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ORIGINAL PAPER

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Treatment of alcohol withdrawal syndrome with a combination of tiapride/carbamazepine

Results of a pooled analysis in 540 patients

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Abstract This was a retrospective study to examine the efficacy, practicability and medical safety of a combination of tiapride and unretarded (fast acting formula) carbamazepine in the treatment of alcohol withdrawal syndrome. In five hospitals using this combination for treatment of alcohol withdrawal, 540 patients who had been treated with this combination were identified. An intensive evaluation of patients files and charts was performed. Details of alcohol history and comorbid disorders were extracted from patient files. Severity of alcohol withdrawal had been assessed using the CIWA-A-Score. Gender differences and differences between patients in their first and at least second withdrawal were computed by means of variance analyses (GLM). At baseline (day 1) mean dosage given was 796 for tiapride and 543 mg for carbamazepine. A pooled analysis of the results showed that, in general, medication was well tolerated. Withdrawal symptomatology as indicated by CIWA-A scores clearly decreased over time. Although a significant number of patients had a history of alcohol withdrawal delirium (103) and epileptic seizures (151), few patients suffered from them during treatment (8 and 5, respectively). Only 24 (4.4%) patients dropped out because of lack of efficacy or change of medication, 15 (2.8%) because of side effects. No case of malignant neuroleptic syndrome was recorded. Data analysis showed gender differences and differences between patients in their first and at least second withdrawal for side effects, complications, and in some CIWA-A-scores. In general, severe complications of withdrawal syndrome were more frequent in men compared to women and in patients with repeated inpatient treatment. In line with previous research, the results from this study give further evidence that a combination of the anticonvulsant carbamazepine and tiapride is an effective and safe treatment for alcohol withdrawal treatment.

Key words alcohol · alcohol withdrawal · carbamazepine · pharmacotherapy · tiapride

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Introduction

The alcohol withdrawal syndrome (AWS) can be explained by a imbalance between inhibitory and

excitatory neurotransmitters, especially a reduced neurotransmission in $GABA_A$ and an enhanced neurotransmission in glutamatergic (NMDA) pathways, as well as an enhanced dopamine release [1].

While the pathophysiology of alcohol withdrawal is well understood, its pharmacotherapy is still a subject of discussion. Current treatment recommendations in the USA for pharmacotherapy of alcohol withdrawal favour treatment with benzodiazepines [2, 3] for moderate to severe withdrawal symptoms. Especially for the management of alcohol withdrawal delirium they are the first line treatment [4]. As an alternative in Europe, clomethiazole, which is not available in the US, is widely used for the treatment of alcohol withdrawal delirium [5, 6].

While for alcohol withdrawal delirium and the more severe forms of withdrawal, control of agitation is essential with clear evidence for an excellent efficacy of benzodiazepines and clomethiazole these drugs have some potential risks or disadvantages that may be relevant, especially (1) a high abuse potential and (2) the risk for respiratory depression, especially in patients intoxicated with alcohol [7]. For these patients, a combination of tiapride and carbamazepine has been suggested for some promising initial results [8].

Carbamazepine (CBZ) is an antiepileptic drug with proven efficacy in epileptic seizures related to alcohol withdrawal but less on other symptoms of alcohol withdrawal or alcohol delirium [9–11 for review see 12, 13]. CBZ is superior to placebo and equal in efficacy to phenobarbital, oxazepam and clomethiazole [14–18]. In a study in 136 outpatients, CBZ was superior to lorazepam in reducing anxiety and sleep disorders during withdrawal [19]. CBZ is frequently used in Europe for the treatment of AWS but a systematic literature review concluded that there is less evidence to support monotherapy of CBZ than the evidence for the use of benzodiazepines [20]. CBZ is registered in Germany for treatment of alcohol withdrawal seizures. Tiapride (TIA), a benzamide, has a D2- and D3-receptor antagonist activity with no affinity for D1 and D4 receptors in limbic brain areas, respectively, the locus coeruleus and striatum [21], and is frequently used for treatment of hyperkinetic disorders including tremor [22, 23]. Current database as reviewed by Lucht et al. [7] suggest TIA to cause neither dependence nor respiratory depression. In addition, TIA does not reduce vigilance during treatment. Tiapride has been suggested for treatment of withdrawal syndrome including outpatients [24]. Previous research suggests tiapride to be effective in psychovegetative symptoms, like hyperhidrosis and tremor, in alcohol withdrawal but not in seizures or hallucinations [25–27, for review see 24]. It is also used for the treatment of agitation in elderly or demented patients [22, 23].

