A new series of 13 buprenorphine-related deaths

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Abstract

Objectives: Buprenorphine at high dosage became available in France in 1996, as a substitution treatment for heroin addicts. Since this date, numerous deaths were attributed to this drug. This paper reports a new series of 13 fatalities involving buprenorphine observed at the Institute of Legal Medicine of Strasbourg, between August 2000 to October 2001.

Design and methods: During the mentioned period, about 800 forensic cases were screened at the laboratory. Buprenorphine and its primary metabolite norbuprenophine were assayed in postmortem specimens by HPLC/MS. From these 13 subjects, 11 were male. Blood levels ranged from 0.3 to 7.7 ng/mL (mean 3.5 ng/mL) and 0.3 to 16.2 ng/mL (mean 2.9 ng/mL) for buprenorphine and norbuprenorphine, respectively. The mean values appear to be within the therapeutic range.

Conclusions: IV injection of crushed tablets, a concomitant intake of psychotropics (especially benzodiazepines and neuroleptics) and the high dosage of the buprenorphine formulation available in France appear as the major risk factors for such fatalities. © 2002 The Canadian Society of Clinical Chemists. All rights reserved.

Keywords: Buprenorphine; Poisoning; Death; Substitution program; LC; MS

1. Introduction

Since its inception as an opiate substitute, methadone and its use has been plagued by bad reputation, insufficient places in programs, at least in France, and inadequate supervision facilities in many existing clinical practices. As a result, there has been a great need for alternative pharmacotherapies for opioid dependence.

Buprenorphine is a semisynthetic opioid derivative, closely related to morphine which is obtained from thebaine after a 7-step chemical procedure. At low doses (typically 0.3–0.6 mg IV or IM), buprenorphine is a powerful analgesic, 25 to 40 times more potent than morphine, with mixed agonist/antagonist activity on central receptors [1].

Under the tradename Temgesic® at dosages of 0.2 mg, buprenorphine has been widely prescribed for about 20 yr for the treatment of moderate to severe pain as well as in anesthesia for the premedication and/or anesthetic induction.

More recently it has been also recognized as a medication of interest for the substitutive management of opiate-dependant individuals. Under the tradename Subutex®, a high-dosage formulation (0.4, 2, and 8-mg tablets for sublingual use) is 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. Patients are not required to take the drug in presence of the physician or pharmacist. Buprenorphine has been proposed as a valuable substitution agent and a possible alternative to methadone because it has been shown to have a safer profile (less respiratory depression and sedation) and weaker withdrawal symptoms following abrupt discontinuation.

Today, this drug is largely used in France for the treatment of about 60 to 80 000 heroin addicts, but can also be easily found on the black market.

Since the first fatality observed by Tracqui et al. [2] in August 1996, several cases were recorded by the French toxicologists. In 1998, Tracqui et al. [3] published a series of 20 fatalities collected from 5 French laboratories. In all cases but one, a concomitant intake of psychotropics (mostly benzodiazepines) was observed.

More recently, a paper presented the results of a new retrospective survey on buprenorphine-related deaths in the

Besides other sources of information (drug enforcement services, customs, intensive care units . . . ), the epidemiologic data collected from forensic toxicologists may be of value to follow the evolution of narcotic deaths in the course of time.

It clearly appears that the total number of buprenorphine-related deaths is largely underestimated by the official statistics, leading to a false conclusion that buprenorphine is a safe alternative to methadone [5].

2. Design and methods

2.1. Autopsy findings

Thirteen from about 800 postmortem examinations at the laboratory of toxicology from the Institute of Legal Medicine of Strasbourg were positive for buprenorphine in blood during the mentioned period. In all cases, autopsies revealed signs of asphyxia (cyanosis, multivisceral congestion, pulmonary edema . . .) but showed no signs of violence. No other cause of death could be established by experienced pathologists.

2.2. Toxicological analyses

Buprenorphine and norbuprenorphine were assayed in postmortem blood by using an HPLC/MS procedure [6]. Briefly, 3 mL blood were extracted at pH 8.4 × 5 mL of chloroform/2-propanol/n-heptane (25:10:65, v/v) (CPH) after addition of 15 ng of buprenorphine-d₄ and norbuprenorphine-d₃, (Promochem, Molsheim, France). After agitation and centrifugation, the organic phase was removed. After evaporation, dry extracts were resuspended in 25 μL methanol, from which 5 μL were injected onto a 4-μm NovaPak (Waters, Milford, MA) C18 column (150 × 2.0 mm, i.d.).

Reversed-phase separation was achieved in 10 min, using a linear gradient of acetonitrile (ACN)/2 mM NH₄COOH buffer, pH 3.0 (ACN 50–85% in 10 min). The detection was carried out on a Perkin-Elmer Sciex (Foster City, CA) API-100 mass spectrometer equipped with a pneumatically assisted electrospray (Ionspray™, Perkin-Elmer Sciex) interface. The ion sampling orifice was held at + 75 V and the electromultiplier at + 2700 V. MS data were collected in single ion monitoring at m/z 414 and 417 (norbuprenorphine and norbuprenorphine-d₃) and 468 and 472 (buprenorphine and buprenorphine-d₄). Under these analytical conditions, the limits of quantitation for buprenorphine and norbuprenorphine in blood were 0.2 and 0.1 ng/mL, respectively.

