basis at 9:00 am, with special regard to frequent carbamazepine-associated adverse events (AE) such as neurological disturbances (dizziness, ataxia, headache), psychic disturbances (drowsiness, asthenia, anorexia), and gastrointestinal symptoms as well as skin reactions [11]. At baseline blood tests such as liver enzymes (Alanine Aminotransferase, ALT, Aspartate Aminotransferase, AST, γ- glutamyltransferase, GGT, Glutamate Dehydrogenase, and GLDH), the pancreas enzyme p-amylase, and a screening for hepatitis B and C, and the human immunodeficiency virus (HIV) were performed. Re-tests for liver and pancreas enzymes were performed once in a week. All adverse events were recorded.

Concerning the blood pressure, an AE was assumed in case of an increase of 15 mm/Hg compared to baseline. Concerning the heart beat rate, an AE was assumed in case of tachycardia (> 100 beats per minute). As to liver enzymes and p-amylase, an AE was assumed in case of an elevation of ≥ 30% compared to baseline level.

All data were entered into the Statistical Package for Social Sciences for Windows, version 12. Categorical and continuous variables were compared using the X^2-test or two-sided *t*-test, respectively.

Results

Two hundred twenty nine patients were screened, and 100 subjects were included. One hundred three patients were excluded due to lack of co-morbid benzodiazepine dependence, 17 patients were excluded due to alcohol and one patient due to barbiturate dependency, three patients had a history of seizures, one patient suffered from a schizophrenic disorder, one patient was pregnant, and three patients declined study participation without giving a reason. Patients included in the study (62 men) were aged an average of 27.3 years (range 19-48). Each fifty patients were randomized into the group 1 (methadone, diazepam, carbamazepine) and the group 2 (methadone, diazepam, placebo). Thirty-two patients suffered from chronic hepatitis C virus infection, one patient from chronic hepatitis B virus infection, none was infected with the human immunodeficiency virus. The average methadone dose at initiation of the treatment was 69.5 mg per day. The average initial diazepam dose was 18.2 mg per day. Fifty-eight patients completed the detoxification treatment as scheduled. A total of 2,211 treatment days were subject to analysis. There were no statistically significant differences between the two groups and no difference of the treatment duration, respectively (Table 1).

Variable	M + D + C* Group 1 (n=50)	M + D + P* Group 2 (n=50)	p
Gender, male	30	32	n.s.
Average age (years)	26.8	27.9	n.s.
Chronic hepatitis B, yes	0	1	n.s.
Chronic hepatitis C, yes	15	18	n.s.
HIV-infection, yes	0	0	n.s.
Average initial methadone dose (mg/day)	72.3 (± 27.1)	66.7 (±29.2)	n.s.
Average initial diazepam dose (mg/day)	18.2 (±7.8)	18.2 (±8.3)	n.s.
Drop-outs	23	19	n.s.
Average duration of treatment / drop-outs (days)	15.2 (±9.3)	15.8 (±9.7)	n.s.
Average duration of treatment / completers (days)	22.7 (±8.3)	23.3 (±8.1)	n.s.

N.S. = Not Significant; M: Methadone; D: Diazepam; C: Carbamazepine; P: Placebo

Table 1: Sociodemographic and medical patient characteristics.

Adverse Event	M + D + C* Group (n=50)	M + D + P* Group (n=50)	p
Ataxia	4	1	n.s.
Skin rash	1	2	n.s.
Tachycardia	1	0	n.s.
Increased blood pressure	1	0	n.s.
Seizures	0	1	n.s.
p-amylase elevation	17	8	<.05
AST elevation	3	5	n.s.
ALT elevation	8	9	n.s.
GGT elevation	11	5	n.s.
GLDH elevation	4	6	n.s.
Sum	**50**	**37**	**<.05**

N.S.: Not Significant; M: Methadone; D: Diazepam; C: Carbamazepine; P: Placebo

Table 2: Frequency of Adverse Events (absolute numbers).