The therapeutic rationale of TIA and CBZ 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 [28]. This may be of relevance for patients with less severe forms of AWS including outpatients [29, 30] or patients with defined medical disorders such as sleep apnoea syndrome [31].

The combination of TIA/CBZ in alcohol withdrawal has been subject of research before. Several pilot studies comparing the combined effects of TIA/CBZ with clomethiazole in alcohol withdrawal showed a similar efficacy in terms of psychopathologic and vegetative symptoms and a somehow faster vegetative recovery with TIA/CBZ [8, 32, 33]. In a controlled open-label study, Lucht et al. [7] found TIA/CBZ to be equally effective in non-intoxicated patients experiencing alcohol withdrawal compared to clomethiazole and diazepam. The number of dropouts in intoxicated patients was higher but a change in medication was possible once the patient had reached the non-intoxicated range.

In addition, in a study on 50 consecutively admitted patients entering an alcohol outpatient detoxification programme, 49 who had received a TIA/CBZ combination successfully ended treatment. The mean initial daily dose for CBZ was 628 mg and 332 mg, respectively, for TIA, thus clearly lower as in studies in inpatients. No serious medical complications or adverse events were observed [29].

To further extend the database on efficacy and side effects on TIA/CBZ in AWS treatment, we performed an extensive retrospective chart review in five psychiatric hospitals using this combination on a regular basis under standardized conditions.

In this context, two other aspects are of interest: are there (1) gender differences and (2) differences between patients in their first and at least second withdrawal.

Subjects and methods

This was an retrospective chart analysis to examine the efficacy, medical safety and practicability of a combination of carbamazepine and tiapride in inpatient alcohol detoxification.

Sample

Inclusion criteria

Patients had to meet ICD-10 [34] criteria for alcohol dependence and to be admitted for alcohol detoxification.

Exclusion criteria

Other substance use except for nicotine.

Selection of patients

Patients were selected in five sites. In the Psychiatric Hospital Chemnitz, 54 patients were included during the period from 01-Dec 04 to 25-Mar 05. All patients were admitted for alcohol detoxification. For the whole period, 152 with alcohol dependence were admitted for detoxification.

Treatment

Patients initially received 4 × 200 mg unretarded (fast acting formula) CBZ and 4 × 300 mg TIA. In 4 other sites, data were collected retrospectively. All patients who had received this combination were included in the analysis: 50 patients in the Psychiatric Hospital of the University of Berlin treated between January 2004 and March 2005, 124 in the Psychiatric Langenberg-Velbert (19.11.04–14.4.05), 151 in the Psychiatric Hospital Wahrendorff-Sehnde (1.10.2004 and 31.3.2005) and 161 in the Psychiatric Hospital University of Giessen. A total of 540 inpatients were included in the pooled analysis. The treatment regimens were not standardized. The dosing and frequency were determined by the ordering physician.

Assessment

The following items were extracted from patient's files and charts using a detailed protocol: sociodemographics, alcohol history including previous treatments, last alcohol intake and neuropsychiatric or somatic disorders, laboratory findings at baseline, duration of treatment, dosage, side effects, adverse events, regular discharge/dropout.

For assessment of alcohol withdrawal, the Clinical Institute Withdrawal Scale (CIWA-Scale) [35] was used. The validated German version of the CIWA-A-scale by Stuppaeck et al. [36] is a 10-item scale, which comprises 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. The CIWA-A-scale symptoms are scored from 0 to 7. Symptoms were assessed by an experienced psychiatrist or medical assistant.

