PHARMACOKINETICS AND METABOLISM OF FUSEL ALCOHOLS

W. Bonte, M.D. *; and B. Kühnholz, M.D. **

SYNOPSIS

Interpretation of blood-congener findings requires knowledge about their biochemical behavior in blood. By means of experiments on human volunteers, we collected data about the effects of resorption, distribution, metabolism, and excretion on blood fusel alcohol levels. Immediately after drinking ends, blood levels of congeners correlate closely with the consumed amounts. In contrast to the ethanol pharmacokinetics, fusel-alcohol elimination follows exponential functions of first degree. Our findings can be useful for the formation of expert opinion in cases of drunken driving and hit-and-run accidents.

INTRODUCTION

After consumption of alcoholic beverages the constituent fusel alcohols can be detected in blood and urine samples of the consumer (Bonte & Busse, 1980; Machata & Prokop, 1971). As the fusel alcohol spectra of different beverage types vary within wide ranges conclusions can be drawn from analytical findings, which could be of forensic interest (Bonte et al., 1981a). To do so requires detailed knowledge about the pharmacokinetic behavior of these short-chain alcohols.

One must consider that we utilize 5 different steps of kinetics (Figure 1). After oral ingestion by consumption of alcoholic drinks the fusel alcohols first have to cross the intestine-blood barrier. In the literature we could not find any statement about speed and complement of the intestinal absorption. They are then distributed in the body fluids and organs. As the water and lipoid solubilities of the alcohols differ greatly, some authors have supposed that especially the long-chain alcohols show other distribution patterns than does ethanol. There may exist something like a depot, which could be responsible for their long-lasting excretion (Bonte et al., 1981b). From the literature we do not know whether the fusel alcohols are dissolved in the blood only in their free form only or whether a conjugation, for example with glucuronic acid, takes place.

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The latter is quite likely, because one can find high concentrations of glucuronides in the urine (Bonte et al., 1981 b). However, we are sure that only the free alcohols are subject to metabolism and we have no doubt that liver-ADH is the appertaining enzyme. So the question is whether the metabolites, aldehydes and ketones, and the corresponding carbon acids can be traced in blood samples. Last but not least: little information can be found about the excretion of the fusel alcohols, their metabolites and glucuronides. The following article presents some results of our experimental work on this theme.

METHODS

During the last years drinking experiments involving altogether about 400 volunteers were carried out in order to investigate the pharmacokinetics of congener alcohols. In addition to alcoholic beverages, synthetic drinks with separate alcohols related to ethanol were dispensed. From the volunteers, blood and urine samples were taken in regular intervals. All blood samples were subjected to ultrasonic disintegration and ultrafiltration. The filtrates and the urine samples were analyzed in direct form and, additionally, after incubation with beta-glucuronidase according to the gaschromatographic method which is presented in Kühnholz and Bonte. (This volume.)

Research was also done on other fluids and post-mortem organ samples and also in vitro experiments.

RESULTS

Concerning the absorption of fusel alcohols we can remark that the alcohols invade the system rapidly (Figure 2). The maximum blood concentrations of most alcohols already exist at the end of the drinking bout. The amount consumed seems to have no influence on this. The investigation of post-mortem material proves that the alcohols are absorbed completely (Figure 3). A distinct and constant decrease of the contents can be observed from the stomach to the jejunum and to the colon for all types of alcohols except for methanol. The main region of absorption seems to take place in the jejunum.

The distribution of alcohols in the organs shows differences between the short- and the long-chain alcohols (Figure 4). Methanol, propanol-1, and the secondary alcohols are distributed analogously to ethanol: exclusively
in the body-water; whereas butanol-1, isobutanol, and 2- and 3-methylbutanol show an increasing lipoid solubility. They are, therefore, characterized partially by considerably more than 100% virtual distribution volume. This implies that the free long-chained alcohols in the blood can be found only in relative low concentrations but, also, that they remain longer in the body because of their larger distribution volume.

Conjugation with glucuronic acid is the more significant the longer the carbon chain of the alcohol (Figure 5). Methanol and ethanol can be found in the blood nearly exclusively in their free form, whereas 2- and 3-methylbutanol-1 can be traced only after incubation of the ultrafiltrate with beta-glucuronidase.

Our investigations on elimination kinetics proved that propanol-1 and isobutanol are eliminated exponentially (Figure 6). Propanol-1 exhibits half-value times of 2.3 to 5.4 hours with a mean of 3.3 hours, represented by the theoretical curve in the figure. The results of our blood analyses lie in the computed confidence intervals. A very close correlation exists between the theoretical maximal attainable concentration, $C_\infty$, which is calculated from the drinking-amount and the measured blood levels.

Isobutanol showed distribution volumes of about 110% - 150% (Figure 7). The half-value-time is between 1.7 and 2.6 hours; the mean is near 2.1 hours. Very good agreement was found between the expected values computed from the drinking-amount and the actual results from the analyses.

Methanol and butanol-2 are distinguished by different kinetics. The blood levels increase after cessation of drinking for quite some time. We were not able to prove an unequivocal correlation between quantity consumed and blood concentration. In contrast to the above-mentioned alcohols, the understanding of the elimination kinetics of 2- and 3-methylbutanol-1 becomes rather complicated because of its strong lipoid solubilities. Our results to date do not allow a definite statement about the exponential function in question, but the correlation between the quantity consumed and the resultant blood concentration is reasonable.

