Delirium tremens:  
A double-blind comparison of diazepam and barbital treatment

P. KRAMP AND O. J. RAFAELSEN

The effect of diazepam and barbital in the treatment of delirium tremens and other acute conditions related to alcohol abuse was evaluated in a double-blind trial. 91 patients participated in the study, 44 in the diazepam group, 47 in the barbital group. The choice of diazepam rather than chlordiazepoxide was motivated by its major anticonvulsine properties.

Barbital was given by the oral route, diazepam as intramuscular injections. Different ways of drug administration to patients with delirium tremens are discussed. It is concluded that the two different ways used in the study probably did not have a noteworthy influence on the results.

All patients were excluded who had taken psychoactive drugs before admission. Nevertheless a considerable part of the patients had diazepam, but not barbital, in the blood before treatment was initiated. This may give support to the use of barbital as a "special purpose drug" in the treatment of these conditions.

The patients were divided into three diagnostic categories, according to the severity of the clinical condition. No difference between the two drugs tested was found in the milder conditions, but barbital was found superior to diazepam in the treatment of fully developed delirium tremens.

Key words: Delirium tremens - treatment - barbital - diazepam - route of administration - drug abuse - methodology.

Delirium tremens (DT) develops after years of alcohol abuse (Cutshall (1965), Salum (1972)). Many pathogenic factors have been proposed, but neither the pathogenesis nor the pathophysiology of DT can be explained. The discussion of whether DT is a withdrawal psychosis or a state of intoxication, as old as the description of the syndrome (Romano (1941)), has still not been resolved (Hemmingsen et al. (1978)). Formerly the treatment of DT was very complex - Piker di Cohn (1937) described a treatment programme involving 15 items, i.e. spinal drainage, stimulants, sedatives and laxantia - but despite many different therapeutic activities, the mortality rate remained high. In a review of the literature Gunne (1957, 1958) found a decreasing mortality rate with an increasing modesty in the treatment; he concluded that no specific treatment was available.

Many psychopharmacological drugs, introduced over the last 20 years, have
been tested in the treatment of DT, but the results have been varying and often conflicting. Reviewing the literature, Favazza & Martin (1974a) found that paraaldehyde and chloralhydrate, phenothiazines, barbiturates, chlordiazepoxide and others were recommended by some, but found less suitable or even contraindicated by others. Illustrative is the use of promazine, where the first reports were optimistic (Figurelli (1958)), but later on this drug has been found to be outright dangerous in the treatment of patients with DT (Golbert et al. (1967)). The reasons for those conflicting data may partly be due to many studies being open without control groups, and they probably reflect the commonly accepted tenet that whenever a physician becomes interested in the syndrome, his results will be approximately 50 % better (Smith (1953)). Another part of the explanation may be that many studies do not distinguish between milder cases, known as impending DT, predelirium or delirium tremens incipiens, and the much more serious condition: fully developed, or "frank", DT. Victor (1966) mentions that many different drugs have been found valuable in the treatment of the milder forms, but none of them seem to be able to change the course – including the mortality – of frank DT. Another problem in evaluating the efficacy of drug treatment is the natural course of the disease. Most patients will improve within 72 hours (Cutshall (1965), Salum (1975)) under proper supporting therapy and rapid treatment of complications. Drug treatment does not seem to change this course significantly. It is, on the other hand, impossible to predict the course of the disorder; about 5–10 % of patients with milder states will develop frank DT (Kaim et al. (1969), Salum (1972)). In a few cases the course may be highly malignant with increasing hyperactivity, hyperpyrexia and other complications, eventually leading to circulatory failure, necessitating immediate and intensive care.

During recent years the use of benzodiazepines in the treatment of DT and other acute complications after alcohol abuse has been advocated by many authors (Kaim (1970), Greenblatt & Shader (1975), Thompson et al. (1975)), and the use of these drugs, especially chlordiazepoxide, has increased considerably (Favazza & Martin (1974b)). The advantages were summarized by Greenblatt & Greenblatt (1972), when stating that the benzodiazepines effectively reduce anxiety and agitation without producing respiratory depression or stupor, the drugs having minimal abuse and dependence potential.

Throughout this paper the term "dependence" will be used according to the WHO recommendation. A definition of dependence is given by Rafaelsen (1972): A type of behaviour based on learning, leading to the appearance of a need, the satisfaction of which has become very important compared with the satisfaction of other needs like hunger, sex, or sleep. Dependency thus exists when satisfaction of this acquired need has consequences for the physical (physical dependence) and/or psychic (psychological dependence) and/or social (social dependence) adaptation of the individual.

Greenblatt & Greenblatt also found it important that the benzodiazepines do not interfere with REM-sleep, and they speculated that disturbances of sleep patterns are important for alcohol abuse as for many of the symptoms related to alcohol withdrawal.
In Denmark barbital (Veronal®, Diemal), a long-acting barbiturate, has been the drug of choice in the treatment of DT for many years. It was introduced in the beginning of this century (Møller (1909a)). In following discussions (Friedenreich (1909), Møller (1909b)) the importance of repeated, often large doses, that is 0.5–1 g, in the initial stage of the disorder was stressed. The aim of the treatment was to sedate the patient to such a degree that he fell asleep and then slept for several hours. After this "critical sleep" the symptoms often disappeared completely. The treatment as outlined in the first reports was found so favourable that barbital has been preferred by Danish psychiatrists for several decades (Sørensen (1959)).