Data analyses

The statistical program SPSS for Windows [37], release 12 was used for statistical analyses. To describe the results, means and standard deviations (SD) were calculated. Analyses of variance (GLM: general linear model) and *t*-tests for independent samples was computed for the examination of gender differences and comparing patients in their first and at least second withdrawal.

Results

Clinical characteristics

A total number of 540 patients were included into the data analysis. Mean age was 45.7 years, 425 (78.7%) patients were male. Patient characteristics are given in Table 1. Mean duration of alcohol dependence was 14.6 years, mean alcohol consumption before admission was 285 g/day. Around 72.4% (n = 391) of patients were intoxicated with a mean alcohol intoxication of 1.6 g/l at admission.

In total, 103 (19.1%) had a history of alcohol withdrawal delirium, 151 (28%) of an epileptic seizure during withdrawal. Gamma-GT at baseline was 141 (SD 246) U/l.

Frequent (>2%) comorbid conditions were affective disorder (N = 64, 11.9%), alcoholic liver disease (N = 49, 9.1%), polyneuropathy (N = 41, 7.6%), adjustment disorder (N = 33, 6.1%), hypertension (N = 22, 4.1%), anxiety disorder (N = 19, 3.5%), abuse or dependence of other drugs (N = 18, 3.3%), schizophrenia (N = 17, 3.1%) and diabetes mellitus (N = 16, 3.0%).

Table 1 Demographic characteristic of subjects (n = 540)

Age (*M*, *SD*)	45.7 (9.4)
Gender (*n*, %)	
Females	115 (21.3)
Males	425 (78.7)
Marital status (*n*, %)	
Never married	176 (32.6)
Married	147 (27.2)
Separated/divorced	193 (35.7)
Widowed	18 (3.3)
No specification	6 (1.1)
Employed (*n*, %)	143 (26.5)
Unemployed (*n*, %)	397 (73.5)
Duration of alcohol dependence (years: *M*, *SD*)	14.6 (9.7)
Quantity of alcohol use in the last week (g/d: *M*, *SD*)	285.9 (266.1)
Respiratory alcohol at the moment of hospitalization (*n*, %)	
Yes	391 (72.4)
No	140 (25.9)
No specification	9 (1.7)
Respiratory alcohol at the moment of hospitalization (g/l: *M*, *SD*)	1.6 (1.3)
Number of pre-treatments—detoxification (*n*, %)	
0	97 (18.0)
1	103 (19.1)
2 and more	271 (50.1)
No specification	69 (12.8)
Number of pre-treatments—rehabilitation (*n*, %)	
0	213 (39.4)
1	149 (27.6)
2 and more	73 (13.6)
No specification	105 (19.4)

Carbamazepine on day 1 was given at a mean dose of 543 mg (max 1200 mg). Tiapride was given at a mean dose of 796 mg (max 2400 mg). Corresponding to maximum of withdrawal symptoms on day 2, maximum dosages of both drugs were given on day 2: 1035 mg of TIA and 680 mg of CBZ (mean values). Results indicate that medication was then gradually reduced over time. Mean dose of both drugs on day 3 were 968 mg for TIA and 601 for CBZ, mean dose on day 4 were 850 mg and 516 mg, respectively. On day 5, mean dose for TIA was 705 mg and 425 mg for CBZ, on day 6, 399 mg and 325 mg, respectively.

Medication was discontinued after 10 days maximum.

