Comparison of fatal poisonings by prescription opioids

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ABSTRACT

There is a rising trend of fatal poisonings due to medicinal opioids in several countries. The present study evaluates the drug and alcohol findings as well as the cause and manner of death in opioid-related post-mortem cases in Finland from 2000 to 2008. During this period, fatal poisonings by prescription opioids (buprenorphine, codeine, dextropropoxyphene, fentanyl, methadone, oxycodone, tramadol) increased as a share of all drug poisonings from 9.5% to 32.4%, being 22.3% over the whole period. A detailed study including the most prevalent opioids was carried out for the age group of 14–44 years, which is the most susceptible age for drug abuse in Finland. Poisonings by the weak opioids, codeine and tramadol, were found to be associated with large, often suicidal overdoses resulting in high drug concentrations in blood. Methadone poisonings were associated with accidental overdoses with the drug concentration in blood remaining within a therapeutic range. The manner of death was accidental in 43%, 55% and 94% of cases in codeine, tramadol and methadone poisonings, respectively. The median concentration of codeine and the median codeine/morphine concentration ratio were higher in codeine poisonings (1.4 and 22.5 mg/l, respectively) than in other causes of death (0.09 and 5.9 mg/l, respectively). The median concentrations of tramadol and O-desmethyltramadol were higher in tramadol poisonings (5.3 and 0.8 mg/l, respectively) than in other causes of death (0.6 and 0.2 mg/l, respectively). In methadone poisonings, the median concentration of methadone (0.35 mg/l) was not different from that in other causes of death (0.30 mg/l). Sedative drugs and/or alcohol were very frequently found in fatal poisonings involving these prescription opioids.

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1. Introduction

Strong opioids, such as buprenorphine, fentanyl, methadone, morphine and oxycodone, are used against severe pain as well as in opioid maintenance treatment, whereas weak opioids, such as codeine, propoxyphene and tramadol, are used against mild to moderate pain. Opioids are frequently associated with fatal poisonings due to their ability to cause oversedation and respiratory depression. Internationally, heroin has continuously been a major opioid drug of abuse, and mortality is steadily high among those who inject heroin [1–3]. However, in several countries there is an increasing trend of fatal poisonings due to medicinal opioids [2,4–6]. This phenomenon has caused special concern in the United States [7].

Interpretation of opioid blood concentrations within forensic toxicology is not straightforward since the therapeutic and toxic concentrations of most opioids overlap completely [8]. The magnitude of opioid effect and the outcome of poisoning depend on a multitude of factors, such as tolerance, concomitant central nervous system depressant drug use, route of intake, central sleep apnoea, and circumstantial and environmental factors, such as whether the person is physically active or with other people vs. alone without help if an adverse reaction occurs [5,9,10]. Fatal opioid poisonings have been especially associated with the concomitant use of benzodiazepines and alcohol [10,11].

Numerous individual reports have been published on fatal opioid poisonings, but the stress has been on illicit drugs, especially heroin, while data on prescription opioids is scarcer [12,13]. The post-mortem toxicology profiles of common prescription opioids have not been thoroughly investigated. Furthermore, if only obvious cases of poisoning are included, as is usual in case notes and smaller case series, the results may show a bias towards higher opioid blood concentrations. Such studies seldom allow for comparison of findings between poisonings and other causes of death, which is a crucial question in cause-of-death investigations.

In our previous paper [10], we studied buprenorphine-related deaths, taking advantage of the high medicico-legal autopsy rate [14] and the comprehensive post-mortem toxicology database generated in Finland [15]. In the present study, we analyse post-mortem cases involving other prevalent prescription opioids such as codeine, methadone and tramadol and compare these findings to buprenorphine using the same primary data. We include all opioid-positive subjects registered in the database from 2000 to 2008. For the age group of 14–44 years, we divide the data into two
groups, opioid poisonings and opioid-related cases with other primary causes of death, and elaborate these two groups in terms of blood concentrations, age, gender and the manner of death.

2. Material and methods

2.1. Data collection

In Finland, approximately 50,000 deaths occur yearly, and a medico-legal autopsy is performed when death has been sudden and unexpected. Deaths related to accidents, crime, poisoning, suicide, occupational illness or medical procedures are always investigated by a forensic pathologist. All post-mortem toxicology samples taken at autopsy—over 6000 per year—are analysed in our laboratory. Our data consisted of all deaths in Finland in which a case was registered and a comprehensive post-mortem toxicological analysis performed in 2000–2008. During the study period, toxicological analyses were performed on 53,328 subjects, of which 40,020 were men. The subgroup of 14–44-year-olds was chosen to focus on the group most susceptible to drug abuse. This group comprised 12,891 cases (10,182 men), and one or several opioids were detected in 1363 cases (1103 men). Children under 14, of which there were 15 cases, were excluded because the primary cause of death was disease or accident in each case and all had been treated with opioids without intentional drug abuse. The youngest opioid abuser in our data was 14 years old.

