The first case involving repetitive sexual abuse linked to the use of buprenorphine is reported. Under the tradename Subutex®, buprenorphine is largely used for the substitution management of opiate-dependent individuals, but it can also be easily found on the black market. A 14-year-old boy was found dead at the home of a well-known sex offender of minors. At the autopsy, no particular morphological changes were noted, except for pulmonary and visceral congestion. There was no evidence of violence, and no needle marks were found by the pathologist. Toxicological analyses, as achieved by liquid chromatography–mass spectrometry, demonstrated both recent and repetitive buprenorphine exposure in combination with nordiazepam. Buprenorphine concentrations were 1.1 ng/mL and 23 pg/mg in blood and hair, respectively. The boy’s death was attributed to accidental asphyxia in a facilitated repetitive sexual abuse situation due to the combination of buprenorphine and benzodiazepines, even at therapeutic concentrations. The use of buprenorphine as a sedative drug was not challenged by the perpetrator.

Introduction

The use of a drug to modify a person’s behavior for criminal gain is not a recent phenomenon. However, the sudden increase in reports of drug-facilitated crimes (sexual assaults, robbery, etc.) has caused alarm in the general public. Drugs involved can be pharmaceuticals, such as benzodiazepines (e.g., flunitrazepam, lorazepam, etc.), hypnotics (e.g., zopiclone, zolpidem), sedatives (e.g., neuroleptics, some anti-H1), anesthetics [e.g., gamma-hydroxybutyrate (GHB), ketamine], drugs of abuse (e.g., cannabis, ecstasy, LSD), or more often ethanol. Most of these substances possess amnesic properties, and therefore, the victims are less able to accurately recall the circumstances under which the sexual offence occurred. As they are generally short-acting, they impair an individual rapidly. Because of their low dosage, except for GHB, a surreptitious administration into beverages such as coffee, soft drinks (cola), or, even better, alcoholic cocktails is relatively simple (1).

To perform successful toxicological examinations, the analyst must follow some important rules: 1. obtain as soon as possible the corresponding biological specimens (blood, urine, and hair); 2. use sophisticated analytical techniques [liquid chromatography–mass spectrometry (LC–MS), headspace gas chromatography–mass spectrometry (GC–MS), tandem MS]; and 3. take care on the interpretation of the findings. To address this problem, guidelines for toxicological investigations were published in both the United States (2) and France (3).

Urine analysis of drug use in cases of alleged sexual assault demonstrated in 3303 urine samples that ethanol, either alone or in combination with other drugs, was the most common substance found, followed by cannabis and benzodiazepines (4). In Paris, the largest study (5) conducted in France revealed that most frequently used drugs were benzodiazepines and related hypnotics. GHB was very seldom found. In our series at Strasbourg (6), zolpidem appears as the most common substance. A large number of drugs detectable in victims or suspected to have been used in drug-facilitated rapes has been identified (2–4). Among them, buprenorphine was never mentioned. A literature search for papers on “sexual assault or crime by buprenorphine” cited in the Analytical Abstracts and Medline databases was unable to produce any citation, as searched in March 2003.

Buprenorphine is a semisynthetic opioid derivative, closely related to morphine which is obtained from thebaine after a seven-step chemical procedure. At low doses (typically 0.3 to 0.6 mg intravenous or intramuscular), buprenorphine is a powerful analgesic, 25–40 times more potent than morphine, with mixed agonist/antagonist activity on central receptors (7).

More recently, it has been also recognized as a medication of interest for the substitutive management of opiate-dependent individuals. Under the tradename Subutex, a high-dosage formulation (0.4-, 2-, and 8-mg tablets for sublingual use) has been available in France since February 1996 in this specific indication. Contrary to methadone, delivered on a daily basis in specific centers and continuous survey of the patient by urine analysis achieved each week, Subutex may be ordered by any physician up to 28 days, and is supplied by any pharmacist. Today, this drug is largely used in France for the treatment of about 80,000–90,000 heroin addicts, but it can also be easily found on the black market.
We present here a case where buprenorphine was used to induce sedation to obtain nonconsensual sexual activity, resulting in the accidental death of the victim by respiratory failure.

Case History

A 14-year-old Caucasian boy was found dead at the home of a well-known child sex offender. According to the police report, this was not the first time the boy was seen around his apartment. A blister of Subutex was discovered on the scene. The autopsy, performed a day later, revealed signs of asphyxia (e.g., cyanosis, multivisceral congestion, pulmonary edema, etc.), but showed no signs of violence. No other cause of death could be established by the pathologist. Postmortem samples, including femoral blood, urine, bile, stomach contents, and hair (2 cm), were collected for toxicological analysis. Several weeks after death, when presented with the results of hair analysis, the rapist admitted repetitive administration over a prolonged period of weeks of both buprenorphine and clorazepate to induce sedation in order to achieve sexual abuse.

Materials and Methods

Buprenorphine and norbuprenorphine were assayed in postmortem specimens by using a high-performance liquid chromatographic–mass spectrometric (HPLC–MS) procedure (8).

Briefly, 3 mL blood or urine or 1 mL hydrolyzed bile or stomach contents was extracted at pH 8.4 with 5 mL of chloroform/2-propanol/heptane (25:10:65, v/v) (CPH) after addition of 15 ng of deuterated standards, buprenorphine-d4 and norbuprenorphine-d3. After neutralization with NaOH, the solubilization medium was extracted using 5 mL of the same ternary solvent, followed by the same extraction process as for biological fluids.

