Caffeine fatalities—four case reports

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Abstract

Four cases of fatal intoxications with caffeine are described. Caffeine is widely available in beverages and in different OTC-products, in many of them in combinations with other drugs like ephedrine. Caffeine is not as harmless as one might believe. An overdose of caffeine alone, intentional or not, might be deadly. It seems to be warranted to include caffeine in the drug-screening of forensic autopsy cases. It is not motivated from a medical point of view to sell pure caffeine over the counter.

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1. Introduction

Caffeine has been used as a pharmaceutical in the treatment of apnoea of premature infants, is a component in some analgesics and above all is used as a stimulant in a number of beverages. It is also an ingredient in "look-alike drugs" or healthfood products sold as appetite supressants [1].

Caffeine has long been recognized as an addictive substance. Numerous toxic effects have been described. Death due to caffeine overdose is considered rare and case reports of death from caffeine toxicity are not very frequent. However, over the years there have been a number of reports concerning deaths mainly due to intake of "look-alike drugs" containing caffeine [2–7].

Caffeine is a natural alkaloid methylxanthine. The pharmacodynamic profile of caffeine is similar to that of theophylline, another methylxanthine. Both block the adenosine receptor, which is considered to be the mechanism of action in concentrations normally reached [8] and act as a phosphodiesterase inhibitor. Caffeine increases the intracellular calcium concentration, causes noradrenaline release and sensitises dopamine receptors [1]. The resulting pharmacological effects of caffeine include central nervous system and cardiac stimulation.

The toxic effects of caffeine include vomiting, abdominal pain and CNS symptoms, including agitation, altered conscious state, rigidity and seizures. The cardiovascular effects include supraventricular and ventricular tachyarrhythmias.

The direct cause of death is often described to be ventricular fibrillation. It has been shown in anesthetized rats that ventricular fibrillation accounts for the lethal outcome of caffeine poisoning [9].

In humans a blood concentration greater than 100 $\mu$g/ml is considered lethal [10,11].

In this paper we report four fatal intoxications with caffeine which we have seen during the last year. In Sweden 95\% of all autopsies in forensic medicine are routinely screened for alcohol and about 150 different substances, mainly pharmaceuticals.

2. Materials and methods

At the autopsy blood from the femoral vein was collected and potassium fluoride was added as a preservative to a concentration of 1–2\%. The samples were stored at +4 °C until analysed. Ethanol was analysed in duplicate by head-space gas-chromatography and the mean value was reported. The limit of quantification was 0.10 mg/ml. Drugs including caffeine were analysed by capillary gas-chromatography with a nitrogen specific detector as described in detail previously [12]. Ephedrine was analysed...
by a massspectrometric method after alkaline extraction with ethyl-acetate and derivatization with trifluoroaceticaid-anhydrid. D8-methamphetamine was used as internal standard and the ions monitored for quantification were m/z 154 for the internal standard and m/z 154 for ephedrine with m/z 118 and 110 as qualifier ions.

3. Case reports

3.1. Case 1

A 54-year-old male was found dead at a nursing home where he was living. He was known as an ethanol and drug abuser and suffered from schizophrenia and hepatitis C. In the morning the same day as he was found dead he had bought 250 caffeine tablets (100 mg) at the pharmacy and 150 tablets were remaining. At the autopsy chronic hepatitis, chronic pulmonary emphysema and coronary artery sclerosis were found.

3.2. Case 2

A 21-year-old male was found dead in his home. He was recently discharged from a psychiatric clinic and had previously tried to commit suicide at four different occasions and he had been a drug abuser for about 6 years. The same day as he was found dead he had bought two boxes of 100 pills caffeine, 100 mg, which were empty when he was found. A suicide note was also found at the scene. At the autopsy no histopathological examination was performed.

3.3. Case 3

This 31-year-old male was found dead in his home shortly after his return to the country after 1 year work abroad. Four years ago he tried to commit suicide with drugs. At the autopsy no pathological changes were detected even though putrefaction complicated the examination. In the stomach about 100 tablet residues were detected.

3.4. Case 4

A 47-year-old woman found dead on the floor in her home. She was known as an alcoholic and had previously suicide attempts. She had got 100 tablets of Letigen, a drug containing caffeine and ephedrine.