The post-mortem database included a forensic pathologist’s referral, laboratory analysis results, and information extracted from the death certificate issued by a forensic pathologist. The referral contained a brief description of the circumstances of death and the main autopsy findings. The laboratory data contained analysis results for opioids, benzodiazepines, alcohol and other drugs. Information from the final death certificate included the age and gender of the deceased as well as the cause of death and contributory factors according to the International Classification of Diseases (ICD-10) and the manner of death (World Health Organisation, WHO).

A case was classified as an opioid poisoning if a forensic pathologist had determined in the death certificate the cause of death as poisoning of a particular opioid. In other opioid-related cases, one of the opioids was found but the cause of death was other than poisoning by the opioid.

2.2. Data restrictions

Only such cases were included in which an opioid had been identified in post-mortem femoral blood. Consequently, fatal opioid poisonings in which the cause of death was based on opioid findings in specimens other than post-mortem blood, such as urine or antemortem hospital serum, were excluded.

Heroin poisonings were excluded when calculating codeine/morphine ratios and morphine concentrations, because in heroin poisonings high morphine concentrations primarily implicate heroin rather than codeine use.

2.3. Toxicological analysis

Comprehensive toxicological analysis of blood and urine samples was performed using a multi-technique approach as described earlier [10].

2.4. Statistical analysis

Medians were used as summary statistics of the data, because the concentration distributions of the opioids and benzodiazepines were skewed. The significance levels of the differences between the medians were calculated using the Mann–Whitney test. When comparing several groups, for example to determine differences between manners of death in opioid poisonings and other causes of death, a Kruskall–Wallis test was applied. SPSS 15.0 was used for statistical analysis.

3. Results

The number of fatal poisonings by prescription opioids has increased in Finland. Fig. 1 shows the number of fatal prescription opioid and heroin poisonings during 2000–2008. The number of fatal heroin poisonings has decreased to almost zero, while the proportion of fatal prescription opioid poisonings out of all fatal drug poisonings has increased from 9.5% (52 cases) in 2000 to 32.4% (179 cases) in 2008, being 22.3% over the whole period.

Table 1 shows a comparison between fatal poisonings and other causes of death for codeine, tramadol, methadone and the previously reported buprenorphine [10] in terms of case characteristics and toxicological findings in the age group of 14–44 years. Table 2 shows a corresponding comparison in terms of median drug concentrations and parent drug to metabolite ratios in blood.

In codeine poisonings, the manner of death was accident in 43.2%, suicide in 39.9%, unclear in 16.2% and disease in 0% of cases, while in other causes of death the figures were 36.0%, 28.0%, 10.8% and 24.4%, respectively. The differences in manner of death between codeine poisonings and other causes of death were not significant. The median concentration of codeine and the median codeine/morphine concentration ratio were higher in poisonings than in other causes of death. Fig. 2 shows that the distribution of codeine concentrations and codeine/morphine concentration ratios in codeine poisonings was flat, whereas the lowest codeine concentrations and lowest codeine/morphine concentration ratios were predominant in other causes of death. There were no single-drug codeine poisonings. Benzodiazepines were found more frequently and other opioids less frequently in codeine poisonings than in other causes of death.

In tramadol poisonings, the manner of death was accident in 54.8%, suicide in 31.3%, unclear in 13.9% and disease in 0% of cases.

Table 1

<table>
<thead>
<tr>
<th>Opioid poisonings</th>
<th>Codeine</th>
<th>Tramadol</th>
<th>Methadone</th>
<th>Buprenorphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poisons (%)</td>
<td>146 (40.6)</td>
<td>117 (33.6)</td>
<td>48 (47.1)</td>
<td>182 (46.5)</td>
</tr>
<tr>
<td>Mean age (year)</td>
<td>32</td>
<td>29</td>
<td>30</td>
<td>27</td>
</tr>
<tr>
<td>Suicides (%)</td>
<td>39.9</td>
<td>31.3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Other opioids detected (%)</td>
<td>15.1</td>
<td></td>
<td></td>
<td>18.8</td>
</tr>
<tr>
<td>Benzodiazepines detected (%)</td>
<td>85.8</td>
<td></td>
<td></td>
<td>85.5</td>
</tr>
<tr>
<td>1 benzodiazepine (%)</td>
<td>25.7</td>
<td>34.2</td>
<td>33.3</td>
<td>31.3</td>
</tr>
<tr>
<td>≥2 benzodiazepines (%)</td>
<td>60.2</td>
<td></td>
<td></td>
<td>51.3</td>
</tr>
<tr>
<td>Alcohol ≥0.5% detected (%)</td>
<td>37.7</td>
<td></td>
<td></td>
<td>14.5</td>
</tr>
<tr>
<td>Alcohol or BDZ detected (%)</td>
<td>93.8</td>
<td></td>
<td></td>
<td>89.6</td>
</tr>
</tbody>
</table>