In addition to buprenorphine specific analysis, a complementary screening of the postmortem blood and urine was performed in all subjects using immunoassays (FPIA), UV spectrophotometry (carbon monoxide), GC/FID (methamphetamine, ethanol), head-space GC/NPD (cyanides), head-space GC/MS (usual organic solvents) and LC/DAD + GLC/MS (pharmaceuticals, drugs of abuse).

3. Results

Generally, when interpreting a blood concentration from a postmortem case, the toxicologist can find helpful informations in databases presenting therapeutic, toxic and lethal concentrations. Unfortunately, there are quite no suitable references in the literature, that is very poor for buprenorphine. At best, therapeutic concentrations can be evaluated from clinical studies to be in the range 2 to 20 ng/mL [7].

No toxic nor lethal concentrations are available, as this drug seems to be a typical French problem. Due to this situation, Tracqui et al. [3] 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. Recent results, collected both in Strasbourg and several other centers confirm these preliminary findings [4].

In this new series, blood levels ranged from 0.3 to 7.7 ng/mL (mean 3.5 ng/mL) and 0.3 to 16.2 ng/mL (mean 2.9 ng/mL) for buprenorphine and norbuprenorphine, respectively. These concentrations were lower than the previous ones [3,4].

From these 13 subjects, 11 were male, most of them with a low socio-professional status. Circumstances of death were strongly suggestive of a drug fatality in about 2/3 of subjects: empty packages of Subutex® and/or remains of buprenorphine (in spoons, straws . . .), other psychotropics (pharmaceuticals or drugs of abuse) or used syringe(s). Evidence of violence was never found at autopsy, but all corpses presented the features of a prolonged asphyxiation (deep cyanosis, multivisceral congestion, pulmonary edema). These signs are very usual in all deaths involving CNS depressants, especially in opiate-related fatalities. Needle marks suggesting recent IV injection(s) were observed in about half of the subjects.

Buprenorphine along with other drugs concentrations are detailed Table 1.

No fatality involving buprenorphine alone was observed: in this series, all cases involved a concomitant intake of psychotropics. In a case from 1979, Banks [8] reported the ingestion of a large dose (35–40 tablets of 0.4 mg) of buprenorphine taken with suicidal intent where symptoms were minimal and recovery complete.

Benzodiazepines ranked first in association, since they were present in 9 observations. The role of associated benzodiazepines had been previously emphasized in several clinical reports of severe, nonfatal respiratory depression observed when giving buprenorphine to anesthesized patients [9]. It is suggested that the CNS-depressant effects of
buprenorphine may be synergically potentiated by some benzodiazepines (otherwise almost harmless if taken alone). In 1999, Clement et al. [10] pointed out the potential risk of death when buprenorphine is administered along with benzodiazepines. Similar interactions probably exist between buprenorphine and other psychotropics, such as neuroleptics and antidepressants. Among the neuroleptics (3 cases), cyamemazine was present in 2 cases. A concomitant intake of other narcotics was observed in 3 cases. These narcotics included morphine, codeine, and propoxyphene. A fatal association involving cocaine and buprenorphine was observed in 3 cases. Although already observed in other parts of France, these were the first cases from our laboratory, clearly demonstrating a new street combination.

Injecting buprenorphine IV after crushing the sublingual tablets probably constitutes another risk factor of potentially fatal overdosage. Most of the clinical reports of buprenorphine-induced respiratory depression concern IV administration [11]. This way of administration involves a quasi-instantaneous saturation of the central opiate receptors and a maximization of buprenorphine bioavailability, in contrast to a poor oral bioavailability (20–30%). According to Pinoit et al. [12], the combination of buprenorphine IV injection with benzodiazepines can be compared for addicts, in term of pharmacological effects to heroin abuse. Substantial risk of injection misuse is associated with large-scale distribution of buprenorphine for drug maintenance treatment. Therefore, Obadia et al. [13] have proposed a more stringent regulation for medical dispensation of buprenorphine than the current French general freedom of prescription for all physicians, including practitioners in ambulatory care. Finally, the high dosage of Subutex® tablets is also likely to play a role in the occurrence of accidents, despite a theoretical 'ceiling effect' (related to the agonist/antagonist duality of buprenorphine pharmacodynamic activity) claimed to reduce this risk [14].

4. Conclusion

This paper has presented a new series of 13 fatalities attributed to buprenorphine overdosage.

The risks incurred by the misuse of buprenorphine seem to arise through a combination of two practices: 1. association of other psychotropics, especially benzodiazepines and neuroleptics, and 2. improper use of the tablet form for IV administration or massive oral doses. The demonstration of potentially lethal effects of the buprenorphine-psycho- tropic(s) association challenges the purported safety of buprenorphine. The total number of buprenorphine-related fatalities in France is probably largely underestimated due to: 1. the drug is difficult to analyze; 2. only some forensic centers shared their data; and 3. in numerous cases of obvious overdose (known drug addict, presence of a syringe or packages of Subutex), no autopsy is requested by the Police or a judge.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Toxicological findings in blood from 13 buprenorphine-related deaths</th>
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<tr>
<td>A</td>
<td>Bup: 5.8 ng/mL</td>
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<td></td>
<td>Norbup: 0.9 ng/mL</td>
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<td>B</td>
<td>Bup: 0.3 ng/mL</td>
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<td></td>
<td>Norbup: 0.3 ng/mL</td>
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<td>C</td>
<td>Bup: 4.9 ng/mL</td>
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<td>Norbup: 2.4 ng/mL</td>
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References