ASSESSMENT OF DIAZEPAM LOADING DOSE THERAPY OF DELIRIUM TREMENS

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(Received 27 July 1995; in revised form 6 November 1995; accepted 1 December 1995)

ABSTRACT — The efficacy of the diazepam loading dose method of treatment of delirium tremens was assessed in comparison with the traditional therapy. The experimental group and the control group comprised 51 and 45 patients respectively. The clinical institute withdrawal assessment for alcohol (CIWA-A) scale was applied to assess the intensity of the symptoms. Diazepam doses in the experimental group oscillated from 40 to 210 mg (mean 86.9 ± 47.2 mg). The control group was receiving diazepam and other psychotropic drugs in divided doses. In the experimental group deliric symptoms were present from 2 to 24 h (mean 6.9 ± 4.8 h), and in the control group from 2 to 123 h (mean 33.8 ± 25.7 h). The results show a large efficacy of the loading dose method corresponding to substantial reduction of the psychosis duration (fivefold in comparison to the control group). The method proved to be safe, with no significant complications.

INTRODUCTION

The ideal drug to treat delirium tremens should be a compound with anxiolytic, anticonvulsant and antipsychotic effect, reducing the activation of the vegetative system (Busch and Frings, 1988). Unfortunately such a drug does not exist. Commonly, as the activity of GABA-ergic neurons is diminished in the alcohol withdrawal syndrome (Airaksinen and Peura, 1987), benzodiazepines or chlormethiazole monotherapy is recommended, because of the GABA-ergic effect of these drugs. Another reason for their use is their cross-tolerance with alcohol (Gross et al., 1974).

The choice of benzodiazepines is recommended because of their more significant anticonvulsant activity and lower toxicity; even if therapeutic doses are greatly exceeded, lethal intoxication is seldom observed; usually only when patients take other psychotropic drugs or drink alcohol (Fresecott, 1983). As all benzodiazepines act on the same receptor, their efficacy is comparable (Greenblatt, 1992; Hollister et al., 1993). However, the results of treatment of the alcohol withdrawal syndrome with diazepam in divided doses did not prove to be effective (Shaw et al., 1981; Rewekant et al., 1989; Szelenberger et al., 1989). This method does not ensure a proper therapeutic concentration of diazepam (Rickels, 1983; Long, 1984; Rewekant et al., 1989). This is particularly so during the first life-threatening 48 h.

Diazepam-loading is an alternative to the existing methods of treatment. Diazepam is given orally 20 mg every 1–2 h until the improvement of the clinical condition is achieved (Sellers et al., 1983). Therapeutically adequate concentrations are reached during the first 48 h, with no further increase to toxic or even life-threatening levels (Sellers and Naranjo, 1985; Naranjo and Sellers, 1986; Matsumoto et al., 1992). Because of the fact that diazepam and its metabolites have a long biological half-life (Kaplan, 1980), the therapeutic concentration is maintained, after the loading dose, during the following days (Naranjo and Sellers, 1986; Matsumoto et al., 1992).

In the present study, we have compared the efficacy of the diazepam loading method with
traditional therapy with the drug in the treatment of alcoholic delirium tremens.

MATERIALS AND METHODS

Patient characteristics and selection

The loading dose method was applied in 51 patients of the Nowowiejski Hospital in Warsaw, the Psychiatric Hospital in Pruszków and the Psychiatric Hospital in Żabki, from April 1990 to October 1994. The experimental group consisted of 46 males and five females, aged 26–60 years, suffering from alcohol withdrawal syndrome with delirium (according to ICD-10) (World Health Organization, 1992). Patients with alcohol withdrawal syndrome without delirium, mixed dependence, other alcoholic and non-alcoholic psychoses, and patients who shortly before the hospitalization received any psychotropic medication (e.g. from emergency doctors) were excluded from the study. We also did not include patients with the following contraindications for diazepam administration: recent head injury, diseases related to a possible respiratory insufficiency, hepatic insufficiency, and presence of alcohol in blood upon admission.

