Phenobarbital versus diazepam for delirium tremens – a retrospective study

Ida Hjermø Michaelsen[1], John Erik Anderson[2], Anders Fink-Jensen[3], Peter Allerup[4] & Jakob Ulrichsen[1]

ABSTRACT

INTRODUCTION: Delirium tremens (DT) is a severe and potentially fatal condition that may occur during withdrawal from chronic alcohol intoxication. The purpose of the present study was to compare the effects and the rates of complications of phenobarbital and diazepam treatment in DT.

MATERIAL AND METHODS: Data were collected retrospectively from the medical files of patients who had received DT treatment (n = 194) at two psychiatric departments located in the general Copenhagen area in the 1998-2006 period. At one department, all patients were treated with phenobarbital (n = 53), while the treatment regimen at the other department was changed from phenobarbital (n = 53) to diazepam (n = 88) in 2002.

RESULTS: Length of DT and hospitalization, mortality and rate of pneumonia (26%) were not affected by treatment. A subpopulation (9%) in the diazepam group was resistant to treatment. Respiratory depression occurred in 4% of the phenobarbital and in 1% of the diazepam-treated patients. Wernicke's encephalopathy was established in 47% of the patients.

CONCLUSION: Phenobarbital is a safe alternative to diazepam in the treatment of DT.

In its full-blown form, delirium tremens (DT) is the most dramatic and serious of complications to alcoholism. The clinical manifestations initially comprise severe physical alcohol withdrawal symptoms such as tremor, sweating, tachycardia, increased temperature and psychomotor agitation all in response to a sufficient decrease in blood alcohol concentration. Within 0-72 hours, the patient becomes visually hallucinated and delirious with insomnia and clouding of consciousness which typically fluctuates markedly over time. Withdrawal seizures are seen in approximately 20% of the patients and typically occur before the patient becomes hallucinated and delirious [1, 2]. DT is a true medical emergency with a 15% mortality rate [2].

World-wide, benzodiazepines seem to be the preferred drugs in DT treatment [3]. In Denmark, however, barbiturates have been used in the treatment of DT for more than 100 years [4]. It has been demonstrated that barbiturates are superior to benzodiazepines in DT [5], but due to the risk of respiratory depression, some Copenhagen psychiatric departments have recently changed their treatment in favour of benzodiazepines.

The purpose of the present retrospective study was to compare the effects and complications of phenobarbital and diazepam treatment in patients who were admitted with DT.

MATERIAL AND METHODS

Subjects were patients with DT who were admitted to the Department of Psychiatry, Rigshospitalet and the Department of Psychiatry, Bispebjerg Hospital, in the period from 1 January 1998 to 31 December 2006. The files of these patients were studied retrospectively. Repeat cases of DT in any patient were allowed. All of the following inclusion criteria had to be fulfilled:

– An International Classification of Diseases 10, F10.4 diagnosis
– A history of alcoholism and heavy alcohol intake within the 96 hours preceding admission
– Two of the following physical alcohol withdrawal symptoms: tremor, sweat or psychomotor agitation
– Visual hallucinations
– A turbid and disoriented state.

All patients from Rigshospitalet were treated with phenobarbital. At Bispebjerg Hospital, phenobarbital was used from 1 January 1998 to 31 December 2001 (four years), while patients who were admitted in the period from 1 January 2002 to 31 December 2006 (five years) were treated with diazepam. Thus, DT patients were divided into the following three groups:

– PB Rigshospitalet: DT patients at Rigshospitalet who were treated with phenobarbital
– PB Bispebjerg: DT patients at Bispebjerg Hospital who were treated with phenobarbital
– DZP Bispebjerg: DT patients at Bispebjerg Hospital who were treated with diazepam.

The phenobarbital dose was 100-200 mg hourly (administered intravenously or orally), while diazepam was typically administered as a 10-20 mg intravenous dose given hourly. If no effect was achieved, diazepam was adminis-

tered more frequently, i.e. two, three or four times an hour. The aim was to make the patient fall asleep.

Baseline data

We recorded gender, age, substance abuse, biochemical and clinical findings including blood alcohol concentration (BAC), withdrawal seizures and symptoms compatible with thiamine deficiency, i.e. cognitive disturbances, ocular paralysis and ataxia at gait. Previous detoxifications were also registered (**Table 1**).

Treatment effect

The effect of phenobarbital and diazepam was measured by length of stay and by DT duration.

Medicine

Alcohol withdrawal patients from the DZP Bispebjerg group who did not initially show signs of DT received a varying amount of chlordiazepoxid before diazepam was administered. As a measure of the total benzodiazepine dose, we defined the various diazepam equivalents as follows:

Diazepam equivalent = dose of diazepam (mg) + 1/10 × (dose of chlordiazepoxid) (mg).

