EFFECTS OF HIGH LEVELS OF DIAZEPAM AND ALCOHOL IN PRACTICE.

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The medicolegal examiner is often confronted with the problem to interpret the influence of tranquilizers on traffic security, criminal responsibility or on affects. This expert investigation is based by no means on sure knowledge. On account of the widespread use of these drugs and because of the frequent introduction of new preparations, but also because of the changing effects under the combined action (alcohol and drugs), an extensive exchange of mind between the treating doctors, medical experts, toxicologists and investigating officials about patients or addicts is necessary to secure a well informed legal safety.

In the Western countries, at least, benzodiazepines belong to the mostly prescribed substances. In agreement with this frequent use abuse has also increased (Bant 1975; Le Bellec et al. 1980; Poser et al. 1980).

Out of this group of the benzodiazepines, diazepam has the priority (Gelbke et al. 1978). There exists, especially about diazepam, such an extensive literature that even weekly or daily papers inform about this problems, as it has been recently reported in the "Observer Living" about the "Dangers of Tranquillity". Numerous publications also deal with the combination effects between diazepam and alcohol (Mørland et al. 1974;
Hayes et al. 1975; Laisi et al. 1979; Lutze et al. 1979), showing normally, that alcohol produces an increasing effect on diazepam or diazepam increases the ethanol influence. In several systematic clinical experiments on humans with alcohol and diazepam the ethanol dose was limited to about 1 g/kg with a simultaneous diazepam dose between 5 and 10 mg. Haffner et al. (1973) compared diazepam doses up to 20 mg in male volunteers with ethanol in amounts producing blood levels of approximately 0.1%, but not in coincidence with drug and alcohol. Experiments with higher doses of diazepam and a simultaneous relevant alcohol uptake are out of question because of the therewith associated possible risks. The interest is therefore great for cases with high diazepam blood levels in connection with alcohol. But such cases are limited to practical observations.

Gelbke et al. (1978) determined diazepam by radioimmunoassay and gas chromatography in 2050 unselected blood or serum specimens of subjects, who were suspected of driving under the influence of alcohol between the years 1974 and 1975. A "cut off" limit of 20 ng/ml was selected. Diazepam was found in 46 samples corresponding to 2.24%. From these cases 5 samples showed diazepam concentrations of more than 500 ng/ml, but only three showed simultaneous alcohol influence (fig.1).
<table>
<thead>
<tr>
<th>case</th>
<th>age</th>
<th>sex</th>
<th>declared diazepam uptake (g/kg)</th>
<th>concentration in blood of diazepam (ng/ml)</th>
<th>concentration in blood of desmethyldiazepam (ng/ml)</th>
<th>consciousness</th>
<th>degree of drunkenness</th>
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<tbody>
<tr>
<td>1</td>
<td>44</td>
<td>♂</td>
<td>20 mg</td>
<td>1.68</td>
<td>457</td>
<td>200</td>
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<td>2</td>
<td>22</td>
<td>♂</td>
<td>not</td>
<td>1.46</td>
<td>635</td>
<td>230</td>
<td>dizzy</td>
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<tr>
<td>3</td>
<td>37</td>
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<td>not</td>
<td>1.57</td>
<td>622</td>
<td>32</td>
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<td>18</td>
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<td>20 mg</td>
<td>1.41</td>
<td>1500</td>
<td>traces</td>
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</tr>
<tr>
<td>5</td>
<td>26</td>
<td>♂</td>
<td>20 mg</td>
<td>2.03</td>
<td>1280</td>
<td>785</td>
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<td>43</td>
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<td>2 tabl.</td>
<td>2.08</td>
<td>766</td>
<td>1140</td>
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<tr>
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<td>39</td>
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<td>1 tabl.</td>
<td>0.58</td>
<td>955</td>
<td>500</td>
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<td>2 tabl.</td>
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<td>2630</td>
<td>2700</td>
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</tr>
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<td>9</td>
<td>29</td>
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<td>40 mg five days before</td>
<td>0.93</td>
<td>1002</td>
<td>50</td>
<td>clear</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>not</td>
<td>2.52</td>
<td>0</td>
<td>0</td>
<td>clear</td>
</tr>
<tr>
<td>10</td>
<td>36</td>
<td>♂</td>
<td>15 mg</td>
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<td>566</td>
<td>197</td>
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<tr>
<td>11</td>
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<td>♂</td>
<td>15 mg</td>
<td>0.70</td>
<td>506</td>
<td>112</td>
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</table>

Fig. 3: 11 cases with diazepam and alcohol between the years 1978 and 1979 from own material

In fig. 3 are noted the respective declarations of the subjects about their diazepam uptake during the withdrawal of blood, followed by the corresponding blood alcohol concentration (mean values of each 2 ADH- and 2 GLC-measurements). The determination of diazepam and its main metabolite desmethyldiazepam was according to the methods, described by Gelbke et al. (1977) with a radioimmunological screening and a gas chromatographic determination of the two benzodiazepines. The classification about the consciousness and the degree of drunkenness were drawn from the medical reports and the statements by witnesses.

These investigations present, that only in the cases 1 and 9 determined levels of diazepam and desmethyldiazepam respectively agree with the claimed diazepam intake. Case 1 was a 44 year-old woman, who had taken 2 tablets Valium 10® 8 1/2 hours before the withdrawal of blood. She exhibited the severest mental disorders of all the 11
Fig. 2: Occurrence of diazepam in 44 blood speci-
of persons who had claimed diazepam intake
at the blood withdrawal

Here seven cases exhibited diazepam concentrations above
the normal therapeutic highest levels about 400 ng/ml with
simultaneous alcohol concentrations over 0.5 g/kg.

