TREATMENT

An Open Trial of Gabapentin in Acute Alcohol Withdrawal Using an Oral Loading Protocol

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Abstract — Aims: Anticonvulsants are increasingly being advocated for the treatment of acute alcohol withdrawal syndrome (AWS) to avoid the addictive properties of established medications. Because earlier works showed that moderate gabapentin doses were too low to clearly ameliorate severe AWS, we tested a higher gabapentin entry dose. Methods: Inpatients (n=37) with severe alcohol withdrawal symptoms (Clinical Institute Withdrawal Assessment for Alcohol revised (CIWA-AR) score ≥15 points) were included. Further inclusion criteria were: age between 18 and 70, no relevant psychiatric and somatic co-morbidity requiring an acute intervention and stabilization, no pregnancy, no delirium tremens, no severe cognitive deficits and no other substance use disorders (except nicotine). Current use of the following medications was not allowed: benzodiazepines, z-drugs, lithium, disulfiram, β-blockers, neuroleptics, anticonvulsants and antidepressants. Ten females and 27 males were included. All patients had given written informed consent. The project was carried out in accordance with the Declaration of Helsinki and was approved by the local ethics commission.

Scores on Hamilton Anxiety (HAMA) and Hamilton Depression (HAMD) were documented at baseline and the end in all subjects (Hamilton 1959, 1960). An entry dose of 800 mg gabapentin was administered at baseline (CIWA-AR ≥15). Breath alcohol concentration (BAC) <0.2%. When AWS improved within the next 2 h, patients were defined as ‘early responders’ and were given 600 mg gabapentin q.i.d. reaching a total of 3200 mg of gabapentin in the first 24 h (loading protocol). On the next day, 600 mg gabapentin q.i.d. were given. At Day 3, ‘early responders’ received 400 mg gabapentin q.i.d. and on Day 4 tapering of minus 400 mg per day started. When CIWA-AR did not improve or worsened within 2 h after the entry dose, patients were defined to be ‘early non-responders’ to 800 mg gabapentin and treated as usual with clomethiazole or clonazepam (Kosten and O’Connor, 2003; Fig. 1A).

A pharmacological effect of gabapentin could be expected at the starting dose of 800 mg. According to the manufacturer’s specification, a peak plasma concentration between 4 and 5 μg/ml is attainable in prior studies within 2–3 h after oral administration of one 800 mg capsule (Parke-Davis 2000, personal communication). Gabapentin is known to readily cross the blood–brain barrier and to elevate brain GABA (Petroff et al. 2000).

METHODS

Inpatients suffering from alcohol dependence (ICD-10: F10.25) and displaying severe AWS according to the Clinical Index of Alcohol Withdrawal-Revised (CIWA-AR; Sullivan et al. 1989; CIWA-AR score ≥15 points, Kosten and O’Connor, 2003) were included. Further inclusion criteria were: age between 18 and 70, no relevant psychiatric and somatic co-morbidity requiring an acute intervention and stabilization, no pregnancy, no delirium tremens, no severe cognitive deficits and no other substance use disorders (except nicotine).

INTRODUCTION

Benzodiazepines, and in some European countries clomethiazole, are the pharmacological treatment of choice in the management of alcohol withdrawal syndrome (AWS; Kosten and O’Connor 2003; Leggio et al. 2008). To avoid addiction and other liabilities of these drugs, novel anticonvulsants are increasingly studied in this field (Johnson et al. 2005; Leggio et al. 2008). Considering its pharmacodynamics and pharmacokinetics, the GABAergic anticonvulsant gabapentin seems well suited to the treatment of acute AWS (Bonnet et al. 1999). In addition to promising data from animal experiments (Bailey et al. 1998; Dooley et al. 2000), there are case reports (Johnson et al. 2005), retrospective studies (Voris et al. 2003) and comparative prospective trials (Mariani et al. 2006; Myrick et al. 2009) that support this idea. The only published placebo-controlled study, however, did not find gabapentin superior to placebo as an adjunct to clomethiazole in treatment of acute AWS (Bonnet et al. 2003): moderate gabapentin initial doses around 400 mg (increased to 1600 mg in the first 24 h) did not ameliorate severe AWS (Bonnet et al. 2003).

Therefore, we tested a higher gabapentin entry dose (800 mg, loaded up to 3200 mg in the first 24 h in the ‘early-responder group’, see below) using a novel protocol which, although open, should allow a faster differentiation between the putative effects of the tested drug and the effects of required rescue medication (Fig. 1).