In an open study Nielsen (1965) found that about half of the patients with DT admitted to hospitals in Copenhagen, were treated with barbital. There was a trend that barbital was used in the more severe cases, but despite this, the patients recovered faster in the barbital group compared with groups treated with other drugs, e.g. meprobamate or chlorprothixene.

In the same monograph the mortality rate of DT during various treatment programmes is discussed. There are obvious difficulties in comparing various materials, collected in different countries with different classification practice, e.g. a death may be registered due to DT as well as to chronic alcohol abuse. In spite of this it seems clear that the mortality rate in Denmark, about 4% in the 1950's, was lower as compared with several other countries, using other treatment programmes.

Barbiturates are seldom used in other countries, the disadvantages often mentioned being the risk of intoxication with respiratory depression, coma and other complications, together with the abuse potential of these drugs (Greenblatt & Greenblatt (1972)). Benzodiazepines in the treatment of DT were introduced in Denmark, as in other countries, about 15 years ago (Larsen (1963)). In an open study chlordiazepoxide was found superior to barbital (Christensen & Strandbygaard (1968)), but controlled studies have not been performed, and it is still under discussion whether the classical treatment with barbital should be abandoned (Sørensen (1976)). The present study was undertaken to compare under double-blind conditions barbital and diazepam in the treatment of DT and other acute complications of alcohol abuse.

MATERIAL

The study comprises all the patients admitted in 1972–76 to the Department of Psychiatry, Rigshospitalet, with impending or frank DT, who fulfilled the inclusion criteria:

1. The patients should have a history of alcohol abuse.
2. The actual condition should be related to the abuse.
3. The actual condition should be an acute event; patients with a chronic alcoholic hallucinosis, for example, were not included.
4. The severity of the symptoms should be such that the patients would be admitted and treated according to the general routine of the department.

As a minimum, the patients should have intense gross tremor of the extremities
and intense perspiration, and the duration of the symptoms should be at least some hours.

The exclusion criteria were:
1. Intake of psychopharmaca (prescribed by physicians or taken spontaneously by the patients themselves), during the last 24 hours before treatment was considered. This was done partly because of the difficulties in evaluation if patients had had more than one treatment, and partly to the possibility of drug interaction.
2. All patients who had alcohol in the blood at the time of treatment were excluded, to avoid any possible interaction between alcohol and the drug given. In practice a breathalyzer was used to detect alcohol in the expired air.

Somatic illness was not an exclusion criterion, as long as the patient could be treated along the lines outlined above.

The material thus comprised a wide spectrum of clinical states, frank DT as well as milder conditions. There exists no generally accepted definition of DT due to the ongoing discussion about aetiology and pathogenesis, but a generally accepted description of the syndrome involves at least the following core symptoms: Tremor, hallucinations and disorientation (Criteria Committee, National Council of Alcoholism (1972), Keller (1977)). From the onset, one could not expect the given drug treatment to have the same efficacy in cases of different severity. For that reason the material was divided according to a classification made by Izikowitz and described by Salum (1972). It is based on symptoms and signs present before and during the acute state, and it gives well-defined categories also in the less serious clinical states. The categories are defined as follows (Salum (1972)):

Grade 1: Tremor without hallucinosis.
Grade 2: Tremor and also hallucinosis, but not disorientation.
Grade 3: Tremor, hallucinosis and also disorientation during some part of the present state.

Patients who were not hallucinated at the time of admission to the hospital, but who claimed that hallucinations had been present recently, were placed grade 2. Grade 3 comprised the proper or frank DT in accordance with the earlier mentioned description of DT.

METHODS

The patients were allocated double-blind to treatment with either barbital (by the oral route) or diazepam (by intramuscular injection). Dose equivalence between the two drugs was stipulated in a pilot study. The maximum intake the first 24 hours (in 10 doses) was estimated not to exceed 5 g barbital or 200 mg diazepam. Back calculation led thus to single doses of 500 mg barbital and 20 mg diazepam. At maximum, six doses could be given the next 24 hours, thereafter four doses per 24 hours. In special cases, however, and after conference with the physicians responsible for the study, more doses than stated above could be given.
All patients received tablets as well as injections when medication was given: half of the patients got active tablets, i.e. barbital 500 mg plus placebo-injections, the other half placebo-tablets plus diazepam 20 mg i.m. No fixed treatment schedule was used. The treatment was given individually according to the clinical condition of the patients. Dose intervals of half an hour were used in the beginning of the treatment to sedate the patient within 3 hours to such a degree that he fell asleep. It should, however, be possible to wake up the patient at any time; he should be able to eat and drink by himself. If this was not the case, it was interpreted as the patient having been overdosed.

Concomitant medical care was given when necessary, e.g. antibiotics for recognized infections, fluid therapy for dehydration, according to the general principles of the department. All the patients received a poly-B-vitamin preparation, but no psychoactive drugs besides barbital/diazepam were used. All patients were treated in a closed ward where alcoholic beverages of any kind were unavailable. The patients' physical status and mental condition were regularly observed by nurses: physical status: blood pressure, pulse rate, temperature, tremor and perspiration; mental condition: disorientation, hallucinations, agitation and sleep. Starting at time of admission the registrations were done every half hour; when the condition improved the intervals were increased depending on the clinical condition. All observations were charted in a special file.