Treatment and assessment of patients

We checked our patients for the presence of alcohol, benzodiazepines or barbiturates in their blood. Then, diazepam (Relanium, Polfa) was administrated per os in 10–20 mg doses every 1–2 h. Clinical state was assessed by means of the clinical institute withdrawal assessment for alcohol (CIWA-A) scale (Shaw et al., 1981): nausea and vomiting (0–7), tremor (0–7), sweating (0–7), occurrence of hallucinations (0–3), tactile disturbances (0–6), auditory disturbances (0–6), visual disturbances (0–6), clouding of sensorium (0–4), quality of contact (0–7), anxiety (0–7), agitation (0–7), thought disturbances (0–3), seizures (0–7), headache (0–7), flushing of face (0–2). The administration of the drug was interrupted when the sum of the points in the CIWA-A scale was <10 (Shaw et al., 1981; Sellers et al., 1983). The duration of psychosis was measured from the start of therapy to the time the patients became asymptomatic.

The control group consisted of 45 patients (40 males and 5 females), aged 21–55 years, selected on the same principles, hospitalized at the same time and in the same hospitals. Patients were randomly selected, depending on the presence of a physician participating in the study on diazepam loading-dose treatment of delirium tremens. Other physicians treated the patients by local regimes. Apart from the psychotropic treatment, all patients received fluids i.v. and B vitamins.

Because of the risk of possible deterioration of the patients’ condition, and therapeutic difficulties caused by the coexisting somatic disorders (Gross et al., 1974; Thompson et al., 1975; Wiżnowski and Rybakowski, 1980; Gillman and Lichtigfeld, 1990), the general state of patients in both groups was assessed by means of a previously prepared questionnaire (Szelenberger et al., 1989) during the first 24 h. Treatment units were equipped with basic emergency drugs including flumazenil (Anexate–Roche), a selective benzodiazepine antagonist (Klotz and Kanto, 1988).

Drug monitoring

The concentration of diazepam (D) and desmethyldiazepam (DD) was assessed by the fluorescence polarization immunoassay method (FPIA) with an Abbott Tdx® analyser. D and DD concentrations were examined only in the experimental group. Drug monitoring was performed to: (a) detect the moment of approaching the critical concentration in certain subjects; (b) evaluate the drug level at which adverse events could occur; (c) establish if the therapeutic concentration was achieved within the first 48 h. Blood samples were collected six times: before the start of therapy, 1 h after the administration of the first dose, 1 h after the last dose, and on the third, the fifth and the seventh days of the hospital stay. The choice of the 1 h interval of blood collection after administration of the drug coincides with the time of attaining diazepam’s maximal concentration [1 h after oral administration (Greenblatt and Shader, 1985; Nicholson, 1989)].

In the statistical analysis, the Mann–Whitney test was used (Norusis, 1990). The research was approved by the Local Ethics Committee.

RESULTS

Table 1 presents the patients’ characteristics, from which it is clear that the only significant
Table 1. Characteristics of the patient groups

<table>
<thead>
<tr>
<th>Numbers</th>
<th>Experimental group</th>
<th>Control group</th>
<th>Statistical data$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>51</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>46</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>5</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>$38.5 \pm 7.0$</td>
<td>$38.2 \pm 6.8$</td>
<td>$U = 1120.5, P = 0.84$</td>
</tr>
<tr>
<td></td>
<td>(26–60)</td>
<td>(21–55)</td>
<td></td>
</tr>
<tr>
<td>Alcohol abuse (years)$^a$</td>
<td>$14.6 \pm 5.6$</td>
<td>$14.1 \pm 5.8$</td>
<td>$U = 937.5, P = 0.17$</td>
</tr>
<tr>
<td></td>
<td>(3–25)</td>
<td>(4–22)</td>
<td></td>
</tr>
<tr>
<td>Last drinking bout (days)$^a$</td>
<td>$78.9 \pm 195.9$</td>
<td>$65.3 \pm 104.7$</td>
<td>$U = 720.5, P = 0.02$</td>
</tr>
<tr>
<td></td>
<td>(7–1400)</td>
<td>(4–540)</td>
<td></td>
</tr>
<tr>
<td>Daily ethanol consumption (ml)$^a$</td>
<td>$324.1 \pm 137.8$</td>
<td>$263.7 \pm 117.9$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(100–675)</td>
<td>(30–675)</td>
<td></td>
</tr>
</tbody>
</table>

$^a$ Values are means ± SD with range in parentheses.

