Buprenorphine-Related Deaths Among Drug Addicts in France: A Report on 20 Fatalities

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Abstract

This paper reports a series of 20 fatalities involving a high-dose, sublingual buprenorphine (BUP) formulation recently marketed in France for the substitutive therapy of opiate addicts. The files were recorded over a 16-month period from five different urban areas in France. All subjects but one were male, aged 14-48 (mean 26.6). BUP and its primary metabolite norbuprenorphine (norBUP) were assayed in postmortem fluids and viscerae by HPLC-MS. Blood levels for BUP and norBUP ranged from 1.1 to 29.0 ng/mL (mean 8.4 ng/mL) and 0.2 to 12.6 ng/mL (mean 2.6 ng/mL), respectively, that is, within or slightly over the therapeutic range. BUP exhibited extensive tissue distribution, with average postmortem concentrations of 6.0, 35.0, 45.5, and 80.0 ng/g in the myocardium, kidney, brain, and liver, respectively. In blood, as in viscerae, norBUP levels were generally lower than BUP. The highest concentrations were found in the bile for both BUP (range 575-72,650 ng/mL) and norBUP (range 41-30,000 ng/mL). Therefore, bile may represent a sample of choice for postmortem screening. BUP was identified in 9 of the 11 hair samples assayed at concentrations ranging from 6 to 597 ng/g (mean 137 ng/g), whereas norBUP was never detected. Intravenous injection of crushed tablets, a concomitant intake of psychotropics (especially benzodiazepines), and the high dosage of the BUP formulation available in France appear to be the major risk factors for such fatalities.

Introduction

Buprenorphine (BUP) is a semisynthetic opioid derivative closely related to morphine and congener alkaloids that is obtained from thebaine after a seven-step chemical procedure. At low doses (typically 0.3 to 0.6 mg intravenous or intramuscular), BUP is a powerful analgesic, 25-40 times more potent than morphine, with mixed agonist/antagonist activity on central receptors. Under the tradename Buprenex in the U.S. and Temgesic in most European countries, it has been widely prescribed since the early 1980s for the treatment of moderate to severe pain (especially of surgical or neoplastic origin) and in anesthesiology for premedication and/or anesthetic induction.

More recently it has been also recognized as a medication of interest for the substitutive management of opiate-dependent individuals. Under the name Subutex (Schering-Plough, Levallois-Perret, France), 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. According to a national program set up by the French Ministry of Health, this drug is distributed at a moderate level of control that may be regarded as a "liberal" (and economic) alternative to the methadone substitution previously organized in specific detoxication centers only: Subutex may be ordered by any physician up to 28 days and is supplied by any pharmacist. Patients are not entailed to take the drug in presence of the physician or pharmacist. Urine controls are not mandatory and, in practice, are almost never realized.

In September 1997, about 40,000 people were treated with Subutex, which is roughly one-fourth of the estimated number of heroin addicts in France. Although successful from a general point of view, this substitution program unfortunately led to some deviations: development of a black market, frequent misuse by intravenous injection of crushed tablets, and association to other psychotropics. Adverse effects (locoregional complications at injection sites, withdrawal syndromes) resulting from these unexpected practices have been recently documented, but, to our knowledge, no fatal overdosages involving BUP have been reported. This paper presents an exceptional series of 20 fatalities attributed to BUP in which both the parent drug and its primary metabolite norbuprenorphine (norBUP) were assayed in various postmortem samples by means of high-performance liquid chromatography coupled to mass spectrometry (HPLC-MS).

Materials and Methods

Subjects

Of the 20 fatalities, 11 (subjects 1–11) originated from Strasbourg and vicinity, and they were consecutively recorded over a 16-month period in the framework of a prospective study carried out at the Medico-Legal Institute of Strasbourg (MLIS). Since the discovery of the first case in August 1996, an HPLC-MS screening for BUP and norBUP is systematically performed on postmortem blood in all suspect deaths investigated.
Toxicological analyses