The medication continued until psychotic symptoms, tremor and sweat had disappeared. The study of a patient finished at the time of the last drug dose. The responsible physician could, however, at any time stop the patient's participation in the study programme if the clinical condition indicated special problems necessitating special procedures.

Before treatment was initiated a general physical examination was performed. A blood sample was taken from the majority of the patients to ascertain the pre-study serum concentration of the investigational drug, i.e. to see whether patients treated with barbital had been taking this drug, or patients treated with diazepam had been taking diazepam, prior to the study. During the study, blood samples were taken every morning, or at least 3 hours after the last medication, to determine the serum concentration of the drug given. The blood samples were analyzed by laboratory technicians without knowledge of the research protocol or the treatment of the individual patient. Blood samples from patients treated with barbital were analyzed within 24 hours, samples from patients treated with diazepam were centrifuged and the separated plasma stored at -20°C until analyzed. Within the first days after the patient's admission blood samples were taken to determine alkaline phosphatase and alanine amino transferase.

**Analyses**
The serum concentration of diazepam and its main metabolite N-desmethyl-diazepam was determined by gas chromatography, the concentration of barbital by UV spectrophotometry.

**Statistical methods**
The Mann-Whitney U-test, chi-square test and Fisher's exact test were used to
Table 1. Patients accepted for the study (n = 91) and patients excluded from the study (n = 18) for reasons unrelated to the treatment

|                  | Diazepam | Barbital | Total |
|------------------|----------|----------|-------|
| Accepted for study | 44       | 47       | 91    |
| Excluded         |          |          |       |
| Incorrect diagnosis | 5        | 3        | 8     |
| Previous medication | 3        | 4        | 7     |
| Insufficient information | 2        | 1        | 3     |
| Total no.        | 54       | 55       | 109   |

test the significance of the differences. A $P$-value less than 0.05 was considered statistically significant.

RESULTS

In all, 109 patients took part in the study; 18 of those were excluded for reasons unrelated to the treatment, 10 in the diazepam-group, eight in the barbital-group (Table 1). Of these 18 patients, eight were excluded due to incorrect diagnosis, i.e. five patients who did not fulfil the inclusion criteria, and three cases where it was considered, at the admission of the patient, that the acute state was related to alcohol abuse, but the course showed the diagnosis to be incorrect, e.g. a patient with a hysterical character structure who simulated DT. Seven patients were excluded because investigational treatment was, mistakenly, started in spite of information of drug treatment during the last 24 hours before admission. In three cases information was too incomplete to evaluate the course.

The material thus consists of 91 patients, 44 treated with diazepam, and 47 with barbital. Table 2 shows that the two treatment groups are comparable as to diagnostic category, sex, age and weight. As expected, more patients belonged to grade 1 than to grades 2 and 3.

No patients died, and serious complications did not appear. Rehydration with intravenous fluid was only necessary in a very few cases in each treatment group. One patient in each of the two drug groups developed a single convulsion during the acute state. None of the patients developed signs or symptoms indicating pronounced intoxication with investigational drug. The code was broken three times, each time because of unsatisfactory effect of the treatment. The physician responsible for the treatment found it unsafe to continue the treatment without knowing which drug was given; in all three cases the drug was diazepam. Those three patients are included in the analysis of the results.

Two of the three patients belonged to grade 2 when treatment was initiated; their general condition was not markedly affected. In spite of treatment, they deteriorated during the next few hours with intense agitation, clouding of consciousness and rising temperature. In both cases the treatment was continued with diazepam, but now given intravenously. One patient needed 700 mg diazepam i.v. during the following 48 hours before sufficient effect was obtained, the other one needed 100 mg i.v. during the next few hours before his condition improved. The third patient was from the start classified
Table 2. Distribution of patients (n = 91) according to diagnostic classification, sex, age, and weight

| Diagnosis  | Diazepam, n = 44 | Barbital, n = 47 |
|------------|------------------|------------------|
| Grade 1    | 23               | 19               |
| Grade 2    | 8                | 11               |
| Grade 3    | 13               | 17               |
| Sex        |                  |                  |
| M          | 39               | 42               |
| F          | 5                | 5                |
| Age        |                  |                  |
| \(\bar{x}\)    | 42       | 43               |
| s.d.       | 10               | 9                |
| Range      | 22–62            | 21–62            |
| Weight     |                  |                  |
| \(\bar{x}\)        | 73.7     | 71.6             |
| s.d.       | 10.4             | 13.2             |
| Range      | 56–95 (n = 39)   | 50–100 (n = 43)  |

in grade 3. He was treated for 37 hours without effect, but also without aggravation of the condition. The code was then broken, but at the same time the patient fell asleep and slept for 10 hours, after which time he needed no further medication.

Table 3 shows the course and duration of the acute state, estimated by the number of hours until last and last-but-one dose, the total number of doses given and time to sleep (defined as 3 hours of uninterrupted sleep). No marked differences are seen, except in grade 2, where patients treated with barbital fell asleep earlier than patients treated with diazepam; the same tendency is seen in grade 3, but this difference is not statistically significant.

A global assessment concerning the administration and the effect of the treatment is shown in Table 4. The following factors were taken into account in assessing the administration: frequency and adequacy of medication according to the clinical condition, dosage schedule, common medical care, and signs of overdosage. In estimating the effect of treatment the following were considered: time interval from treatment start to signs of sedation, course of clinical condition, and the patients' ability to cooperate. Due to the inherent ambiguity of this kind of evaluation, the results are registered only as "satisfactory" or "non-satisfactory".

