Serious overdoses involving buprenorphine in Helsinki

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Background: Buprenorphine is used as maintenance therapy for opioid-dependent patients. In comparison with other opioids it is thought to be safer because it is less likely to cause serious respiratory depression. However, concomitant use of psychotropics, especially benzodiazepines, and intravenous injection of dissolved buprenorphine tablets increase the risk of a serious overdose.

Methods: As part of a larger retrospective study of opioid overdoses in Helsinki, the emergency medical services (EMS) records from January 1995 to April 2002 were reviewed for overdoses involving buprenorphine. Hospital records were reviewed when available.

Results: We report 11 overdoses in which buprenorphine was involved. The classic symptoms and signs of an opioid overdose (respiratory depression, miosis and central nervous system depression) were present in most of the cases. At least eight of the patients had an overdose that was potentially fatal. One of the patients had a heroin overdose and was reportedly ‘treated’ by his friends with intravenously administered buprenorphine.

Conclusion: The high-dosage formulation of buprenorphine used for opioid-dependent patients might have caused several dangerous and potentially fatal overdoses in Helsinki. However, it does cause considerably less serious overdoses than heroin. Drug abusers might be intravenously administering buprenorphine themselves to treat heroin overdoses.

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Key words: Buprenorphine; EMS; overdose.

Deaths involving an overdosage of buprenorphine have been reported infrequently outside of France (1–3). In all but two of the 137 cases of fatal overdoses recorded in France, other drugs, most often benzodiazepines, had also been taken (1, 2). Another well-recognized risk factor in these patients was the use of crushed tablets injected intravenously (1, 2). The high-dosage oral buprenorphine formulation (Subutex®; 0.4-, 2- and 8-mg sublingual tablets) has been available in France since 1996 as maintenance therapy for opioid dependency (1, 2). With the illegal import of buprenorphine tablets, accidental overdoses of buprenorphine could also become more frequent in other countries. We report 11 cases of buprenorphine overdosage in Finland from January 1996 to April 2002.

Methods

As part of a larger retrospective study of opioid overdoses in Helsinki, the EMS records from January 1995 to April 2002 were reviewed manually case by case. Records of patients who either had classic symptoms and signs of an opioid overdose (respiratory depression, miosis and central nervous system depression) and/or reported opioid use were retrieved, and of those, patients with reported involvement of buprenorphine and a Glasgow Coma Score (GCS) of 8 or less and/or signs of respiratory depression (cyanosis, breath rate less than 12/min, respiratory pauses or/and decreased peripheral oxygen saturation) were included in the study. Hospital records were retrieved and reviewed when available. Information on what drugs were used was based on the oral report of the patient or his/her friends or relatives. There was no toxicological conformation for the role of buprenorphine. Approval of the Ethics Committee and the Head of Department was sought for the study.

Results

The records of 308 patients were retrieved. The majority of the cases were heroin overdoses and buprenorphine was involved in 12 of the cases. One of the patients was excluded because he had a GCS of 11.
and no clear signs of respiratory depression. One of the patients (no. 4) was included because he was reportedly given buprenorphine (Subutex™) intravenously after going into respiratory arrest following intravenous heroin use.

Six of the buprenorphine overdosages occurred in the year 2000 and two in the year 2001, and one case was found each in the years 1996, 1997 and 2002. Of the 11 patients, all but one (case 1, in 1996) were male. The median age of the patients was 24 years (range 20–30 years). In the first two cases, the preparation used was Temgesic®, and since the year 2000, only Subutex® overdoses were recorded. The clinical findings and the efficacy of naloxone administration are presented in Table 1. Buprenorphine had been used intravenously in seven cases and by the oral route in one of the cases; in the remaining three cases, no information was available. There was concomitant use of benzodiazepines in three cases, ethanol in four and heroin in two.

The median dose of naloxone was 0.4 mg (range 0.2–0.8 mg). Three of the patients did not require naloxone for treatment of their overdose (patients 4, 9 and 10) but received a dose of naloxone before they were left at the scene. Only one of the patients did not respond to naloxone administration (patient number 3). He was intubated and transported to an emergency department (ED) for further observation and treatment. Three of the patients were sedated or disoriented after naloxone administration (patients 2, 7 and 11) and were also transported to an ED. Patient number one was transported purely because of the custom of that time of transporting all opioid overdose patients to an ED.

### Discussion

Buprenorphine, especially the high-dosage formulation meant for the treatment of opioid dependency, seems to have a role as a drug of abuse in Helsinki. There has been an increase in the number of buprenorphine overdoses since 2000. In accordance with previous studies (1, 2), in most of the cases there was concomitant use of other central nervous system depressing drugs and/or ethanol and intravenous use of crushed sublingual tablets. One of our patients was treated by a friend with intravenous buprenorphine after a heroin overdose, which had lead to respiratory depression. To our knowledge, such initiative has not been reported earlier.

The present report is part of a retrospective study on opioid overdoses in Helsinki (manuscript in preparation). Shortly, in 1995 the Helsinki EMS treated nine patients with an opioid overdose, and in 2000 the number of overdoses was 111. At the time, seven of the patients had reported involvement of buprenorphine, and in 2001 there were 49 heroin, two buprenorphine and one opium overdose.