Retention rate and side effects

Of 540 patients included in the study 153 patients (28.3%) ended treatment premature. Reasons for dropout are given in Table 2. In most cases, patients dropped out due to lack of motivation (N = 110, 20.4%). In 39 cases (7.2%), termination of treatment was related to medication. In 7 dropout cases (1.3%), medication was considered to be ineffective, further in 17 (3.1%) patients medication was changed. In 15 (2.8%) of the dropout cases, the medication was dis-

Table 2 Reasons for drop out

	Total n = 153 of 540 (28.3%)	
	n	% (% of 540)
Related to medication—number of patients (see Table 3)	39	25.5 (7.2)
Others—number of patients	114	74.5 (21.1)
Reasons (multiple answers possible)		
Lack or motivation	110	71.9 (20.4)
Somatic disease	8	5.2 (1.5)
Complications	21	13.7 (3.9)
Alcohol delirium	7	4.6 (1.3)
Epileptic seizures	2	1.3 (0.4)
Hallucinations	2	1.3 (0.4)
Korsakoff's syndrome	2	1.3 (0.4)
Other complications	14	9.2 (2.6)
Collateral disorders	1	0.7 (0.2)
Hypertensive crisis—shifting to department of internal medicine	1	0.7 (0.2)
Femoral neck fracture	1	0.7 (0.2)
Patient left hospital	1	0.7 (0.2)
Relapse	1	0.7 (0.2)
Vertigo	1	0.7 (0.2)
Agitation/anxiety, possible Wernicke's syndrome	1	0.7 (0.2)
Incompatibility of CBZ	1	0.7 (0.2)
Possible Korsakoff's syndrome	1	0.7 (0.2)

continued due to side effects, in most cases sedation or somnolence (n = 14, 2.6%). In addition, in 30 (5.6%) patients with regular discharge side effects were recorded, in 26 (6.7%) including sedation vertigo and or somnolence, too.

In 1 (0.2%) patient each, the medication was discontinued because of dyskinesia or ataxia. One other patient from the regular discharge group suffered from dyskinesia, two from ataxia. In 8 patients (1.5%), medication was discontinued because of a concurrent somatic disorder (side effects see Tables 2, and 3).

A subsequent analysis on the frequency of side effects revealed an excess of reports on sedation and somnolence in the Langenberg-Velbert site. Of the 124 patients treated in this hospital 40 (32.3%) reported somnolence or sedation while in all other centres only 2 other patients claimed of this. Dosages of TIA and CBZ given in this centre were higher than in the other centres (day 1: CBZ 767 mg, TIA 1124 mg; day2: CBZ 761 mg, TIA 1215 mg, day3: CBZ 583 mg, TIA 1192 mg, day 4: CBZ 527 mg, TIA 1204 mg on average).

Withdrawal symptoms and complications

CIWA-A-scores over time are given in Fig. 1. Mean CIWA-A-Score at treatment begin was 12.3 (SD 8.3). CIWA-A-score clearly decreased over time to 9.8 on day 2 to 2.6 on day 9 (see Fig. 1).

A total of 5 (0.9%) patients suffered from epileptic seizures, 5 on the initial, 2 on the second and 1 on the fourth day were noted. Of the 151 patients who had a history of seizures only 4 experienced seizures during detoxification, in one case it was the first one.

Around 1.5% (N = 8) cases of delirium were observed during treatment. Of the 103 patients who had a history of an alcohol withdrawal delirium only 5 suffered from another delirium under this combination, in 3 cases the delirium was the first one.

Gender differences

Gender differences resulted for side effects and complications of medication and within the CIWA analyses framework. As more females claimed of dyskinesia (T = −2.9; p < 0.01), sedation, vertigo, somnolence (T = −2.5; p < 0.05) and "other side effects" (T = −3.1; p < 0.01), males reported more often ataxia (T = 2.4; p < 0.05). More males than females suffered from the complications such as alcohol delirium (T = 2.9; p < 0.01), epileptic seizures (T = 3.1; p = 0.01), hallucinations (T = 3.2; p < 0.001) as well as "other complications" (T = 3.9; p < 0.001). The CIWA analyses framework showed that more females than males suffered from hyperhidrosis (F = 6.0; df = 1; p < 0.05).