No differences were found in the administration of the treatment. With regard to the effects, the results show a tendency in favour of diazepam in grade 1 and grade 2, but the difference is not statistically significant. On the other hand, we found barbital significantly superior to diazepam \((P < 0.05)\) in the treatment of patients in grade 3, the cases of proper delirium tremens.

To see whether there were any major differences in time to onset of action or in duration of effect between the two drugs, the number of doses per patient
Table 3. The course and duration of the acute state

| Diagnostic classification | Total no. of doses  | Hours to last dose  | Hours to last-but-one dose | Hours to sleep  |
|---------------------------|---------------------|---------------------|---------------------------|----------------|
|                           | Diazepam | Barbital | Diazepam | Barbital | Diazepam | Barbital | Diazepam | Barbital |
| Grade 1                   |          |          |          |          |          |          |          |          |
| Mean                      | 5        | 7        | 26       | 30       | 23       | 25       | 8         | 13       |
| Median                    | 5        | 5        | 25       | 26       | 21       | 15       | 6         | 9        |
| Range                     | 1-13     | 2-18     | 1-71     | 3-100    | 2-65     | 1-96     | 1-33      | 1-60     |
| Grade 2                   |          |          |          |          |          |          |          |          |
| Mean                      | 7        | 10       | 43       | 50       | 27       | 39       | 14        | 5        |
| Median                    | 7        | 9        | 41       | 51       | 23       | 36       | 14        | 4        |
| Range                     | 4-11     | 4-20     | 14-78    | 6-93     | 3-56     | 12-82    | 1-29      | 1-12     |
| (P < 0.05)                |          |          |          |          |          |          |          |          |
| Grade 3                   |          |          |          |          |          |          |          |          |
| Mean                      | 9        | 9        | 32       | 46       | 30       | 35       | 11        | 8        |
| Median                    | 9        | 7        | 33       | 38       | 28       | 33       | 9         | 4        |
| Range                     | 1-17     | 1-19     | 3-76     | 1-103    | 1-64     | 0-78     | 1-37      | 1-25     |
Table 4. *A global assessment of the administration and the effect of the two drugs*

Figures given are number of patients

| Administration | Grade 1 |  | Grade 2 |  | Grade 3 |  |
|----------------|---------|---------|---------|---------|---------|---------|
|                | Diazepam | Barbital | Diazepam | Barbital | Diazepam | Barbital |
| Satisfactory   | 18       | 11      | 5       | 10      | 11       | 12       |
| Non-satisfactory | 5       | 8       | 3       | 1       | 2        | 5        |

Effect

|                | Grade 1 |  | Grade 2 |  | Grade 3 |  |
|----------------|---------|---------|---------|---------|---------|---------|
|                | Diazepam | Barbital | Diazepam | Barbital | Diazepam | Barbital |
| Satisfactory   | 21       | 15      | 7       | 8       | 6        | 15       |
| Non-satisfactory | 2       | 4       | 1       | 3       | 7        | 2        |

(P < 0.05)

in 4-hour periods were compared. If marked differences existed there should be a difference between the average number of doses in the first period and/or in some period(s) during the course of treatment. The results are shown in Fig. 1. Patients treated with barbital received in average 2.16 doses, and patients treated with diazepam 1.82, during the first 4 hours after drug treatment was initiated. During the next 4-hour period the figures were respectively 1.35 and 1.17. The figure comprises the first 48 hours for patients where the efficacy was estimated as satisfactory. There is a trend to more doses of barbital given in the beginning of the treatment, but more diazepam doses after 24 hours; the differences are not statistically significant. A corresponding comparison for patients where the efficacy was found non-satisfactory is not possible, since the participation in the study of two out of 10 patients treated with diazepam was interrupted during the second 4-hour period, and especially those patients needed large doses. For the remaining patients no significant differences were found.

The age of the patient seems to play a less important role in relation to the course of treatment and to the efficacy and administration of the treatment. No

![Fig. 1. Average number of doses per patient per 4-hour period during the first 48 hours after treatment was initiated. White columns, barbital. Hatched columns, diazepam. Figures in brackets, number of patients who were treated in the time period.](image-url)
differences were found between younger and elder patients in the whole material or between the two drugs tested in various age groups.

A great part of the patients had an impaired liver function, but neither for barbital nor for diazepam was the efficacy of the treatment related to the liver function.

**Previous medication**

Prior to and during the treatment, blood was sampled from 33 patients treated with diazepam and 46 patients treated with barbital to be analyzed for the drug given. The original purpose was to see whether a "dose-response"-curve could be obtained, but with the method used, this was not possible (Kramp et al. (1978)). However, in 10 of 33 patients treated with diazepam the pre-treatment level of diazepam or its main metabolite N-desmethyl-diazepam was clearly elevated (values > 50 ng/ml for one of the two components). The distribution of age, sex and diagnostic classes in those 10 patients was similar to the material as a whole, just as no differences were found concerning the efficacy and administration of the treatment between this group and the diazepam group as a whole.