Complications

Respiratory complications were defined as follows:

1. Respiratory depression occurred if the respiratory frequency (RF) was below 12 per minute, or if the patient had obstructed airways including apnoea
2. Pneumonia
3. Other respiratory complications: Coughing, low oxygen saturation, RF > 20/min., airway secretion, chronic lung diseases not requiring antibiotic treatment.

Cardiovascular complications were defined as a systolic blood pressure < 90 mmHg or a diastolic blood pressure < 60 mmHg, cardiogenic syncope or electrocardiographically verified arrhythmia or cardiac arrest.

Statistical analysis

Quantitative variables were analysed using analysis of variance while categorical data were analysed by ordinary χ^2 test or Fisher's exact test. If multiple comparisons led to rejection of homogeneity across groups, two-by-two tests were subsequently applied to Bonfer-

FIGURE 1

Mean (± standard deviation) doses of phenobarbital in the phenobarbital Rigshospitalet group (**A**) and phenobarbital Bispebjerg Hospital group (**B**) at day 1, day 2 and for the entire treatment period (total). **C** shows the corresponding diazepam equivalent doses in the diazepam Bispebjerg Hospital group. Diazepam equivalents were calculated as dose of diazepam (mg) + 1/10 x (dose of chlordiazepoxid) (mg).
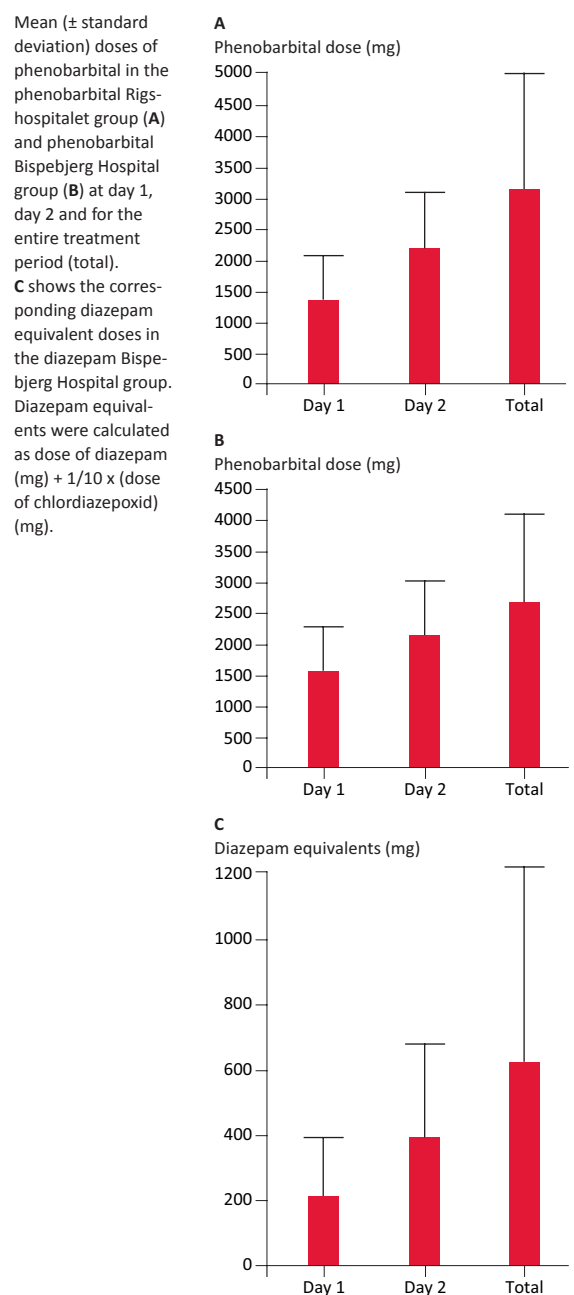

TABLE 1

Alcohol-related baseline data. Number of patients in the three groups who had previously been detoxified at a hospital, had previously suffered from delirium tremens and before developing delirium tremens during the current episode had experienced a withdrawal seizure. Furthermore, the table shows the number of patients in whom the admitting physician suspected Wernicke's encephalopathy and the measured blood alcohol concentration.