According to Kintz (2), fatal overdoses caused by the high-dosage formulation of buprenorphine have not been published outside France, although buprenorphine is also known to be abused by addicts in other countries (4–6). In this study we did not find any deaths caused by buprenorphine, but several potentially fatal overdoses were found. However, much of our data about the drugs involved in the overdoses were based on the information provided by the patients or their friends or relatives, and plasma concentrations of buprenorphine were not analyzed. When considering the patient population, users of illicit drugs, it is possible that the information we

### Table 1

<table>
<thead>
<tr>
<th>#</th>
<th>Year</th>
<th>Benzo</th>
<th>Ethanol</th>
<th>Heroin</th>
<th>Other</th>
<th>GCS</th>
<th>Respiration</th>
<th>Miosis</th>
<th>Naloxone (mg)</th>
<th>GCS</th>
<th>Respiration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1996</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>no</td>
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<td>cyanotic</td>
<td>yes</td>
<td>0.4</td>
<td>15</td>
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<tr>
<td>2</td>
<td>1997</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>3</td>
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<td>yes</td>
<td>0.48</td>
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<tr>
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<td>yes</td>
<td>no</td>
<td>no</td>
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<td>cyanotic</td>
<td>yes</td>
<td>0.8</td>
<td>3</td>
<td>assisted</td>
</tr>
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<td>4</td>
<td>2000</td>
<td>no</td>
<td>no</td>
<td>yes</td>
<td>heroin overdose</td>
<td>15</td>
<td>resp. rate 12/min</td>
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<td>0.2</td>
<td>15</td>
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</tr>
<tr>
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<td>2000</td>
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<td>no</td>
<td>no</td>
<td>no</td>
<td>3</td>
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<td>yes</td>
<td>0.8</td>
<td>15</td>
<td>normal</td>
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<tr>
<td>6</td>
<td>2000</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>8</td>
<td>low SpO2 %</td>
<td>yes</td>
<td>0.4</td>
<td>15</td>
<td>normal</td>
</tr>
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<td>2000</td>
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<td>yes</td>
<td>no</td>
<td>no</td>
<td>3</td>
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<td>14</td>
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<tr>
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<td>2000</td>
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<td>no</td>
<td>yes</td>
<td>no</td>
<td>14</td>
<td>resp. pauses</td>
<td>NA</td>
<td>0.4</td>
<td>15</td>
<td>normal</td>
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<tr>
<td>9</td>
<td>2001</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>14</td>
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<td>NA</td>
<td>0.4</td>
<td>15</td>
<td>normal</td>
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<tr>
<td>10</td>
<td>2001</td>
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<td>NA</td>
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<td>NA</td>
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<td>0.4</td>
<td>15</td>
<td>normal</td>
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<tr>
<td>11</td>
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<td>no</td>
<td>moclobemide, fluoxetine?</td>
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<td>resp. rate 18/min</td>
<td>yes</td>
<td>0.8</td>
<td>12</td>
<td>normal</td>
</tr>
</tbody>
</table>

GCS = Glasgow Coma Score; NA = not applicable.
received was false, because sometimes even the users themselves do not know the exact nature of the substances they use. The naloxone doses that were required seemed to be rather small. Even the highest dose of naloxone used (0.8 mg) is modest considering it should produce only partial reversal, even with doses as high as 2.4–16 mg (7).

Most of our patients had reportedly used crushed buprenorphine tablets intravenously along with other drugs, mainly benzodiazepines, and/or ethanol. Two of our patients had used heroin and buprenorphine concomitantly. These findings are in accordance with the fatal overdoses recorded in France 1996–2001 (1, 2). There were 27 cases of simultaneous use of buprenorphine and other opioids (morphine, codeine, methadone, meperidine and propoxyphene) among the cases (1, 2). In the absence of other drugs and when the proper drug form (that intended for intravenous use) is used, intravenous buprenorphine appears to have a wide margin of safety (8). However, there seems to be an increased risk of respiratory depression with the concomitant use of buprenorphine and benzodiazepines, even at therapeutic doses (9–11). In addition to the pharmacodynamic interaction of buprenorphine and benzodiazepines, respiratory acidosis could increase the active buprenorphine release from tissue proteins (12).

One of the patients was reportedly given buprenorphine intravenously by his friends to reverse respiratory depression caused by a heroin overdose. This could delay the initiation of proper life-saving actions, such as cardiopulmonary resuscitation, or calling of the emergency dispatching center for help. Ultimately, this practice could prove to be fatal for the patient.

The number of buprenorphine overdosages peaked in the year 2000, 1 year after Subutex® became available for maintenance therapy of opioid addicts in Finland. However, this might be purely coincidental. Prior to the year 1999, it was legal to import Subutex® in small quantities for personal use.

In conclusion, the high formulation of buprenorphine used for opioid-dependent patients might have caused several potentially fatal overdoses in Helsinki. However, it does cause considerably less serious overdoses than heroin. Drug abusers might themselves be using intravenously administered buprenorphine tablets to treat heroin overdoses.

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