Only two out of 46 patients treated with barbital had elevated serum barbiturate before treatment was initiated. In both cases the elevation was very modest, 0.10 and 0.65 mg/l respectively, which means that the results may be unspecific and due to other drugs than barbital. Blood samples from six patients treated with diazepam were analyzed for barbital; the pre-treatment value was zero in all six cases. Comparing the two groups, the specificity of the two analyses must be taken into consideration. The analysis for diazepam and its metabolites is very specific, indicating that no other drugs, for instance chlordiazepoxide, will be measured, while in the barbital group the analysis includes many barbiturates. This means that some 30 % (95 % confidence limits 16–49 %) of the patients treated with diazepam had taken this drug before entering the hospital, whereas only a few per cent (95 % confidence limits 0.5–15 %) of the patients treated with barbital had taken some type of barbiturate prior to admission.

**DISCUSSION**

The literature concerning drug treatment of acute complications after alcohol abuse is overwhelming, but for reasons mentioned earlier it is often difficult to compare the results. Cutshall (1965) found chlordiazepoxide of value in milder cases, but often this drug was unable to sedate patients with more serious, prolonged DT. Similarly, Rosenfeld & Bizzoco (1961) found chlordiazepoxide superior to placebo in treatment of "alcohol withdrawal"; even if the drug did not shorten the acute state, it diminished markedly the patient's anxiety and restlessness. Each group consisted of 30 patients; two patients in each group developed DT.

Two big multi-centre studies have evaluated the efficacy of several drugs both in the treatment of "acute withdrawal states" (Kaim et al. (1969)) and in the treatment of proper DT (Kaim & Klett (1972)). In the first study chlordiazepoxide, hydroxyzine, chlorpromazine and thiamine were tested against placebo. Symp-
tomatic improvement occurred in the great majority of patients in all five treatment groups. Individual symptoms appeared to respond more favourably to one or another of the treatments (including placebo), but there was no consistent overall superiority of any of the treatments. On the other hand, chlordiazepoxide was clearly of value in the prevention of both convulsions and progression of the acute states to frank DT; the incidence of those complications was 2% in the chlordiazepoxide group but more than 10% in the other groups, being highest in the group treated with chlorpromazine. The authors proposed that the beneficial outcome of chlordiazepoxide treatment might be due to the existence of cross tolerance between this drug and alcohol. This hypothesis was tested in the delirium tremens study (Kaim & Klett (1972)), where the efficacy of chlordiazepoxide, paraldehyde and pentobarbital, all having some kind of cross tolerance with alcohol, was compared with perphenazine, not exerting cross tolerance with alcohol. Eight patients, from one to three in the different groups, had to be removed from the study because of treatment failure. The efficacy of the drugs was ascertained by the duration and severity of the acute state, and no differences were found between the four drugs. From the two studies it is concluded that cross tolerance between alcohol and the drug used is important in milder cases, but the course of uncomplicated DT is not markedly influenced by the drugs tested. Like many others, the authors stressed the importance of supportive care, the quality of which often may be the factor determining success or failure of the treatment regimen.

In the above-mentioned studies chlordiazepoxide has been the benzodiazepine tested, but diazepam also has been found effective in the treatment of DT (Thompson et al. (1975)). The two drugs are probably equally safe and effective, but diazepam has not been studied as intensively as chlordiazepoxide (Greenblatt & Shader (1974)). Comparison between the two drugs in the treatment of DT has only been undertaken in a few cases. Chambers & Schultz (1965) compared diazepam, chlordiazepoxide and promazine in different conditions related to alcohol abuse, both milder and more severe cases of DT, acute brain syndromes and alcohol hallucinosis. They found both chlordiazepoxide and promazine superior to diazepam in the doses used. However, they used a fixed schedule with medication three times a day, which is probably less appropriate due to the very varying course and duration of the disease.

One of Chambers & Schultz's conclusions was that diazepam is more short-acting as compared with chlordiazepoxide. This is in accordance with the pharmacokinetic properties of the two drugs. Disappearance from blood after a single dose of diazepam is first rapid and then slower. This initial rapid disappearance, with a half-life of only a few hours, is due to distribution; it is followed by a slower elimination rate, with a half-life of 35 hours, but with marked individual differences. Chlordiazepoxide has a half-life of about 10 hours without such an initial rapid disappearance (Greenblatt & Shader (1974)). This difference probably explains the difference in duration of action between the two drugs in the treatment of DT. This is an acute, short event, and a steady state plasma concentration will not be obtained. Diazepam's somewhat shorter duration of action may in some respects be an advantage, the patient being assessed more often,
and a threatening complication may be detected early enough to prevent a more serious course.

Brown et al. (1972) compared chlordiazepoxide and diazepam in the treatment of DT; both drugs were given intravenously. No differences were found in the final outcome, but diazepam appeared to have a more rapid onset of action, enabling the dosage to be adjusted more accurately. These authors suggest that this difference, in conjunction with diazepam's greater anticonvulsive property, makes diazepam preferable to chlordiazepoxide in the treatment of DT.

The more rapid onset of diazepam effect is probably due to the more rapid crossing by this drug of the blood-brain-barrier as compared with chlordiazepoxide. Peak concentration in the cerebrospinal fluid of diazepam was obtained within an hour after a single intramuscular injection of diazepam (Kanto et al. (1975)) whereas peak concentration of chlordiazepoxide after a single dose of 100 mg given intravenously occurred 2–4 hours after the dose was given (Stanski et al. (1977)). This difference will probably often be of minor importance, but in the treatment of DT it may be crucial, as many doses frequently will be necessary to sedate the patient; the more rapid the onset, the less the risk of intoxication.