In our investigations between the years 1978 and 1979
with approximately 6500 samples for blood alcohol deter-
minations, we found 11 cases with diazepam blood concen-
trations above 400 ng/ml and ethanol levels higher than
0.5 g/kg (fig. 3). In most of these cases urine samples were
analyzed too, and we have found no further detectable
substances.
Furthermore, 44 blood specimens of the subjects were analyzed, who had claimed diazepam intake before the blood sample was withdrawn. Diazepam was found in 27 cases, corresponding to 61% (fig.2).
cases in spite of the relative lowest diazepam concentrations.

Case 9 refers to a 29 year-old alcoholic, who took 4 tablets Valium 10® 2 hours before withdrawal of blood and he didn't show any symptoms of deficiency, though there was determined a corresponding blood alcohol level of about 1 g/kg. He had committed a theft and declared to have taken the diazepam overdose the first time. This declaration was, according to the analysis of the blood sample and the relation of diazepam to desmethyldiazepam, thoroughly reliable, because the measured blood levels were in agreement to the known investigations of the literature about the pharmacokinetics after single intake, as newly reported by Greenblatt et al. (1980). In this case 9 we analyzed a blood sample of the same person 5 days before with an ethanol concentration of 2.5 g/kg, also showing no symptoms of deficiency.

In the case 3 and especially case 4 the diazepam intake must be suspected, to have occurred only a short time before the withdrawal of blood. An unknown overdose of diazepam had been taken in suicidal intention in the case 8. But here, the 22 year-old man didn't show any severe symptoms, although the simultaneous blood alcohol level amounted to about 2g/kg.

Discussion

There exist many publications about benzodiazepines, especially diazepam, but contradictory results cause rather confusion than clearness. Vesell (1980) postulates the following points about the pharmacokinetics
as an obligatory information:

1 sites of drug administration
2 sites of drug distribution in the body
3 sites where drugs are metabolized
4 sites of drug elimination from the body
5 sites where drugs bind receptors, thereby producing pharmacological effects

This shows, that many factors in the interaction of drugs and alcohol have to be taken into account. The expert should know the possibilities and he should be able, to differentiate from the probabilities. Out of the practice it is known, that diazepam may produce drowsiness, but also suicide attempts with high diazepam doses have failed (Finkle 1979).

The spectrum effect of benzodiazepines and their small dose effect with the simultaneous inefficiency of overdoses let suppose, that there are one or more specific benzodiazepine receptors. Such receptor was found among other things in the brain, by means of $^3$H-diazepam as neurotransmitter-receptor, likewise as a high related plasma-albumin-receptor. Only dosage and pharmacokinetics probably play a part among differences of the individual derivative effect, e.g. Tranxilium® (chlorazepate) works as desmethyldiazepam after quick metabolism (Staak and Moosmayer 1978).

Just so exciting as are the recently published serious withdrawal symptoms (Poser 1980), which bring the benzodiazepines closer to the narcotic drugs is likewise the fact, that under the influence of alcohol higher benzodi-
azepine blood levels are found than expected (Gelbke et al. 1978). There are indications pointing out, that alcohol depresses the clearance of benzodiazepine metabolites and alters the binding to albumen and that through the widening of the vessels a quicker resorption takes place (Hoyumpa et al. 1980).

From our practical experiences and in agreement with one part of the literature it may be deducted, that a dose dependent effect cannot be predicted if alcohol plays a role. Bonnichsen et al. (1970) established on 42 drivers with an alcohol blood level of more than 0.5 g/kg and a simultaneous diazepam effect likewise no dose dependant symptoms. However, the diazepam concentrations of 24 cases were found between 5000 and 27000 ng/ml. This may lie round a tenth power too high.

Too many unsteady factors play their parts, especially habit and the individual enzyme equipment (partly as genetic factor), to set up binding rules. All manufacturers caution against the unexpected combination effect of benzodiazepines with alcohol. Should a consumer in full knowledge of this warning take both drugs at the same time (or another combination), one must assume therefore, that he has done it with premeditation to get drunk.

According to German law an 'actio libera in causa', an action of own's free will, which can establish a liability to punishment, should later a crime in a state of drunkenness committed. Careful chemical analyses limit the unpleasant room of action of the estimation. There are no main effects of diazepam to expect, if the test result is negative. The relation of benzodiazepines to its metabolites permits deductions for the reaction time and for the dose (Aderjan and Schmidt 1980). Overdoses within the half live time can be good estimated. Further estimation possibilities from quantitative analysis data are outlined.
Chronic misuse can be read under favourable conditions from the profile of the active substance in blood and urine.

Summary

The alarming increase in offences under the influence of alcohol and benzodiazepines represents a challenge to the medicolegal and forensic-toxicologic experts. The aim is to evaluate the statistical casuistry after careful analysis and to take notice of the spectrum of the possible effects. Safe estimation guidelines cannot, at present, be laid down.
References


Finkle BS et al. (1979) J. Amer. med. Ass. 242: 429


Gelbke HP, Schlicht HJ, Schmidt GG (1978) Häufigkeit positiver Diazepam-Befunde in Blutproben alkoholisierter Verkehrsteilnehmer. Z. Rechtsmed. 80: 319 - 328


Lutze J, Gelbke HP, Schmidt GG (1979) Zur Leistungsbeeinträchtigung durch Alkohol und Diazepam. Z. Rechtsmed. 82: 327 - 336