	PB Rigshospitalet (N = 53)	PB Bispebjerg (N = 53)	DZP Bispebjerg (N = 88)	p
Previously detoxified, n (%)	39 (74)	39 (74)	73 (83)	NS[a]
Previous DT, n (%)	16 (30)	13 (25)	33 (38)	NS[a]
Seizures, n (%)	14 (26)	14 (26)	15 (17)	NS[a]
Wernicke's encephalopathy, n (%)	29 (55)	24 (45)	38 (43)	NS[a]
Blood alcohol concentration, g/l, mean ± standard deviation	0.90 ± 1.4	0.92 ± 1.5	1.53 ± 1.5	0.049[b]

DT = delirium tremens; DZP = diazepam; NS = non-significant, p > 0.05; PB = phenobarbital.
a) χ^2. b) Analysis of variance.

roni-adjusted significance levels. The hypothesis that the number of DT cases per year was similar in the PB Bispebjerg and the DZP Bispebjerg group was tested using exact Poisson test. The general level of significance (p) was 0.05. If not otherwise specified, data are presented as mean ± standard deviation (SD).

Study approval
The study was approved by the Danish Data Protection Agency.

Results
The inclusion criteria were fulfilled by 53 cases in the PB Rigshospitalet group, 53 cases in the PB Bispebjerg group and 88 cases in the DZP Bispebjerg group. The mean (± SD) frequency of DT patients per year during the study period was PB Rigshospitalet 5.9 ± 1.8, PB Bispebjerg 12.8 ± 4.1 and DZP Bispebjerg 17.0 ± 8.7. There was a trend toward an increase in the incidence of DT at Bispebjerg Hospital when diazepam was used compared to when phenobarbital was used (exact Poisson test, p = 0.061).

The length of the delirious period was 5.85 ± 6.3 days in the PB Rigshospitalet group, 5.30 ± 2.6 days in the PB Bispebjerg group and 6.64 ± 4.2 days in the DZP Bispebjerg group, while the length of hospitalization in the three groups was 13.0 ± 13, 12.2 ± 10 and 12.3 ± 11 days, respectively. No significant intergroup variation was observed for any of these two variables. The DT reaction lasted from one to 42 days in all three groups.

Cumulated doses of phenobarbital and diazepam equivalents are shown in **Figure 1**. In the DZP Bispebjerg group, 36 patients (41%), who had previously had DT or were known to suffer from epilepsy, also received carbamazepine 200 mg three times daily at day one. In the two phenobarbital groups, carbamazepine was only administered once in each group (2%). The use of haloperidol was detected in 15 (28%) patients in the PB Rigshospitalet group, 17 (32%) patients in the PB Bispebjerg group and 49 (56%) patients in the DZP Bispebjerg group. The mean ± SD doses of haloperidol administered to these 81 patients were 36.5 ± 73.2 mg, 10.8 ± 9.7 mg and 21.3 ± 21.2 mg in the PB Rigshospitalet, the PB Bispebjerg and the DZP Bispebjerg groups, respectively.

Three patients died during DT, one from each treatment group. All had serious somatic complications, including 1) head trauma, facial fractures, atrial flutter and ketoacidosis, 2) chronic obstructive lung disease and cardiac insufficiency and 3) unstable diabetes mellitus. In addition, one patient from the PB Rigshospitalet group who had developed ileus following DT died after surgery. All patients died from respiratory and cardiovascular insufficiency (**Table 2**).

TABLE 2

Respiratory and cardiovascular complications. The numbers of deaths, respiratory- and cardiovascular complications. In addition, the numbers of patients transferred to the intensive care unit and the number of patients treated in respirator are presented.

	n (%)			
	PB Rigshospitalet (N = 53)	PB Bispebjerg (N = 53)	DZP Bispebjerg (N = 88)	p[a]
Fatal outcome	2 (4)	1 (2)	1 (1)	NS
Respiratory complications	18 (34)	21 (40)	38 (43)	NS
Respiratory depression	3 (6)	1 (2)	1 (1)	
Pneumonia	11 (20)	15 (28)	24 (27)	
Other[b]	5 (9)	5 (9)	13 (15)	
Intensive care unit	8 (16)	5 (9)	12 (14)	NS
Respirator treatment	7 (13)	4 (8)	4 (5)	NS
Cardiovascular complications	5 (9)	9 (17)	9 (10)	NS
Arrhythmia	2 (4)	3 (6)	3 (3)	
Blood pressure < 90/60 mmHg	3 (6)	5 (9)	6 (7)	
Cardiogenic syncope	0 (0)	1 (2)	0 (0)	

DZP = diazepam; NS = non-significant, p > 0.05; PB = phenobarbital.
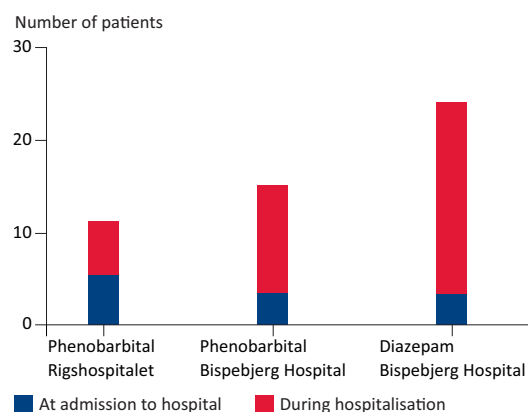a) χ^2. b) Respiratory complications due to other reasons were coughing, low oxygen saturation, respiratory frequency > 20/min., airway secretion or mucus and chronic lung disease.