The main reason for us to choose diazepam was the good anticonvulsive property of this drug (Boyer (1966)). In this respect the two drugs here tested seemed to be equal. One patient in each group developed a single epileptic seizure, not necessitating special procedures, where Philipp et al. (1976) found the frequency of convulsions in patients with DT to be about 10–20%.

In our study no significant differences were found between the two drugs tested in the treatment of the milder cases, but there was a trend to favour diazepam in the global assessment of efficacy. On the other hand, we found barbital significantly superior to diazepam in the treatment of proper DT. Our diazepam results seem to be in accordance with those from many of the previous studies. Diazepam will most often be an effective treatment, but in a few cases the acute state will progress, and in the treatment of frank DT it may not be ideal. In this respect, barbital is the most effective drug and, used in the way outlined here, it seems to be a safe and favourable treatment of DT and other acute complications of alcohol abuse.

**Route of administration**

In our study barbital was administrated per os, diazepam intramuscularly. This raises the question of whether the different routes of administration could at least partly be responsible for the differences in outcome between the two drugs. Lous (1954) found that barbital was easily absorbed from the gastro-intestinal tract; the peak concentration after a single dose (1,500 mg per os) was obtained after 6 hours. From the illustrations by Lous it can be seen, however, that already after 2 hours a level very near the peak concentration was obtained. During severe intoxications the absorption is delayed, probably due to immobility of the gastro-intestinal tract.

Data concerning the plasma concentration after i.m. injection of diazepam are conflicting and conclusions are difficult to draw. After a single dose, the
maximum concentration seems to be higher and earlier after oral administration as compared with the i.m. route (Hillestad et al. (1974a), Sturdee (1976)). In patients pretreated with diazepam, however, the i.m. route provided much higher plasma diazepam concentrations than did the oral route (Sturdee (1976)). After a single dose, patients who exercised obtained a higher plasma concentration following intramuscular injection as compared with patients who took the drug by mouth (Assaf et al. (1974)), probably due to the higher blood flow in the muscles during exercise. Patients with DT are in most cases hyperactive and drugs are nearly always given in repeated doses. We therefore presume that the intramuscular administration of diazepam to patients with DT is not inferior to oral medication. On this basis we find it justified to conclude that the two different ways medication was administered in our study have not influenced the results significantly.

Following intravenous injection of both diazepam and chlordiazepoxide, the peak concentration is obtained within a few minutes, and the concentration following intravenous injection is much higher as compared with the other routes of administration (Greenblatt & Shader (1974)). This may in some respects be an advantage, the patients being sedated within a very short time. There may, however, be some problems using the i.v. route as a routine. The patients are often very agitated and this may complicate an injection programme. The doses required to sedate a patient during ongoing DT vary considerably. Giving the drug intravenously one obtains high serum concentrations, but with a concomitant risk of overdosing the patient even if the drug is given very slowly and under careful observation of the clinical condition. Intravenous benzodiazepine treatment of a DT patient should therefore always be performed by a physician, and, as a rule, emergency equipment should be available. For those reasons we find the oral or the i.m. route to be the most favourable as a routine, but, as also seen in our study, intravenous administration may become necessary.

Drug abuse
Salum (1972) found that only 9% of 1,751 patients with DT or other acute complications after alcohol abuse had detectable barbiturates in their blood at the time of admission; only 4% had a concentration higher than 0.1 mg/l. The material was collected up to 1961, before the introduction of the benzodiazepines. In our material only two patients had small amounts of barbiturate in the blood at admission, whereas about one third of the patients treated with diazepam had taken this drug prior to hospitalization. Generally it is stated that the dependence potential of diazepam and other benzodiazepines is low. Abuse in a more narrow sense seems to be relatively uncommon, but the risk of dependence on benzodiazepines seems to be higher in persons who earlier have had an abuse of alcohol or other antianxiety agents (Lingjærde (1971)).

The question whether there is an increasing abuse of benzodiazepines among alcoholics cannot be answered by our study. All patients who said that they had taken drugs in the days before admission were excluded, and it is difficult to decide how often diazepam, nevertheless taken by one third of the patients, has been part of a more prolonged abuse or how often it has been an acute
event, where the patients had taken the drug to suppress the first symptoms of the oncoming delirium. N-Desmethyl-diazepam was, however, higher than diazepam in about half of the patients, which indicates that the use or abuse has been of some duration in these patients (Hillestad et al. (1974b)). The difference in relative numbers of patients with sedative or antianxiety drugs in their blood in our material and in the material of Salum may either represent differences between drinking and social patterns of Danish and Swedish alcoholics or a trend to an increasing combination of alcohol and drugs during the last 10–15 years. If the tenet of increased combination is true, this may lend support to the therapeutic use of barbital. This drug is seldom used nowadays, which means the acute state can be treated with a “special purpose drug”, where the use of diazepam, known and perhaps periodically used by many patients, may give rise to an increased abuse of this drug among alcoholics when they realize its alcohol-resembling effect, and its ability to suppress some of the most undesirable symptoms of alcohol abuse.