Table 2. The somatic disorders and abnormalities detected in both patient groups during hospitalization

<table>
<thead>
<tr>
<th>Somatic disorders and abnormalities</th>
<th>Experimental group ($n = 51$)</th>
<th>Control group ($n = 45$)</th>
<th>Statistical data$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased levels of aminotransferases and/or bilirubin</td>
<td>34 (67%)</td>
<td>27 (61%)$^a$</td>
<td>$U = 1062.5$</td>
</tr>
<tr>
<td>Electrolyte abnormalities</td>
<td>25 (49%)</td>
<td>16 (36%)$^a$</td>
<td>$U = 1013.5$</td>
</tr>
<tr>
<td>Hypokalaemia</td>
<td>16 (31%)</td>
<td>11 (25%)$^a$</td>
<td>$U = 1015.5$</td>
</tr>
<tr>
<td>Hyperkalaemia</td>
<td>1 (2%)</td>
<td>0</td>
<td>$U = 0.89$</td>
</tr>
<tr>
<td>Hyponatraemia</td>
<td>4 (8%)</td>
<td>2 (5%)$^a$</td>
<td>$U = 1006.5$</td>
</tr>
<tr>
<td>Hypernatraemia</td>
<td>4 (8%)</td>
<td>3 (7%)$^a$</td>
<td>$P = 0.38$</td>
</tr>
<tr>
<td>Anaemia</td>
<td>11 (22%)</td>
<td>9 (20%)$^a$</td>
<td>$U = 1109.5$</td>
</tr>
<tr>
<td>Increased ESR</td>
<td>8 (16%)</td>
<td>9 (20%)$^a$</td>
<td>$U = 1011.5$</td>
</tr>
<tr>
<td>Hypertension (&gt;160/95 mmHg)</td>
<td>11 (22%)</td>
<td>14 (31%)</td>
<td>$P = 0.20$</td>
</tr>
<tr>
<td>Temperature &gt;38°C</td>
<td>2 (4%)</td>
<td>7 (16%)</td>
<td>$U = 101.5$</td>
</tr>
<tr>
<td>Tachycardia (&gt;100 beats/min)</td>
<td>30 (59%)</td>
<td>28 (62%)</td>
<td>$P = 0.05$</td>
</tr>
<tr>
<td>Polyneuropathy</td>
<td>3 (6%)</td>
<td>3 (7%)</td>
<td>$U = 1032.5$</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1 (2%)</td>
<td>2 (4%)</td>
<td>$P = 0.42$</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>–</td>
<td>2 (4%)</td>
<td>$U = 111.5$</td>
</tr>
<tr>
<td>Diseases of urinary system</td>
<td>1 (2%)</td>
<td>2 (4%)</td>
<td>$P = 0.55$</td>
</tr>
</tbody>
</table>

$^a$ 44 patients were assessed, one patient refused blood testing.

$^b$ Mann–Whitney test.

ESR = erythrocyte sedimentation rate.
Table 3. The range and mean concentrations of diazepam (D) and desmethyldiazepam (DD) in blood

<table>
<thead>
<tr>
<th>Statistical data</th>
<th>1 h after the first dose</th>
<th>1 h after the last dose</th>
<th>3 days after last dose</th>
<th>5 days after last dose</th>
<th>7 days after last dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td>256 ± 157</td>
<td>1031 ± 803</td>
<td>611 ± 319</td>
<td>474 ± 328</td>
<td>338 ± 187</td>
</tr>
<tr>
<td>Range</td>
<td>(18-776)</td>
<td>(353-3400)</td>
<td>(179-1693)</td>
<td>(100-1634)</td>
<td>(105-787)</td>
</tr>
</tbody>
</table>

Cut-off level: 12 ng/ml.
The range of D + DD concentration in control subjects treated with diazepam by the traditional method was: low: 63.7–86.3 ng/ml; medium: 255–345 ng/ml; high: 595–805 ng/ml.

difference between the control and experimental groups is the greater previous alcohol consumption in the latter patients.

The total amount of diazepam applied in the loading dose method varied between 40 and 210 mg (mean: 86.9 ± 47.2 mg). Because of suspicion of toxic hepatitis, two patients received oxazepam in doses of 300 and 400 mg, equivalent to 50 and 67 mg of diazepam (Bezchlibnyk-Butler et al., 1989).

In the control group, 43 patients were treated with diazepam in divided doses, with the total amount varying from 60 to 9840 mg (average: 1784 ± 1800 mg per treatment) (20–80 mg pro die; mean ± SD: 46.5 ± 18.3 mg); 29 patients were receiving haloperidol in divided doses, 5–30 mg pro die (mean 12.1 ± 5.7 mg); eight patients were treated with promethazine 25–150 mg pro die (mean: 103.1 ± 52.2 mg); hydroxyzine 100–300 mg pro die (mean: 157.1 ± 72.8 mg) was administered in seven patients; three patients were receiving clormethiazole 600–900 mg pro die (mean: 700.0 ± 141.4 mg). One patient was treated with perazine 150 mg pro die, one with chlorpromazine 50 mg pro die, and another with oxazepam 180 mg pro die.