In total 87 adverse events were registered. None fulfilled criteria of a serious adverse event. Adverse events most frequently seen comprised of an elevation in the p-amylase (n=25), ALT-elevation (n=17), and GGT-elevation (n=16). Patients in the group 1 suffered significantly more often from a p-amylase elevation (17 versus 8; p<.05). Moreover the total number of adverse events was significantly higher in the group 1 (methadone, diazepam, carbamazepine) as compared to the group 2 (methadone, diazepam, placebo; 50 versus 37; p<.05). Concerning other adverse events, there were no statistically significant differences between groups (Table 2). The adverse events "seizure, ataxia, skin rush, tachycardia, increased blood pressure occurred in the first week of treatment. The blood examinations were made after the second week of treatment. All adverse events happened during the treatment period.

One patient suffered from a seizure on day four, and was then excluded from the study. As the patient belonged to the group 2,

carbamazepine medication was introduced. A re-examination revealed a history of seizures, which the patient did not report upon inclusion in the study.

Discussion

A standard or consented protocol for detoxification of poly-drug users is lacking, and studies examining this issue are scarce. Tapering and discontinuation of the respective substance class generally characterize detoxification protocols. The use of additional medication has to be carefully evaluated regarding benefits and risks. Detoxification from opiates and benzodiazepines by a linear dose reduction may be associated with an exacerbation of withdrawal symptoms, which can be avoided by additional use of carbamazepine [8,9]. Carbamazepine, however, frequently is associated with adverse drug reactions, including hepatotoxicity [11].

In a randomized, double blind design our study shows that treatment outcomes in combined opiate and benzodiazepine detoxification either by administration of methadone, benzodiazepines and carbamazepine (group 1) or methadone, benzodiazepines and placebo (group 2) are comparable. The safety profile of the methadone / benzodiazepine protocol was superior to the methadone / benzodiazepine / carbamazepine protocol in that the absolute number of AEs and the number of p-amylase elevation was significantly lower. The lower number of AEs did not come as a surprise. However, we expected to find significantly fewer elevations of liver transaminases in the group 2 (methadone, diazepam), which was not the case. The number of GGT-elevations in the group 1 (methadone, diazepam, carbamazepine) doubled that of group 2 (methadone, diazepam); even if this difference failed to reach statistical significance it points to the frequent association of carbamazepine administration and GGT-elevation [14]. As opiate dependent subjects suffer from multiple hepatotoxic risk factors, such as infections with hepatitis viruses, alcohol consumption and cigarette smoking, additional iatrogenic noxas should be avoided [12]. Also in the group we studied, more than every third subject suffered from chronic hepatitis C virus infection. P-amylase elevation as an indicator of pancreatitis after administration of carbamazepine has been described, but is clearly less frequent than transaminase elevation [15,16]. Possibly, opiate dependent subjects receiving carbamazepine run an especially high risk of developing pancreatitis. In terms of pancreatic toxicity opiates are classified as class I drugs, indicating high evidence for pancreatic damage [15].

In contrast to de Wet and colleagues, we did not observe an exacerbation of the opioid withdrawal syndrome. In the sample of de Wet and colleagues, there was a need for higher initial benzodiazepine doses (30.3 mg vs. 18.2 mg in our group). Possibly exacerbation of opiate withdrawal in concurrent benzodiazepine withdrawal is especially enliven by high initial benzodiazepine doses. Occurrence of a seizure during withdrawal in one subject with an undisclosed history of seizures underscores the importance of a detailed anamnesis.

This study is limited by the lack of use a standardized instrument to monitor withdrawal symptoms. On the other hand, the daily clinical evaluation was standardized as to the parameters examined, and staff has a long-standing experience in addiction treatment.

Overall, this study shows that concurrent opiate and benzodiazepine withdrawal can effectively and safely be managed by tapering and discontinuation of opiates and benzodiazepines. However, initial diazepam doses of 30 mg or higher or its respective equivalent may additionally require carbamazepine to avoid exacerbation of opiate withdrawal. Special attention should be given to subjects with a history of seizures. Our study results should be replicated in a larger multicentre trial.

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