4. Results and discussion

The results from the toxicological analysis are summarized in Table 1 as well as the cause and manner of death according to the decision of the responsible forensic pathologist. Ethanol was not detected in any of the cases and caffeine was the only drug in case 3. In the other cases, high concentrations of orphenadrine (2.2 µg/g) in femoral blood and therapeutic concentrations of thioridazine (1.1 µg/g) were found in case 1, and in case 4 a high concentration of ephedrine (4.8 µg/g) was detected in femoral blood. In case 2 therapeutic concentrations of venlafaxine and its metabolite O-desmethylvenlafaxine with femoral blood concentrations of 0.5 and 0.1 µg/g, respectively, were found.

We describe four cases were caffeine was found in concentrations considered lethal. In two of the cases the manner of death was suicide according to the forensic pathologist. In the other two cases the manner of death is considered uncertain. In one of the cases Letigen was taken, that is an anorectic drug used in Denmark, from which death due to intake of the drug has been reported earlier [5,7]. In the case described here the drug was bought in Denmark. In Sweden caffeine is sold as an OTC-product, containing

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Toxicological results⁴</th>
<th>Cause of death</th>
<th>Manner of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>54</td>
<td>M</td>
<td>Ethanol negative</td>
<td>Intoxication by caffeine</td>
<td>Uncertain</td>
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<tr>
<td></td>
<td></td>
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<td>173 caffeine</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>2.2 orphenadrine</td>
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<td></td>
<td></td>
<td></td>
<td>1.1 thioridazine</td>
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</tr>
<tr>
<td>2</td>
<td>21</td>
<td>M</td>
<td>Ethanol negative</td>
<td>Intoxication by caffeine</td>
<td>Suicide</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>210 caffeine</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>0.5 venlafaxine</td>
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<td></td>
<td></td>
<td>0.1 O-desmethylvenlafaxine</td>
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<tr>
<td>3</td>
<td>31</td>
<td>M</td>
<td>Ethanol negative</td>
<td>Intoxication by caffeine</td>
<td>Suicide</td>
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<td></td>
<td>153 caffeine</td>
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<tr>
<td>4</td>
<td>47</td>
<td>F</td>
<td>Ethanol negative</td>
<td>Intoxication by caffeine</td>
<td>Uncertain</td>
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<td>200 caffeine</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>4.8 ephedrine</td>
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</tbody>
</table>

⁴ Concentrations in µg/g femoral blood.
100 mg tablets in boxes of 100 or 250 pills. In the two suicidal cases the victims had bought the tablets in order to commit suicide. The lethal blood level is considered to be 80–100 µg/g blood, which corresponds to an intake of 50–100 tablets. For comparison it can be mentioned that a cup of coffee contains about 100 mg caffeine. In three of the cases other substances were found. In the case with Letigen ephedrine was found, which is the other component of this product. There are number of interactions described for caffeine [13], mainly via the enzyme CYP1A2 which metabolises caffeine to paraxanthine but also a number of pharmaceuticals, however none of the substances found in our cases seems to interact with caffeine.

Caffeine is well absorbed following oral administration and peak plasma levels is considered to be reached within 15–45 min. This means that the toxic effects after an overdose will appear quickly.

The pharmacokinetics of caffeine is dose-dependent, at high serum levels elimination follows zero-order kinetics. In adults the half-life is said to be 5 h after a dose of 250–500 mg [14]. This means that the half-life after an overdose will be considerably longer. The plasma level after a cup of coffee is around 1–2 µg/g blood as compared to 150–200 in our cases. In autopsy cases we only report concentrations above 10 µg/g. During 2002 we found caffeine above this limit in 58 cases (the cases reported here excluded) out of 4500 cases analysed. The mean concentration was 14.4 µg/g with a range from 10 to 37. The toxic effects of caffeine include vomiting and abdominal pain and CNS symptoms, including agitation, altered conscious state, rigidity and seizures. The cardiovascular effects include supraventricular and ventricular tachyarrhythmias.

The direct cause of death is often described to be ventricular fibrillation.

The conclusion is that it is important to remember that an overdose of tablets containing caffeine cause fatal intoxications, it is used for intentional suicide but there are also cases where accidental intoxications must be suspected. The latter seems to be the case when so-called look-alike drugs are used. Caffeine has some characteristics that makes it more risky than usually considered. It is easy to obtain, the effect is quick, the pharmacokinetics is dose-dependent and there are interactions with pharmaceuticals among them antidepressants, that substantially raise the plasma level of caffeine after concomittant intake [15]. Reports of caffeine intoxications are not very frequent. Four cases during 1 year in Sweden is notable and it seems justified to include caffeine in the routine screening at a forensic toxicology laboratory. One might question whether pure caffeine should be so easily accessible. It is hardly motivated from a medical point of view.

References