Comparison of patients in their first and at least second withdrawal

This comparison showed differences for side effects and complications of medication and within the CIWA analyses framework, too. Patients with two or more withdrawals suffered more often than patients in their first withdrawal from the side effects ataxia (T = −2.2; p < 0.05), sedation, vertigo, somnolence (T = −6.7; p < 0.001) and "other side effects" (T = −3.8; p < 0.001), and the complications epileptic seizures (T = −2.9; p < 0.01), hallucinations (T = −3.0; p < 0.01), and Korsakoffs syndrome (T = −2.3; p < 0.05).

The CIWA analyses framework showed that more patients in their first withdrawal suffered from nausea/vomiting (F = 4.8; df = 1; p < 0.05), hyperhidrosis (F = 8.4; df = 1; p < 0.01), disorientation (F = 7.8; df = 1; p < 0.01) and headache (F = 12.3; df = 1; p < 0.001).

Discussion

The present retrospective chart analysis in 5 sites using a combination of TIA/CBZ was conducted to further study the efficacy and feasibility of this combination in the treatment of alcohol withdrawal. A total of 540 patients with a long-term history of alcohol dependence and a significant alcohol intake before detoxification were studied. Around 19% had a history of an alcohol withdrawal delirium, 28% of an epileptic seizure. Most patients were still intoxicated at beginning

Table 3 Side effects of medication

	Regular discharge $n = 387$ (71.7%)		Drop out $n = 153$ (28.3%)		All $n = 540$ (100%)	
	n	% (% of 540)	*n*	% (% of 540)	*n*	%
Lack of efficacy	2	0.5 (0.4)	7	4.6 (1.3)	9	1.7
Change of medication	2	0.5 (0.4)	17	11.1 (3.1)	19	3.5
Side effects (multiple answers possible)	26	6.7 (4.8)	15	9.8 (2.8)	41	7.6
Dyskinesia	1	0.3 (0.2)	1	0.7 (0.2)	2	0.4
Ataxia	2	0.5 (0.4)	1	0.7 (0.2)	3	0.6
Sedation, vertigo, somnolence	26	6.7 (4.8)	14	9.2 (2.6)	40	7.4
Other side effects	6	1.6 (1.1)	3	2.0 (0.6)	9	1.7
Nausea	1	0.3 (0.2)	1	0.7 (0.2)	2	0.4
Diarrhoea	1	0.3 (0.2)	0	–	1	0.2
Gait deviation	3	0.8 (0.6)	0	–	3	0.6
Erythema at the hands	0	–	1	0.7 (0.2)	1	0.2
Leukopenia, thrombopenia	0	–	1	0.7 (0.2)	1	0.2
Dysesthesia in the feet	1	0.3 (0.2)	0	–	1	0.2
Total number of patients	30	7.8 (5.6)	39	25.5 (7.2)	69	12.8

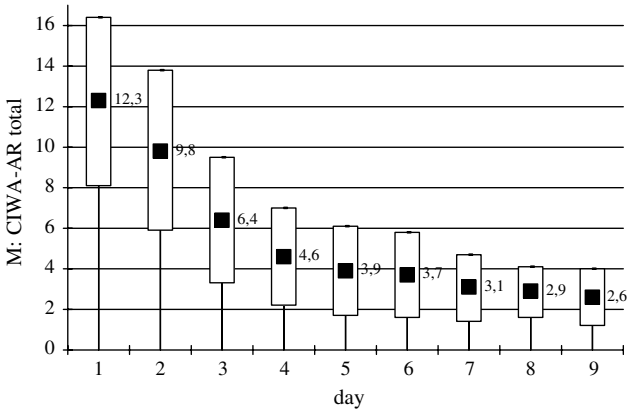

Fig. 1 CIWA-score: Means and standard deviations

of treatment. Data indicate that most patients successfully terminated treatment. Despite a significant number of patients with a history of delirium tremens and alcohol withdrawal seizures very few patients suffered from withdrawal delirium (1.5%) or seizures (0.9%) during detoxification period. Few patients required specific other pharmacotherapy for alcohol withdrawal during treatment. Only 41 (7.6) % of patients suffered from significant side effects, 15 of them dropped out of treatment. About 7 (1.3%) other patients dropped out of treatment for inadequate efficacy, 17 (3.1%) for change of medication.