An overview of respiratory and cardiovascular complications in the DT patients is shown in Table 2. Most respiratory problems were due to pneumonia which affected a total of 50 cases (26%). Most pneumonic infections developed during the hospital period, i.e. a total of 42 compared to 11 cases in which the patient had pneumonia before pharmacological DT treatment was started (**Figure 2**). There was a trend towards a group effect (p = 0.09) caused by an increase in the number of pneumonia cases developed during the treatment period in the DZP Bispebjerg group compared with the number of pneumonia cases at admission.

Respiratory depression only occurred in five cases

FIGURE 2

Distribution of delirium tremens patients with pneumonia according to whether pneumonia was present upon admission or developed during hospitalization. No significant group effects were found.

Number of patients

Phenobarbital Rigshospitalet — Phenobarbital Bispebjerg Hospital — Diazepam Bispebjerg Hospital

■ At admission to hospital   ■ During hospitalisation

Delerium tremens. The image was made by a 45-year-old male in 1919 whose psychiatrist had invited him to illustrate any hallucinations experienced during a delirium tremens period. The image was kindly made available to Ugeskrift for Læger by Medicinsk Museion, University of Copenhagen.

(Table 2). Thus four patients had obstruction of the airways, while one patient had a continuous depression of the respiratory frequency (9-11 breaths per minute during sleep) following a cumulated 13.400 mg dose of phenobarbital administered over the course of a 20-day period.

13% of the patients were transferred to an intensive care unit (ICU) before, during or after DT treatment with no difference across the three groups (Table 2). Some were treated at the ICU before developing DT due to traffic accidents or suicide attempts, while some patients were transferred to an ICU for safety reasons rather than respiratory insufficiency. Thus, eight (9%) patients in the DZP Bispebjerg group did not respond satisfactorily to the diazepam regimen. Despite large doses of diazepam equivalents (1,274 ± 632 mg, range 410-2,540 mg), the patients were unable to fall asleep. These patients were transferred to the ICU with a view to changing treatment to phenobarbital in a safe setting. They received 906 ± 430 mg of phenobarbital, which in all cases resulted in termination of the DT.

A total of 93 patients (48%) were fixated in bed with a leather belt at some time. No significant group differences were detected in this respect.

DISCUSSION

The present study shows that phenobarbital is a relatively safe and equipotent alternative to benzodiazepines for the treatment of DT. Thus, we found no significant differences concerning the length of DT, length of stay or complications between patients treated with phenobarbital and patients treated with diazepam. In line with another study [5], some of our findings suggest that phenobarbital is more efficient than diazepam.

First, a considerable number of patients treated with diazepam (9%) did not respond to this drug, a result which is in total agreement with previous findings of diazepam resistance in DT patients [6-9]. Second, we detected a trend towards an increase in the number of patients developing DT when diazepam rather than phenobarbital was used to treat DT (p = 0.06). This increase in DT incidence could, of course, be due to other factors than differences in the potency of the two drugs. For instance, the nursing staff who administered the medicine may have been more cautious when administering a new drug, and a greater focus on the alcohol withdrawal treatment in general may have changed the diagnostic behaviour so that the proper diagnosis of DT, i.e. F10.4, was used to a greater extent. It should also be mentioned that an antidote, i.e. flumazenil, exists for benzodiazepines, but not for barbiturates.

Mortality was quite low in all three groups in the current study, considering that all patients with DT, including those with severe and potentially lethal somatic conditions, were included in the study. As to respiratory complications, the overwhelming majority were caused by pneumonia. In a total of 11 patients (6%), pneumonia was present upon admittance to the hospital rather than being a treatment complication. In the benzodiazepine-treated group, the ratio of patients who developed pneumonia during the delirious reaction to patients with pneumonia upon admittance was higher than in the two phenobarbital groups, although the difference did not reach statistical significance (Figure 2). As the risk of developing pneumonia during DT is increased if pharmacological treatment is insufficient [8, 9], the present distributional findings are compatible with the hypothesis that phenobarbital is more potent than diazepam.