RESULTS

CIWA-AR fell to below 15 points in 27 (73%) patients within 2 h after administration of one 800 mg gabapentin capsule.
ANOVA revealed a significant decline of CIWA-AR values in the ‘early responding’ group, with the largest decline within 2 h after 800 mg gabapentin from 17.3 ± 2.6 to 8.0 ± 3.6 points ($P<0.001$). However, three of these ‘early responders’ experienced seizures ($n=2$) or worsening AWS ($n=1$) in the next 36 h, so that only 24 (65%) completed the study as ‘responders’. They were reclassified as ‘non-responders’ and switched to clonazepam (Fig. 1A). Treatment duration (mean ± SD) was 10.6 ± 3.6 days in the responding group. HAMA (14-item) and HAMD (21-item) scores improved from 10.5 ± 6.5 and 10.8 ± 5.1 points at baseline to 3.1 ± 4.8 ($P<0.001$) and 3.6 ± 3.7 ($P<0.001$) points at the end of the study, respectively ($n=27$).

The 10 ‘early non-responding’ patients had a mean CIWA-AR score of 20.1±4.6 points at baseline and deteriorated to 21.5±4.65 points in spite of 800 mg gabapentin within 2 h (Fig. 1B). Patients with the highest initial CIWA-AR scores (26 and 29 points) were both ‘early non-responders’. Mean treatment duration was 14.4 ± 7.9 days in this group. HAMA and HAMD scores improved from 20.1±3.5 and 20.3±4.2 points at baseline to 12.6±7.7 ($P=0.001$) and 11.4±6.8 ($P<0.001$) points at the end of treatment, respectively ($n=10$).

Six (22.2%) of the 27 ‘early responders’ and five (50%) of the 10 ‘early non-responders’ had new-onset adverse clinical events (ACE; Table 1). With the exception of the two seizures, all other ACE were judged to be mild. There was no further seizure, no delirium or other serious ACE during the entire study. Gabapentin-specific changes in electrocardiogram (ECG) or clinical laboratory tests did not occur.

‘Early non-responders’ were characterized (i) by a significantly more severe acute AWS ($P=0.026$) leading most probably to overall longer treatment duration ($P=0.052$) and (ii) by significantly greater anxious and depressive complaints according to HAMA and HAMD (both $P<0.001$). Heart rate ($P=0.08$) and blood pressure ($P=0.08$) tended to be higher in non-responders. This group also reported smoking more cigarettes than the ‘early responders’ ($P=0.052$). There were no significant differences between responders and non-responders with respect to drinking history, number of alcohol-associated sequelae, laboratory results and ECG changes.

**DISCUSSION**

Non-response to gabapentin in this sample was predicted by a more severe AWS (mean CIWA-AR>20) with and greater anxiety and depressive symptoms. Therefore, we suggest that oral 800 mg gabapentin (loaded up to 3200 mg in the first 24 h) is helpful only in reducing less severe and less complicated acute AWS. Similar conclusions were drawn from compara-
Exceptional trials using 2400 mg gabapentin (vs phenobarbital, Mariani et al. 2006) and 1200 mg gabapentin (vs lorazepam, Myrick et al. 2009) in the first 24 h to treat severe (baseline CIWA-AR ≥ 15 points) and moderate (baseline CIWA-AR < 15 points) acute AWS, respectively. Our suggestion is slightly tenuous because of the open label design, small sample size and lack of a placebo or active-comparison medication. The strengths of this study are that the baseline withdrawal severity was not moderate (CIWA-AR 17.3 ± 2.6 points) and that 24 of 37 (65%) patients completed detoxification without rescue medication. The putative efficacy of gabapentin loading should be proved by further better controlled studies on larger samples. Nevertheless, prior non-pharmacological studies (e.g. as reviewed by Williams and McBride 1998) did not report the rapid reduction of symptoms in severe AWS that we have presented here with 800 mg gabapentin, which argues against our finding being a placebo or psychological effect.

However, two (7.4%) 'early responders' developed an epileptic seizure within 36 h of the treatment. This rate was clearly higher than in our previous controlled study (61 inpatients/no seizures/but supplementary clomethiazole; Bonnet et al. 2003) and weakens the utility of our loading protocol. It cannot be ruled out that this was due to the longer interval without any further protecting rescue medication (1 h in our previous study (Bonnet et al. 2003), 2 h in the present study). In the literature, however, seizure rates near 10% were not the exception in severe AWS even with effective pharmacological treatments (Williams and McBride, 1998; Hillbom et al. 2003).

REFERENCES


