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ORIGINAL PAPER

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A combination of carbamazepine/tiapride in outpatient alcohol detoxification

Results from an open clinical study

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Abstract This was an open, prospective study to examine the efficacy, practicability and medical safety of a combination of carbamazepine and tiapride in outpatient detoxification of alcohol-dependent patients. Patients were carefully screened for relevant neuropsychiatric disorders and then seen on a daily outpatient basis. Patients received medication if the initial CIWA-A score exceeded 16 points. Fifty consecutively admitted patients entered the program; 49 (98 %) successfully ended treatment. The mean initial dose for carbamazepine was 628 mg or 332 mg for tiapride. No serious medical complications or adverse events were observed. In general, medication was well tolerated. Withdrawal symptomatology as indicated by CIWA-A scores clearly decreased over time. Most frequently named side effects were sedation (63 %), hyperhidrosis (49 %), lack of drive (38 %), dry mouth (31 %) and orthostatic dysregulation or vertigo (22 %). Results from this study suggest that a combination of the anticonvulsant carbamazepine and tiapride is an effective and safe treatment for outpatient alcohol detoxification in patients with moderate severity of withdrawal syndrome.

Key words alcohol · alcoholism · outpatient detoxification · carbamazepine · pharmacotherapy · tiapride

Introduction

While outpatient rehabilitation of alcoholism is widely accepted [12, 29] outpatient detoxification is still a widely neglected issue although a number of studies suggest its practicability and safety [7, 40]. The pharmacotherapy of outpatient alcohol detoxification has not been extensively studied. Current treatment recommendations in the USA for pharmacotherapy of alcohol withdrawal favor treatment with benzodiazepines [17] for moderate to severe withdrawal symptoms. As an alternative, clomethiazole, which is a combination of carbamazepine and tiapride, has been recommended with some promising initial results [5]. Carbamazepine is an antiepileptic drug with clear efficacy in epileptic seizures related to alcohol withdrawal [34] but not on other symptoms of alcohol withdrawal [1, 10, 23, 28, 37]. The drug is registered in Germany for treatment of alcohol withdrawal seizures. Tiapride, a benzamide, has a selective D2- and D3-receptor antagonist activity in limbic brain areas or the locus coeruleus [25] and is frequently used for treatment of hyperkinetic disorders including tremor [3, 24]. Tiapride has been advocated for management for withdrawal syndrome especially for alcoholic outpatients [21]. Some previous comparative studies suggest tiapride to be effective in psychovegetative symptoms in alcohol withdrawal but not in seizures or hallucinations (1, 13, 18, 22, for review see 21). None of the studies has addressed tiapride's role in outpatient detoxification.

The therapeutic rationale between the combination of carbamazepine and tiapride is the combined effect on both seizure risk and psychovegetative symptoms in alcohol withdrawal, without a significant risk for an abuse potential or risk of overdose [2]. Recently Franz et al. [9] reported results of two pilot studies comparing the combined effects of tiapride (TIA)/carbamazepine (CBZ) with clomethiazole in alcohol withdrawal. Both studies revealed similar efficacy in terms of psychopathologic and vegetative symptoms and somehow faster vegetative recovery with TIA/CBZ.

We report data of an open clinical trial on a combination of carbamazepine and tiapride in a structured outpatient detoxification program.

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Subjects and methods

This was an open, prospective study to examine the efficacy, medical safety and practicability of a combination of carbamazepine and tiapride in outpatient detoxification of alcohol-dependent patients. The psychosocial outpatient treatment program had been launched in a special alcohol outpatient clinic in 1998 and is supported as a model project by major health care insurance companies in Germany. Details of the program have been described in detail elsewhere [30, 32].

During detoxification, patients were seen on a daily basis for 5–7 (max. 10) days.

Inclusion criteria

Patients had to meet ICD–10 [40] and DSM-IV criteria for alcohol dependence.