The duration of delirium in the experimental group varied from 2 to 24 h (mean: 6.9 ± 4.8 h), and in the control group between 2 and 123 h (mean: 33.8 ± 25.7). The difference was significant (Mann–Whitney test: U = 265.0, P < 0.001).

Table 2 represents the somatic disorders and abnormalities detected in both groups during hospitalization. No significant differences between control and experimental subjects were noted. Rum fits before the development of delirium tremens occurred in five patients in the experimental group and two patients in the control group. History revealed that in the past rum fits were experienced by eight patients in the experimental group and nine patients in the control group. No deaths occurred in either group.

The range and mean concentrations of diazepam (D) and desmethyldiazepam (DD) are presented in Table 3.

DISCUSSION

The results demonstrate the efficacy of diazepam loading in the treatment of delirium tremens: the psychosis duration was almost fivefold shorter compared to the control group. Our findings confirm those reported by the authors of the method (Sellers et al., 1983), who observed a mean syndrome duration of 7 h. Other studies reported a mean syndrome duration of 5.3 h (Heinäla et al., 1990), and improvement within the first day of hospitalization (Manikant et al., 1993). In our previous studies, we obtained similar results; the mean syndrome duration was 7 h (Wasilewski et al., 1995).

In three subjects in the experimental group, the withdrawal symptoms subsided after 2 h; the total diazepam amount was 40 mg, which suggests that therapy was started during the final phase of delirium tremens. However, these three separate cases did not influence the results significantly.

There were no differences between the groups concerning mean alcohol abuse duration and mean drinking bout; however, mean daily ethanol consumption was significantly higher in the experimental group. Patients’ general condition did not differ in both groups.

There were no complications observed during diazepam loading therapy. The possibility of central respiratory complications was considered
both during the selection and the therapy. Before
the onset of the treatment, the concentrations of
benzodiazepines, barbiturates and alcohol in blood
were assessed. Basic emergency equipment and
drugs, including flumazenil (Anexate–Roche) as
antidote, were present in every treatment unit, but
their use was not necessary. Moreover, rapid
monitoring of D and DD concentrations during
therapy provided an additional means of safety
assessment. Laboratory results could thus have
important implications for decision-making on
continuation or interruption of treatment. In our
study, however, such action was not necessary.

There are data on cases of coma at levels of
D + DD of 3000 ng/ml, and fatal cases at levels
4800 ng/ml in patients without alcohol depen-
dence (Finkle et al., 1979). However, there were
also cases of patients with blood diazepam
concentrations ranging from 20 000 to 30 000
ng/ml, with rapid recovery from serious con-
sciousness disorders including coma (Prescott,
1983). In one of our patients, who received the
total dose of 200 mg of diazepam over 11 h, the
D + DD concentrations 1 h after the end of
therapy reached 3400 ng/ml. In another patient
who received the same dose over 10 h, the
maximum D + DD concentrations were 2500
ng/ml. A third patient, who received a total dose
of 180 mg of D over 10 h, had D + DD concentra-
tions of 3212 ng/ml. In these three cases (in whom
the analysis done by the FPIA method was
confirmed by the high performance liquid chro-
matography), no respiratory or circulatory com-
lications nor interruption of verbal contact
occurred. The lack of overdose symptoms in these three patients,
may be due to cross-tolerance, or possibly a
decreased sensitivity of benzodiazepine receptors
(Korpi, 1994).

It is known that, in several delirium tremens
cases with severe hallucinations and agitation or
with a complicated and a long-lasting course,
treatment with benzodiazepines may prove insuf-
ficient (Rosenbloom, 1988). The proponents of the
diazepam loading dose method themselves
(Naranjo and Sellers, 1986) recommended admin-
istration of haloperidol in such cases. They
suggested that haloperidol should not be applied
as the basic drug, but only as an adjunctive
therapy. Other butyrophenone derivatives could
also be used (Rosenbloom, 1988), but in our
experience this was not necessary.

In conclusion, we believe that the diazepam
loading dose method constitutes substantial pro-
gress in the pharmacotherapy of delirium tremens,
because it brings substantial reduction of psycho-
sis duration. It requires, however, additional
training of staff, because every patient requires
individual assessment before subsequent drug
administration. The method seems safe when
appropriate safety standards are followed.

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