**Final remarks**
The interpretation of a study like the present one, even when performed under double-blind conditions, is difficult. From time to time the nurses mentioned that they, after a few doses of the blind medication, knew which drug was given. Barbital has been the drug of choice for years in our department; the whole staff was very familiar with its effects and mode of onset. The nurses stated that diazepam had a more rapid onset, but that the duration of action was shorter and that the patients showed a tendency to relapse. An analysis of the way the drug was administered did not show significant differences, but nevertheless there was a tendency to confirm the nurses' statement (Fig. 1). Another factor which may tend to break the blindness of the study is the way the two drugs influence the symptoms. Beforehand the similarity and dissimilarity of the two drugs, e.g. on the order of symptom disappearance, cannot be predicted. If it is possible for the staff to recognize “the old drug” by the way it functions, the blindness is psychologically broken, and treatment with the well-known drug will probably be administered more efficiently.

Another problem is the transferability of our results to other departments. We still find that barbital is a safe and perhaps the most effective drug, especially in a psychiatric department. It has many advantages, e.g. in relation to the question of drug abuse. On the other hand no serious complication occurred in the diazepam group and even if the code was broken three times, it was possible to continue the treatment with diazepam during the acute state, even though large doses, given by intravenous infusion, were required. Administration of diazepam intravenously is common in several medical specialities. Many departments will be familiar with this drug, whereas a safe administration of repeated large doses of barbital may be a problem. If the DT is complicated with a concomitant somatic illness, the drug treatment should be undertaken with special care, but in general both drugs are well tolerated – also in patients with somatic diseases. Using barbital, which is excreted unchanged in the urine, to patients with impaired kidney function, or using diazepam, which is metabolized by the
liver, to patients with impaired liver function, the risk of overdosing the patients does exist, but this can easily be avoided by careful clinical observation. Patients not allowed to take anything by mouth, e.g. due to pancreatitis, represent a special problem. Here we find diazepam given intravenously the drug of choice, even though many complications, and a high rate of mortality, have been found among patients with DT in connection with severe acute somatic disease treated with chlordiazepoxide (Sroczynski & Lunding (1976)).

CONCLUSIONS
Drugs used in the treatment of DT should have a sedating effect, they should prevent convulsions, they should be easy to give, they should have a rapid onset of effect, and the same drug should be suitable both to the milder and to the more severe cases. No drug seems to fulfil all the desirable properties for the treatment of DT, but among the many agents used, we find the long-acting barbiturates, for instance barbital, and the benzodiazepines the most favourable. Among the benzodiazepines we prefer diazepam, partly because of the rapid onset and the short duration of the effect, partly because of its ability to prevent convulsions. Which drug to choose depends on many factors, among which are concomitant somatic illness, and the setting in which the treatment is performed, i.e. a psychiatric ward with great experience of DT therapy or a somatic ward with more scattered cases. The difference between the drugs here proposed seems to be little, and is certainly of minor importance compared with the importance of optimal and careful general medical care.

ACKNOWLEDGEMENTS
Thanks are due to Palner Forsbøl, M.D., and Rasmus Fog, M.D., who participated in various parts of the study. We also wish to thank Tage Hansen, cand. pharm., and Per Rønsted, cand. pharm., The Dumex Company, Copenhagen, Denmark, who provided the investigational drugs, performed the diazepam determinations and participated in the statistical analysis. Finally we want to thank Johannes Christiansen, cand. pharm., Department of Clinical Chemistry, Rigshospitalet, who performed the barbital determination.

REFERENCES
Assaf, R. A. E., J. W. Dundee & J. A. S. Gamble (1974): Factors influencing plasma diazepam levels following a single administration. Brit. J. clin. Pharmacol. 1, 343–344.
Boyer, P. A., Jr. (1966): Anticonvulsant properties of benzodiazepines. (A review). Dis. nerv. Syst. 27, 35–41.
Brown, J. H., D. E. Moggey & F. H. Shane (1972): Delirium tremens: A comparison of intravenous treatment with diazepam and chlordiazepoxide. Scot. med. J. 17, 9–12.
Chambers, J. F., & J. D. Schultz (1965): Double-blind study of three drugs in the treatment of acute alcoholic states. Quart. J. Stud. Alcohol 26, 10–18.
Christensen, J. K., & N. Strandbygaard (1968): Libriumbehandling af akutte alkoholiske urotilstande. Ugeskr. Læg. 130, 763–766.
Cutshall, B. J. (1965): The Saunders-Sutton syndrome: An analysis of delirium tremens. Quart. J. Stud. Alcohol 26, 423–448.
Favazza, A. R., & P. Martin (1974a): The treatment of delirium tremens: Controversy in the literature. J. Amer. med. Wom. Ass. 29, 219–221.
Favazza, A. R., & P. Martin (1974b): Chemotherapy of delirium tremens: A survey of physicians' preferences. Amer. J. Psychiat. 131, 1031–1033.
Figurelli, F. A. (1958): Delirium tremens. J. Amer. med. Ass. 166, 747–750.
Friedenreich, A. (1909): Veronalbehandling af Delirium Tremens. Ugeskr. Læg. 71, 1321–1322.
Golbert, T. M., C. J. Sanz, H. D. Rose & T. H. Leitschuh (1967): Comparative evaluation of treatments of alcohol withdrawal syndromes. J. Amer. med. Ass. 201, 113–116.
Greenblatt, D. J., & M. Greenblatt (1972): Which drug for alcohol withdrawal? J. clin. Pharmacol. 12, 42W31.
Greenblatt, D. J., & R. I. Shader (1975): Benzodiazepines in clinical practice. Raven Press, New York, pp. 17–42, 217–229, 242–245.
Greenblatt, D. J., & R. I. Shader (1974): Benzodiazepines in clinical practice. Raven Press, New York, pp. 17–42, 217–229, 242–245.