Exclusion criteria

Polysubstance use, history of severe alcohol-related disorders (seizures, alcohol psychosis), major psychiatric disorders (e. g., schizophrenia, suicidality), severe cognitive deficits, severe medical disorders (pneumonia, tuberculosis or other infectious diseases), head injury, severe liver cirrhosis, erosive gastritis, pancreatitis, reduced physical state and cardiovascular disorders.

For assessment of alcohol withdrawal the Clinical Institute Withdrawal Scale (CIWA scale [26, 36]) was used. The validated German version of the CIWA-A scale by Stuppaeck et al. [35] is a 12-item scale which comprises the following items: blood pressure, pulse rate, respiratory rate, body temperature, seizures, nausea/vomiting, tremor, hyperhidrosis, tactile/auditory/visual disturbances, orientation, concentration, nervousness/anxiety and headache. In contrast to the original scale by Sullivan et al. [36] with grades from 0–7, the German CIWA-A scale uses grades from 1 (not existent) to 6 (maximum), except for seizures. The minimum score of the scale is 11 (no symptoms).

Patient characteristics

Of the patients, 31 (62 %) were male, 19 (38 %) female with a mean age of 43.4 (24–72) years and an alcohol history of 11.9 (1–45) years on average. Gamma-GT at baseline was 117.6 [8–908] U/L. Last daily alcohol consumption was 179 (max 320) g/day. Of the patients, 25 (50 %) were still intoxicated at treatment beginning (BAC > 0). Of the patients, 15 (30 %) had been treated as inpatients for alcohol dependence previously.

Medication

Patients received vitamins and minerals, if necessary. Withdrawal symptoms were measured on a daily basis. Patients with a CIWA-A score > 16 received medication. Although the study followed a flexible dosage regime, patients usually received an initial dosage of 300 mg tiapride and 600 mg carbamazepine/d for 5–7 days in the unretarded form. Depending on severity of alcohol withdrawal, medication was given at the initial dose over several days and then reduced.

Results

Carbamazepine on day 1 was given at a mean dose of 628.5 mg (200–800 mg); 31 (62 %) of the 50 patients received a standard dose of 600 mg. Tiapride was given at a mean dose of 332.6 mg (max 400 mg), whereby 33 patients received a 400 mg dose, 7 patients a 300 mg dose.

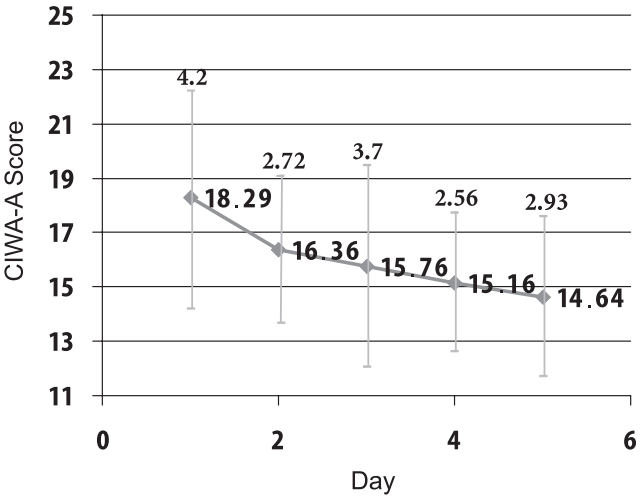

Fig. 1 Outpatient detoxification with carbamazepine and tiapride (N = 50). CIWA-A mean score is given with the standard deviation noted above it.

Medication was gradually reduced over time. Mean dose of both drugs on day 2 were 625.0 mg for carbamazepine or 332.6 for tiapride; mean dose on day 3 was 622.5 mg or 332.6 mg. On day 4 mean dose for carbamazepine was 616.6 mg or 334.7 mg for tiapride, while on day 5 it was 582 mg or 326 mg. Medication was discontinued after 7 days maximum.