Metabolites of the alcohols can very often be found in the blood. They indicate that the respective congener must have been consumed, but are not quantitatively correlated with the consumed amount.
Direct excretion into expired air, secretions, and urine plays a comparatively small part in the elimination of fusel alcohols; it is less than 5%. From our experience, an estimate of time since cessation of drinking can be made on the basis of the ratio of conjugated to free alcohols (Figure 8). We found in all cases that the ratio increases markedly with the time although. Allowance must be made for individual variation in the rate of glucuronide formation.

DISCUSSION

As has been shown, as with propanol-1 and isobutanol, conjugation, lipoid solubility, and excretion play only minor roles in the elimination of the alcohols from the blood. Their kinetics are nearly exclusively due to enzymatic metabolism. That may be the reason why in these instances unequivocally exponential elimination curves could be produced. (They can be mathematically described by the approximation formula $y = C_0 \cdot e^{\text{-}k \cdot (0.5 \cdot t_1 + t_2)}$, where $k$ is the elimination constant, and $t_1$ and $t_2$ the drinking time or the interval after cessation of drinking, respectively).

Much more complicated is the behavior of the secondary and the long-chain alcohols. However, in all cases narrow time-dependent correlations were found between drinking amounts and blood levels. This means that one of these parameters can be calculated from knowledge the other. Even time calculations are practicable when urine samples are available.

Our findings opened new advances in the handling of a series of forensic problems which deal especially with drunken driving. In Germany, hit-and-run drivers, when met under the influence of alcohol at home, very often claim to have drunk just before the arrival of the police (i.e., after the accident) although it is supposed that it was the alcohol which was responsible for the accident. (Usually a high-proof beverage, such as brandy or whisky, has been consumed. Although the most common party beverage, indeed, is beer). In such cases we recommend congener analyses. Expert opinions based on our methods are widely accepted by the courts (Kühnholz et al., 1983).

CONCLUSIONS

1) After consumption of alcoholic beverages the constituent fusel alcohols can be detected in blood and urine.
2) A close quantitative correlation exists between the quantity of congeners consumed and their resultant blood levels. This can be used for forensic purposes.

3) One cannot estimate the quantity of congeners consumed from urine concentrations. However, the ratio of conjugated to free alcohols in urine may be used to estimate time since cessation of drinking.

REFERENCES


Figure 1. Pathway of fusel alcohols after ingestion of alcoholic beverage.
Figure 2. The blood level curves of most fusel alcohols peak by the end of the drinking bout and decline exponentially thereafter.

Figure 3. Congener contents of the gastrointestinal tract of corpses.
Table 1. Distribution of free aliphatic alcohols in the watery and non-watery compartments of the body.

<table>
<thead>
<tr>
<th>Alcohol</th>
<th>Water (%)</th>
<th>Solids (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methanol, Ethanol</td>
<td>70</td>
<td>30</td>
</tr>
<tr>
<td>Propanol-1, Butanol-2</td>
<td>70</td>
<td>30</td>
</tr>
<tr>
<td>Isobutanol, Butanol-1</td>
<td>54</td>
<td>46</td>
</tr>
<tr>
<td>2,3-Methylbutanol-1</td>
<td>100</td>
<td>0</td>
</tr>
</tbody>
</table>

Figure 4. Distribution of free aliphatic alcohols in the watery and non-watery compartments of the body.

Table 2. Ratio of free and conjugated alcohols in the blood.

<table>
<thead>
<tr>
<th>Alcohol</th>
<th>Free (%)</th>
<th>Conjugated (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methanol, Ethanol</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Propanol-1, Butanol-2</td>
<td>80</td>
<td>20</td>
</tr>
<tr>
<td>Isobutanol, Butanol-1</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>2,3-Methylbutanol-1</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

Figure 5. Ratio of free and conjugated alcohols in the blood.
Figure 6. Invasion and elimination kinetics of propanol-1. The curves represent means and confidence limits of the theoretical calculations; the vertical beams mark the distribution of the values found experimentally.

\[
y = c_0 \cdot e^{-k_1 \cdot t_1} \\
y = c_0 \cdot e^{-k_2 \cdot (0.5 \cdot t_1 + t_2)}
\]

\[
c_0 = \frac{\text{dose (mg)}}{\text{body weight} \cdot r} \quad k_1 = \frac{-\ln(1 - e^{-0.5 \cdot k_2 \cdot t_1})}{t_1} = 0.83 \text{(mean)} \quad k_2 = 0.21 \text{(mean)}
\]

\[
r_{\text{overweight}} = 0.6 \quad r_{\text{norm weight}} = 0.7 \quad r_{\text{underweight}} = 0.8 \quad t_1 = 2 \text{ hrs}
\]

Figure 7: Invasion and elimination kinetics of isobutanol.

\[k_1 = 0.63 \quad k_2 = 0.34 \text{ (means)} \quad r_0 = 1.5 \quad r_n = 1.3 \quad r_u = 1.1 \quad t_1 = 2 \text{ hrs}\]
Figure 8. The temporal relations of the ratios between conjugated and free alcohols in the urine.