Hillestad, L., T. Hansen, H. Melson & A. Drivenes (1974a): Diazepam metabolism in normal man, I. Clin. Pharmacol. Ther. 16, 479–484.
Hillestad, L., T. Hansen & H. Melson (1974b): Diazepam metabolism in normal man, II. Clin. Pharmacol. Ther. 16, 485–489.
Kaim, S. C. (1970): Optimal therapy of the alcohol withdrawal state. Curr. Psychiat. Ther. 10, 156–160.
Kaim, S. C., & C. J. Klett (1972): Treatment of delirium tremens. Quart. J. Stud. Alco-
hol 33, 1065–1072.
Kaim, S. C., C. J. Klett & B. Rothfeld (1969): Treatment of the acute alcohol with-
drawal state: A comparison of four drugs. Amer. J. Psychiat. 125, 1640–1646.
Kanto, J., L. Kangas & T. Siirtola (1975): Cerebrospinal-fluid concentrations of diaze-
pam and its metabolites in man. Acta pharmacol. (Kbh.) 36, 328–334.
Keller, M. (1977): A lexicon of disablements related to alcohol consumption. In Ed-
wards, G., M. M. Gross, M. Keller, J. Moser & R. Room (eds.): Alcohol-related dis-
abilities. WHO Offset Publication No. 32, Geneva, pp. 23–60.
Kramp, P., T. Hansen & P. Rønsted (1978): Serum concentrations of diazepam and
barbital in treatment of patients with delirium tremens. (To be published).
Larsen, E. F. (1963): Librumbehandling af Delirium Tremens. Nord. psykiatr. T. 17, 292–294.
Lingjærde, O. (1971): Bruk og misbruk av benzodiazepiner. Nord. Med. 86, 1065–1073.
Lou, P. (1954): Kvantitative, kemiske barbitursyrestudier hos mennesker. Thesis. Munksgaard, Copenhagen.
Møller, V. F. (1909a): Veronalbehandling af Delirium Tremens. Ugeskr. Læg. 71, 1253–
1259.
Møller, V. F. (1909b): Korrespondance. Veronalbehandling af Delirium Tremens. Uge-
skr. Læg. 71, 1388.
Nielsen, J. (1965): Delirium Tremens in Copenhagen. Acta psychiat. scand., Suppl. 187.
Philipp, M., N. Seyfeddinipur & A. Marneros (1976): Epileptische Anfälle beim Deli-
rium tremens. Nervenarzt 47, 192–197.
Piker, P., & J. V. Cohn (1937): The comprehensive management of delirium tremens.
J. Amer. med. Ass. 108, 345–349.
Rafaelsen, O. J. (1972): A definition of dependency. In Paton, W. D. M., & J. Crown (eds.): Cannabis and its derivatives. Pharmacology and experimental psychology. Oxford University Press, London, p. 196.
Romano, J. (1941): Early contributions to the study of delirium tremens. Ann. med. Hist. 3, 128–139.
Rosenfeld, J. E., & D. H. Bizzoco (1961): A controlled study of alcohol withdrawal. Quart. J. Stud. Alcohol, Suppl. 1, 77–84.

Salum, I. (1972): Delirium tremens and certain other acute sequels of alcohol abuse. Acta psychiat. scand., Suppl. 235.

Salum, I. (1975): Treatment of delirium tremens. Brit. J. Addict., Suppl. 1, 75–80.

Smith, J. A. (1953): Methods of treatment of delirium tremens. J. Amer. med. Ass. 152, 384–387.

Sørensen, A. (1976): Abstinensbehandling. Editorial. Ugeskr. Læg. 138, 2579.

Sørensen, B. F. (1959): Delirium tremens and its treatment. Dan. med. Bull. 6, 261–263.

Sroczyński, Z., & M. Lunding (1976): Anaesthesiologiske synspunkter ved behandlingen af delirium tremens. Nord. psykiat. T. 30, 426–435.

Stanski, D. R., D. I. Greenblatt & A. Selwyn (1977): Plasma and cerebrospinal fluid concentrations of chlordiazepoxide and its metabolites in surgical patients. Psychopharmacol. Bull. 13, 53–54.

Sturdee, D. W. (1976): Diazepam: Routes of administration and rate of absorption. Brit. J. Anaesth. 48, 1091–1096.

Thompson, W. L., A. D. Johnson, W. L. Maddrey & The Osler Medical Housestaff (1975): Diazepam and paraldehyde for treatment of severe delirium tremens. Ann. intern. Med. 82, 175–180.

Victor, M. (1966): Treatment of alcoholic intoxication and the withdrawal syndrome. Psychosom. Med. 28, 636–650.

Criteria Committee, National Council on Alcoholism (1972): Criteria for the diagnosis of alcoholism. Amer. J. Psychiat. 129, 127–135.

Received December 23, 1977

Peter Kramp, M.D.
Department of Psychiatry
Rigshospitalet
9, Blegdamsvej
DK-2100 Copenhagen Ø
Denmark