† Significant higher percentage, p < 0.05.
‡‡ Significant higher percentage, p < 0.001.
BDZ = benzodiazepines.
* Data reported in [10].
while in other causes of death the figures were 31.3%, 34.3%, 7.7% and 23.2%, respectively. The differences in manner of death between tramadol poisonings and other causes of death were not significant. The median concentrations of tramadol and O-desmethyltramadol were higher in poisonings than in other causes of death. Fig. 3 shows that the distribution of tramadol concentrations in tramadol poisonings was flat, whereas the lowest tramadol concentrations were predominant in other causes of death. The distribution of O-desmethyltramadol showed less difference between tramadol poisonings and other causes of death. There were three cases of single-drug tramadol poisoning, with tramadol and O-desmethyltramadol concentrations of 1.6 mg/l and 0.6 mg/l; 2.4 mg/l and 0 mg/l; and 8.1 mg/l and 1.5 mg/l, respectively. Benzodiazepines were found more frequently and alcohol less frequently in tramadol poisonings than in other causes of death.

In methadone poisonings, the manner of death was accident in 93.8%, suicide in 0%, unclear in 6.3%, and disease in 0% of cases, while in other causes of death the figures were 53.7%, 14.8%, 3.7%, and 25.9%, respectively. The differences in manner of death between methadone poisonings and other causes of death were significant. In methadone poisonings, the median concentration of methadone was not different from that in other causes of death. There were no single-drug methadone poisonings. Fig. 4 shows that the distribution of methadone concentrations in methadone poisonings was similar to that in other causes of death.

4. Discussion

The disappearance of heroin from the Finnish drug scene after the outbreak of the Afghan war in 2001 can be clearly seen in Fig. 1. However, contrary to most other countries, heroin never came
In tramadol poisonings, the median concentration of tramadol (5.3 mg/l) and its metabolite O-desmethy tramadol (0.8 mg/l) were significantly higher than in other causes of death (0.6 and 0.2 mg/l, respectively), but the tramadol/O-desmethyltramadol ratio did not differ significantly. This finding suggests a longer survival time in tramadol poisonings compared to codeine poisonings, related to the fact that the elimination half-life of O-desmethyltramadol is longer than that of tramadol. Previous studies with well defined data have reported median tramadol concentrations of 0.5–850 mg/l in accidental tramadol poisonings [17], and 1.4 g/l in poly-drug poisonings [24]. In previous studies, benzodiazepines have been present in tramadol-related poisonings in 47% [17] and 33% [27] of cases. Additional opioids have been found in as many as 53% [17] and 67% [27] of cases. In our study, however, the number of benzodiazepine findings was remarkably higher and the number of additional opioid findings remarkably lower.

In methadone-related cases, there was no significant difference in median methadone concentrations between methadone poisonings (0.35 mg/l) and other causes of death (0.30 mg/l). Previous studies with well defined data have reported median methadone concentrations of 0.3 mg/l in single-drug poisonings [23], 0.4 mg/l in poly-drug poisonings [24], and 0.40 mg/l in cases of drug poisoning [23]. These results are quite consistent with our findings. Fatal poisonings seem to be very seldom caused by codeine alone [23–25]. In codeine-related poly-drug poisonings, benzodiazepines have been previously found in 75% and opioids other than codeine or morphine in 20% of cases [25], which is roughly comparable to our results.

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significant role in drug-related deaths than, for example, in other Nordic countries [16].

5. Conclusions

The profile of fatal poisonings by codeine and tramadol differed from that by methadone as well as that previously reported for buprenorphine [10] in many respects. Firstly, there were noticeable differences in the manner of death, showing evidence of very few suicides by methadone and buprenorphine as opposed to tramadol and codeine. Secondly, the evidence provided by post-mortem blood concentrations used for cause-of-death determination varied between the opioids studied. Codeine poisonings could be well distinguished from other causes of death based on a high codeine concentration, and tramadol poisonings could be distinguished based on high tramadol and O-desmethyltramadol concentrations. Methadone and buprenorphine poisonings, on the other hand, could not be distinguished from other causes of death by the respective parent opioid concentrations in blood. However, we found the parent drug/metabolite ratios in blood were especially useful in distinguishing codeine, tramadol and buprenorphine [10] poisonings from other causes of death. Thirdly, benzodiazepines were involved in fatal poisonings by codeine and tramadol, whereas neither benzodiazepines nor alcohol could be specifically associated with methadone poisonings in this study. As reported earlier, both benzodiazepines and alcohol have been involved in buprenorphine poisonings [10].

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References