BUP and norBUP were assayed in postmortem samples by using an adaptation of an HPLC–MS procedure described elsewhere (4). Briefly, biological fluids (blood, urine, bile, gastric contents; 3 mL each) were extracted at pH 8.4 by 5 mL of chloroform/2-propanol/n-heptane (25:10:65, v/v/v) (CPH) after the addition of 15 ng of tetradeuterated BUP (Radian, Austin, TX). When available, tissue samples (e.g., liver or kidney) were first homogenized (one part tissue in four parts deionized water, w/v) using an IKA Ultra-Turrax homogenizer (IKA, Staufen i. Br., Germany), then underwent a triple liquid–liquid extraction made necessary by the complexity of the biological matrix (CPH at pH 8.4 after addition of BUP-d4, then HCl 0.2N, and final extraction by CPH at pH 8.4 after neutralization by 0.2N NaOH). After evaporation, dry extracts were resuspended in 25 μL methanol from which 5 μL was injected onto a 4-μm NovaPak (Waters, Milford, MA) C18 column (150 x 2.0 mm, i.d.). Reversed-phase separation was achieved in 10 min, using a linear gradient of acetonitrile (ACN)/2mM NH₄COOH buffer, pH 3.0 (ACN 50 to 85% in 10 min). The detection was carried out on a Perkin-Elmer Sciex (Foster City, CA) API-100 MS equipped with a pneumatically assisted electrospray (Ionspray™, Perkin-Elmer Sciex) interface. The ion sampling orifice was held at + 75 V, and the electromultiplier was at + 2700 V. MS data were collected as either total ion chromatograms (TIC) by monitoring the signal over the mass range m/z 200–500 for drug screening or as single ion monitoring (SIM) at m/z 414 and 455 (norBUP), 468 (BUP), and 472 (BUP-d4) for BUP and nor BUP quantitation. Under these analytical conditions, the limits of quantitation for BUP and norBUP in biological fluids were 0.2 and 0.1 ng/mL, respectively. Hair samples (approximately 40 mg) taken from 11 subjects were also extracted then assayed in the same conditions after decontamination by CH₂Cl₂, mechanical pulverization, the addition of BUP-d₄ (1 ng), acidic incubation (1 mL 0.1N HCl, 56°C overnight), then neutralization by NaOH (4).

In addition to BUP/norBUP specific analysis, a complementary screening of the postmortem fluids was performed in all subjects using fluorescence polarization immunnoassay (FPIA) on the Abbott TDx™ analyzer (benzodiazepines, barbiturates, tricyclics, salicylates, and acetaminophen in blood; opiates, cocaine, dextropropoxyphene, cannabinoids, amphetamine derivatives, and methadone in urine), UV spectrophotometry (carbon monoxide in blood), gas chromatography–flame ionization