Respiratory depression only occurred in five patients, most (i.e. four) of whom had acute airway obstruction. This condition is potentially fatal and we therefore strongly recommend that all patients with DT are observed intensely by the nursing staff to facilitate immediate action to create free airways when needed.

The mean cumulative diazepam equivalent dose after 24 hours was approximately 200 mg (Figure 1), which is considerably lower than the dose used in other recent studies. Administering a higher initial dose of diazepam, e.g. 100 mg of diazepam an hour, could have had a positive effect on the length and the incidence of DT [8]. An equivalent argument may be made in relation to the phenobarbital protocol. Only 50-60% of the mean total phenobarbital dose was administered during the first day of treatment in the two phenobarbital groups. In a patient with severe tremor and hallucinations who requires e.g. 2,500 mg of phenobarbital in order to sleep, there is no rationale for not delivering this dose quickly, as long as the patient's vital signs are observed

carefully. We find it justifiable in future controlled experiments to test the effect of a more aggressive diazepam and phenobarbital administration in terms of length of DT and rates of complications.

A large part of the diazepam-treated patients received carbamazepine on their first treatment day (41%), and in many cases haloperidol was used to augment the effects of phenobarbital and diazepam. The present naturalistic design allows no conclusions as to whether these strategies were beneficial, especially since those patients who received haloperidol might have been in a worse condition than the remaining patients.

Obviously, a prospective randomised and blinded design is the optimal way to compare benzodiazepines and barbiturates in DT. However, only two such studies exist [5, 10], and in both of these two previous studies, the drug doses may not have been optimal compared with more aggressive regimens [8]. In addition, patients with severe somatic diseases, patients under involuntary detention and psychotic patients are normally not allowed to enter randomised controlled trials (RCTs), which limits the applicability of conclusions from such studies to the DT populations that real-life physicians need to treat. Observational studies like the present and other [8, 9, 11] may therefore be of great value as a supplement to RCTs for developing clinical DT treatment guidelines.

In conclusion, the present retrospective study showed that phenobarbital was at least as efficient as diazepam for the treatment of DT. In line with previous findings, a subpopulation of the patients failed to respond to diazepam, and in such cases phenobarbital may be a superior treatment option. As to complications, no firm conclusion could be drawn regarding the mortality and rate of pneumonia, which was the most frequent respiratory complication. Respiratory depression was a rare phenomenon that mainly occurred following phenobarbital treatment.

CORRESPONDENCE: *Jakob Ulrichsen,* Ulrichsens Klinik – Psykiatri, Nørre Voldgade 11, 3. sal, 1358 København K, Denmark.
E-mail: jakobulrichsen@mac.com

LITERATURE
1. Hemmingsen R, Kramp P. Delirium tremens and related clinical states: psychopathology, cerebral pathophysiology and psychochemistry: a two-component hypothesis concerning etiology and pathogenesis. Acta Psychiatr Scand Suppl 1988;345:94-107.
2. Victor M, Adams RD. The effect of alcohol on the nervous system. Res Publ Assoc Res Nerv Ment Dis 1953;32:526-73.
3. Mayo-Smith MF, Beecher LH, Fischer TL et al. Management of alcohol withdrawal delirium. An evidence-based practice guideline. Arch Intern Med 2004;164:1405-12.
4. Møller F. Veronalbehandling af delirium tremens. Ugeskr Laeger 1978;71:1253-9.
5. Kramp P, Rafaelsen OJ. Delirium tremens: a double-blind comparison of diazepam and barbital treatment. Acta Psychiatr Scand 1978;58:174-90.
6. Woo E, Greenblatt DJ. Massive benzodiazepine requirements during acute alcohol withdrawal. Am J Psychiatry 1979;136:821-3.
7. Coomes TR, Smith SW. Successful use of propofol in refractory delirium tremens. Ann Emerg Med 1997;30:825-8.
8. Gold JA, Rimal B, Nolan A et al. A strategy of escalating doses of benzodiazepines and phenobarbital administration reduces the need for mechanical ventilation in delirium tremens. Crit Care Med 2007;35:724-30.
9. Hack JB, Hoffmann RS, Nelson LS. Resistant alcohol withdrawal: does an unexpectedly large sedative requirement identify these patients early? J Med Toxicol 2006;2:55-60.
10. Kaim SC. Prevention of delirium tremens: use of phenothiazines versus drugs cross-dependent with alcohol. Adv Biochem Psychopharmacol 1974;9:685-90.
11. Pycha R, Miller C, Barnas C et al. Intravenous flunitrazepam in the treatment of alcohol withdrawal delirium. Alcohol Clin Exp Res 1993;17:753-7.