Of 50 patients included in the study, only 1 patient (2 %) dropped out because of lack of motivation. CIWA-A scores over time are given in Fig. 1. Mean CIWA-A score at treatment beginning was 18.3 (SD 4.2). CIWA-A score clearly decreased over time to 14.6 on day 5. No case of delirium or seizures was observed during treatment. Blood pressure under this medication was stable.

Side effects

Patients were asked daily about possible side effects and adverse events using a checklist. In general the drugs were well tolerated. No serious adverse events were observed during the study and no patient dropped out because of adverse events. With respect to side effects most frequently mentioned symptoms were sedation (46 %), orthostatic dysregulation (22 %), dry mouth (26 %), pruritus (16 %) and diarrhea (16 %). Other side effects were decreased libido (6 %), urine retention (2 %) and obstipation (2 %). No overdose or intoxication was observed in our study.

Discussion

While in Scandinavia, Great Britain and the US a number of outpatient alcohol detoxification models have been studied [5, 6, 19, 38] this is the first German outpatient detoxification model which is supported by health insurance companies as a model project [28, 30]. Clinical studies suggest feasibility of outpatient detoxifica-

tion: Wiseman et al. [40] reported a completion rate of 85 %, similar to other studies [4, 7, 8, 11, 19, 32, 33, 38].

Based on previous findings [22], we used a combination of carbamazepine and tiapride in alcohol outpatient detoxification. The dosages given in our study were somewhat lower than those given in a study of alcoholic inpatients with severe alcohol withdrawal [5]. Pharmacotherapy was initiated in case CIWA-A score exceeded 16 points. CIWA-A scores at baseline suggest a moderate withdrawal symptomatology but clinical and sociodemographic data indicated patients to have a long-term history of alcoholism. In a recent study in alcoholic inpatients, the mean dosage for CBZ was 763–810 mg on day 1 or 915–1183 mg for TIA [9]. The efficacy of carbamazepine in alcohol withdrawal, especially seizures has been shown in a number of studies (10–12, for review see 31). Its efficacy in relapse prevention of alcoholism is less clear [17]. In one study, carbamazepine had already been used for outpatient withdrawal [6].

Tiapride has repeatedly been used in alcohol withdrawal [for review see 31] with clear effect on vegetative symptoms but not on seizures. Thus the combination of both drugs has been recommended for alcohol withdrawal [5]. Tiapride may also be effective in the post-withdrawal period in alcoholics with depressive or anxious symptoms [26].

The clinical results of this explorative trial suggest favorable outcome of pharmaco-treatment with a combination of tiapride and carbamazepine in alcohol outpatient withdrawal. Patients' compliance was excellent. No serious medical complications were observed. In none of the cases was the medication discontinued because of side effects. Withdrawal symptomatology clearly decreased over time. With respect to side effects, sedation (63 %) was most frequently mentioned, probably related to treatment with carbamazepine [31]. Some symptoms (hyperhidrosis, loss of appetite, headache, vertigo, orthostatic dysregulation, gastrointestinal symptoms) could not easily be assigned either to withdrawal or to side effects. Still no specific medical interventions were necessary in any of the cases. No dyskinesias were observed during treatment.

Although patients in our study had a long-term alcohol history (11.9 years on average), the last daily alcohol intake was somewhat lower than in the inpatient groups studied by Franz et al. (179 g/day vs. 280–290 g/day, [9]). This may explain the somewhat lower dosage of TIA/CBZ compared to our study. Yet the CIWA total sum score at baseline in our study was 18 compared to 20 in the Franz et al. study [9]. The mean dosage given in our study was lower compared to other studies in inpatients [9, for review see 31] possibly indicating that lower dosages might be suitable in milder forms of alcohol withdrawal.

In conclusion, current data indicate a combination of carbamazepine and tiapride to be effective in alcohol outpatient withdrawal. Future studies may address dosing issues and include comparative trials with other drugs including benzodiazepines or clomethiazole.

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