| Table 1. Toxicological Data in 20 Fatalities Involving Buprenorphine |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Subject | Blood (ng/mL) | Urine (ng/mL) | Bile (ng/mL) | Liver (ng/g) | Brain (ng/g) | Kidney (ng/g) | Myocardium (ng/g) | Hair (ng/g) | Other compounds |
| no. | BUP* | norBUP | BUP* | norBUP | BUP | norBUP | BUP | norBUP | BUP | norBUP | BUP | norBUP | BUP | norBUP | BUP | norBUP |
| 1 | 2.5 | 2.3 | 15.0 | 16.9 | 69230 | 986 | 54.8 | 25.4 | 7.1 | n.d. | 16.8 | n.d. | 4.6 | n.d. | 27 | n.d. | N, O, F |
| 2 | 1.1 | 1.6 | 24.6 | 23.0 | 47500 | 1750 | 30.4 | 37.9 | 12.9 | n.d. | 36.5 | 74.0 | 3.5 | n.d. | 103 | n.d. | N, F, E |
| 3 | 9.0 | 11.2 | – | – | >1500 | 625 | 115 | 54.2 | – | – | – | – | – | – | n.d. | n.d. | N, E |
| 4 | 12.6 | 21.1 | – | – | 74.6 | 3.2 | 76.1 | n.d. | 14.5 | n.d. | 3.0 | n.d. | – | n.d. | – | – | N, E |
| 5 | 17.7 | 16.6 | 30.5 | 17.3 | >30000 | >30000 | 273 | 64.1 | 151 | 5.8 | 138 | 23.7 | 12.2 | 3.7 | 71 | n.d. | N, O, F (124) |
| 6 | 1.7 | 1.6 | 344 | 39.0 | 770 | 41 | 4.0 | n.d. | 9.1 | n.d. | 3.8 | n.d. | 6 | n.d. | N, O, F |
| 7 | 5.4 | 0.2 | 1033 | 170 | 19410 | 1270 | 54.3 | 4.1 | – | – | 14.7 | 11.0 | 8.8 | 1.6 | 56 | n.d. | F |
| 8 | 4.7 | 2.0 | 301 | 230 | 1745 | 181 | 34.5 | 21.4 | 16.7 | n.d. | 16.0 | 20.9 | – | – | 277 | n.d. | N (2850), O, M, C |
| 9 | 3.4 | n.d. | 240 | 112 | 72650 | 1590 | 57.6 | 57.2 | 16.7 | n.d. | 16.0 | 20.9 | – | – | 70 | n.d. | N, O, P (1830) |
| 10 | 3.1 | 6.2 | 61.8 | 160 | 817 | 214 | – | – | – | – | – | – | – | – | – | – | N |
| 11 | 7.7 | 0.5 | – | – | 40060 | 1557 | – | – | – | – | – | – | – | – | – | – | N |
| 12 | 1.1 | 0.2 | 9.1 | 9.6 | 575 | >1000 | – | – | – | – | – | – | – | – | – | – | N |
| 13 | 4.2 | 1.9 | 32.0 | 41.2 | 10640 | 2041 | – | – | – | – | – | – | – | n.d. | n.d. | N, C |
| 14 | 5.5 | 0.2 | 151 | 19.3 | – | – | – | – | – | – | – | – | – | – | – | – | N |
| 15 | 4.5 | 1.2 | – | – | 40060 | 1557 | – | – | – | – | – | – | – | – | – | – | N |
| 16 | 13.0 | 4.0 | 4.0 | 7.0 | – | – | – | – | – | – | – | – | – | – | – | – | N, O, B, Px, Cy |
| 17 | 19.0 | 12.6 | 137 | 89.9 | – | – | – | – | – | – | – | – | – | – | – | – | N, E, A (960) |
| 18 | 4.9 | 6.6 | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | N, E, A |
| 19 | 29.0 | n.d. | – | – | – | – | – | – | – | – | – | – | – | – | – | – | M |
| 20 | 18.0 | 0.5 | 25.8 | 6.6 | 15180 | 2635 | – | – | – | – | – | – | – | – | – | – | N, D, E (1.16) |

* Abbreviations: BUP, buprenorphine; norBUP, norbuprenorphine; AI, alimemazine; Am, amniptryline; B, bromazepam; C, codeine; CB, clorazepan; Cy, cyamemazine; D, diazepam; E, ethanol; F, 7-aminoflunitrazepam; M, morphine; Mp, meprobamate; N, nordiazepam; O, oxazepam; P, paroxetine; Px, propoxyphene; P, paroxetine; –, not available or not assayed; n.d., assayed and not detected.
* Compounds listed in bold type were present at supratherapeutic blood concentrations (given in ng/mL) or > 0.4 mg/mL for ethanol (given in mg/mL).
Results and Discussion

Personal data, including gender, age, circumstances of death, and autopsy findings, were collected for the 20 subjects. All but one were male, aged 14 to 48 (mean ± S.D. = 26.6 ± 8.2), most of them with a low socio-professional status (two-thirds were unemployed and/or homeless). These features appear very similar to those encountered in the French heroin consumer population (5). Fifteen subjects were already known opiate addicts. Death occurred at home or at another individual’s domicile in 15 cases. Circumstances of death were strongly suggestive of a drug fatality in about one-half of subjects: empty packages of Subutex and/or remains of BUP (in spoons or straws) were present seven times, other psychotropics (pharmaceuticals or drugs of abuse) or used syringe(s) were present near the body in ten and five observations, respectively. 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 typical in deaths involving CNS depressants, especially in opiate-related fatalities. Vomiting had occurred in seven subjects, four of which presented an associated tracheobronchial inhalation (Mendelsson’s syndrome). Needle marks suggesting recent intravenous injection(s) were observed in eight subjects.