According to recent evidence-based guidelines, a specific pharmacologic treatment is recommended in CIWA-A-scores exceeding 15 points (severe withdrawal) [3]. In our study, baseline CIWA-score was 12.3 indicating that most patients suffered from moderate to severe withdrawal.

In line with previous findings, the results of this study give further evidence for a combination of TIA and CBZ to be effective in AWS treatment. The clinical results of this explorative study in a large group of unselected patients suggest a good efficacy and safety profile of a combination of TIA and CBZ in alcohol withdrawal treatment. Patients' compliance was good and no serious medical complications were observed.

The efficacy of CBZ in alcohol withdrawal, especially seizures has been shown in a number of studies before [9]. There is also some preliminary evidence for CBZ to be effective in relapse prevention of alcoholism [38].

TIA has repeatedly been used in alcohol withdrawal with a clear effect on vegetative symptoms but not on seizures. Thus the combination of both drugs has been recommended for alcohol withdrawal [8] and there are some encouraging clinical results especially in alcoholic outpatients [29, 30, 39]. Some evidence suggests TIA also to be effective in the post-withdrawal period in alcoholics with depressive or anxious symptoms [40, 41].

Withdrawal symptoms clearly decreased over time. With respect to side effects sedation, somnolence and dizziness were most frequently mentioned, nearly exclusively in one centre using higher dosages especially of both drugs, especially TIA. Results may indicate that higher dosages of TIA/CBZ may result in a higher incidence of sedation and related side effects. Other relevant side effects were only rarely recorded. Only two cases of dyskinesia and 3 cases of ataxia were observed during treatment.

In general, patients with second or more inpatient treatments for alcohol withdrawal were at a higher risk for complications such as seizures, hallucinations and Korsakoff's syndrome while some psychovegetative symptoms were more frequent in patients with first withdrawal from alcohol. Future studies could address dosing issues in patients with first and repeated withdrawal. Likewise, there were some differences between male and female patients with severe complications of alcohol withdrawal being more frequent in the former. Some side effects of medication were more frequent in females. These results should be discussed with caution, but may indicate a more significant withdrawal syndrome in male compared to female patients. Female alcoholics might require a

somehow lower average dosage than male patients. In this context, additional studies are necessary.

According to our data, the risk of malignant neuroleptic syndrome following TIA treatment in alcoholics is minimal; no case was recorded. Future studies may also focus on monotreatment with CBZ versus a combination of CBZ and TIA as used in our study. To our knowledge there are no data on this subject.

There are a number of limitations of this study that must be addressed. First, this was a retrospective chart review and no control group was studied to compare effects of different medications. Second, patients were not systematically questioned for side effects. While reasons for dropout, change of medication, laboratory abnormalities or adverse events were clearly stated in the patient files it cannot be ruled out that some side effects may have been missed. In addition, minor side effects, which may also be difficult to distinguish from AWS symptoms in some cases, might have been underreported. A more general problem is that some symptoms of AWS (hyperhidrosis, loss of appetite, headache, vertigo, orthostatic dysregulation, gastrointestinal symptoms) are sometimes difficult to distinguish from side effects of medication. Still the number of patients in whom adverse events or change of medication was recorded was remarkably low. Third, no fixed or symptom-triggered dosages were used and medication was given on the basis of the physicians decision. On the other hand, differences in dosing regimen in one centre compared to the others gave evidence for different side effect profile in patients receiving higher dosages of TIA/CBZ.

In conclusion, the data of this study give further evidence that a combination of carbamazepine and tiapride to be effective and safe in the treatment of alcohol withdrawal. Future studies may address dosing issues and include comparative trials with other drugs including benzodiazepines or clomethiazole.

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