In addition to buprenorphine specific analysis, a complementary screening of the postmortem blood and urine was performed using immunoassays (FPIA), UV spectrophotometry (carbon monoxide), GC–flame-ionization detection (meprobamate, ethanol), headspace GC–nitrogen-phosphorus detection (cyanides), headspace GC–MS (usual organic solvents), and LC–diode-array detection + gas–liquid chromatography (GLC)–MS (pharmaceuticals, drugs of abuse).

Results

Buprenorphine and its metabolite, norbuprenorphine were formally identified and quantified in all samples tested. Concentrations are summarized in Table I. Blood analysis revealed recent buprenorphine exposure, with concentrations of 1.1 and 0.2 ng/mL for buprenorphine and norbuprenorphine, respectively.

Buprenorphine is characterized by a weak oral bioavailability and low therapeutic concentrations because of its high lipid solubility. Its main metabolite is desalkyl-buprenorphine or norbuprenorphine, and both drugs are glucuro-conjugated.

Following a single 0.4-mg sublingual dose, Bullingham et al. (9) reported plasma concentrations of buprenorphine in the range of 0.45 to 0.84 ng/mL. According to Kuhlman et al. (10), average peak plasma concentrations of 3.31 ng/mL (range 1.93–7.19 ng/mL) and 1.98 ng/mL (range 0.25–3.90 ng/mL) were observed for buprenorphine in six subjects given 4.0 mg sublingual and buccal, respectively.

The blood buprenorphine concentration in this case can therefore be considered as therapeutic.

Hair testing demonstrated repetitive exposure to the drug. Buprenorphine concentration was 23 pg/mg. Norbuprenorphine was not detected (LOD at 10 pg/mg). This can be considered as a low concentration (11,12), rather indicative of unfrequent administration. For example, Wilkins et al. (12) reported in subjects under treatment, concentrations ranging from 4.5 to 156.8 and 4.8 to 1438.5 pg/mg for buprenorphine and norbuprenorphine, respectively. However, it is not possible to determine the number of exposures. As no segmental analyses were performed, the window of buprenorphine exposure is linked to the length of the hair shaft that was tested. A 2-cm hair shaft was collected

<table>
<thead>
<tr>
<th>Specimen</th>
<th>Buprenorphine</th>
<th>Norbuprenorphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Femoral blood</td>
<td>1.1 ng/mL</td>
<td>0.2 ng/mL</td>
</tr>
<tr>
<td>Non-hydrolyzed urine</td>
<td>9.1 ng/mL</td>
<td>9.6 ng/mL</td>
</tr>
<tr>
<td>Hydrolyzed bile</td>
<td>575 ng/mL</td>
<td>&gt;1000 ng/mL</td>
</tr>
<tr>
<td>Stomach contents</td>
<td>47 ng/mL</td>
<td>–</td>
</tr>
<tr>
<td>Hair</td>
<td>23 pg/mg</td>
<td>Not detected</td>
</tr>
</tbody>
</table>

Table I. Postmortem Concentrations of Buprenorphine and its Metabolite
during autopsy, roughly corresponding to a period of growth of 2 months. From that, it can be concluded that hair findings support administration of buprenorphine, but it is not possible to put forth any further quantitative information.

Using GC–MS and negative chemical ionization, nordiazepam and its metabolite oxazepam were also detected with the following concentrations: 2.81 and 0.39 mg/L, and 5.23 and 0.08 ng/mg for femoral blood and hair, respectively. Blood concentration of nordiazepam can be considered as subtherapeutic.

In 1998, Tracqui et al. (13) attributed 20 fatalities to buprenorphine poisoning, even at therapeutic concentrations, as no other cause of death was obvious. These authors concluded that buprenorphine can be life-threatening without overdosage, when associated with psychotropic drugs (mostly benzodiazepines). Recent results, collected both in Strasbourg and several other centers in France confirm these preliminary findings (14,15).

The role of associated benzodiazepines had been previously emphasized in several clinical reports of severe, nonfatal respiratory depressions observed when giving buprenorphine to anesthetized patients (16). It is suggested that the CNS-depressant effects of buprenorphine may be synergistically potentiated by some benzodiazepines (otherwise almost harmless if taken alone). In 1999, Clement et al. (17) pointed out the potential risk of death when buprenorphine is administered along with benzodiazepines.

Police examinations revealed the following points: the boy was running away from his family home and was sometimes taken home by the offender. To make the boy vulnerable to sexual activity, he was administered a mixture of buprenorphine and benzodiazepine. The aim of these drugs was to induce sedation and to lower inhibitions. There was no intent to poison the boy, even in the case of repetitive administration. The perpetrator, who was not an heroin addict, was charged with accidental homicide due to the administration of a fatal combination of buprenorphine and benzodiazepine associated with a sexual crime.

**Conclusions**

In most cases involving drug-facilitated sexual assaults, ethanol, cannabis or benzodiazepines and related compounds, such as zolpidem are detected. In order for the victim to lose consciousness, these drugs are administered for their sedative properties. Although virtually any psychoactive compound may be used in drug-facilitated sexual assault, buprenorphine, an opioid derivative, was never described in such a crime. We have presented here a case involving this drug, proposed as an analgesic or for the substitutive management of heroin-dependent individuals. It was used to incapacitate the victim, rendering him more vulnerable to sexual activity. Unfortunately, as in drug addicts, a fatal combination with nordiazepam resulted in a fatal respiratory depression. It appears that, because buprenorphine has high potential on the black market, this drug must also be screened for in cases of sexual crimes.

**References**