Toxicological results are given in Table I. BUP was identified in all blood samples, and norBUP in all but two, at concentrations ranging from 1.1 to 29.0 ng/mL (mean 8.4 ng/mL), and 0.2 to 12.6 ng/mL (mean 2.6 ng/mL), respectively. By comparison with the literature, these values appear relatively low, that is, within or slightly over the therapeutic range. Bullingham et al. (6) reported plasma concentrations of BUP ranging from 0.45 to 0.84 ng/mL following a single 0.4-mg sublingual dose. According to Kuhlman et al. (7), 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 BUP in six subjects given 4.0 mg sublingually and bucally, respectively. In four subjects receiving sublingual BUP at various doses (2, 4, 8, 16, and 32 mg), the average peak plasma concentrations were about 4, 7, 8.5, 10.5, and 13.0 ng/mL, respectively; however, the authors said that these results expressed as “BUP equivalents” were probably overestimated because the technique employed, radioimmunoassay, did not distinguish BUP from norBUP and other metabolites (8). These low blood or plasma concentrations, which seem poorly related to the therapeutic efficacy or true degree of toxicity (6,9–13), likely proceed from the high lipophilicity of BUP (heptane/water partition coefficient was 10^3 versus 10^5 for morphine [14]). Whatever the dose and route of administration, BUP distributes almost completely to the extravascular compartments with the predictable consequence of tissue concentrations being markedly higher than blood levels. This is in accordance with animal models, showing an extensive tissue distribution, mainly to the liver and brain (14); in Wistar rats given 0.2 mg/kg BUP intravenously, the following average concentrations were measured at the 6th h: plasma, 0.6 ng/mL; myocardium, 1.8 ng/g; kidney, 4.0 ng/g; brain, 6.0 ng/g; liver, 6.3 ng/g; and adipose tissue, 39.0 ng/g (15). A very similar pattern of distribution was observed in our fatalities; average postmortem concentrations were as follows: myocardium, 6.0 ng/g (range 3.0–12.2 ng/g, n = 6 subjects); kidney, 35.0 ng/g (range 8.1–138 ng/g, n = 7 subjects); brain, 45.5 ng/g (range 7.1–151 ng/g, n = 6 subjects); and liver, 80.0 ng/g (range 4.0–273 ng/g, n = 8 subjects). In the same samples, the mean tissue/plasma concentration ratios for BUP were 1.6 (range 0.2–3.2), 8.5 (range 1.2–33.2), 6.3 (range 3.5–11.7), and 12.9 (range 2.3–27.6), respectively.

As previously shown in pharmacokinetic studies (7,16), norBUP concentrations were markedly lower than BUP levels in most instances. This was observed in the postmortem blood in 16 of 19 cases, with an average BUP/norBUP ratio of 8.5 (range 0.5–36.0). In the viscera, average BUP/norBUP ratios were 2.1 in the kidney (n = 7 subjects) and 6.8 in the liver (n = 8 subjects), whereas norBUP was undetectable in the myocardium in four of six cases and in the brain in five of six cases. The latter result is consistent with experimental studies in which virtually no BUP metabolites were shown to cross the blood-brain barrier (14).

Surprisingly high concentrations of both BUP and norBUP were also observed in the bile. BUP ranged from 575 to 72,650 ng/mL (n = 13 subjects), and norBUP ranged from 41 to >30,000 ng/mL (n = 13 subjects). For BUP, the average bile/plasma ratio was 9638 (range 263–43,178). These outstanding discrepancies between blood and bile are a consequence of the massive biliary excretion of BUP and metabolites (14,17,18). In postmortem situations, bile therefore appears as the sample of choice for a systematic search for BUP. Bile analysis is easily achieved in many laboratories with conventional techniques such as HPLC–DAD, whereas blood determinations require much more sensitive (and expensive) procedures such as HPLC–MS (4), GC–PCI–MS (19), or GC–MS–MS (7,16).

BUP was also detected in 9 of the 11 hair samples assayed, showing chronic use of the drug by the individuals concerned. Although extremely variable from one subject to another (range 6–597 ng/g, mean 137 ng/g), hair concentrations were roughly of the same order (or slightly higher) than those previously measured in hair from six volunteers under chronic treatment by BUP (range 4–140 ng/g, mean 70 ng/g) (4). All of the postmortem hair samples were negative for norBUP.

Fatalities involving BUP alone seem very unusual: in our series, all cases but one (subject 10) involved a concomitant intake of psychotropics. Benzodiazepines (BZDs) ranked first by far; they were present in 18 observations, and of these, 15 were nordiazepam. The role of associated BZDs was previously emphasized in several clinical reports of severe, nonfatal respiratory depressions observed when giving BUP to anesthetized patients (12,20–30). As shown by animal experiments (24), this suggests that the CNS-depressant effects of BUP, which is otherwise almost harmless if taken alone, may be synergically potentialized by some BZDs. Similar interactions probably exist between BZDs and other opioids such as methadone (31,32). Injecting BUP intravenously after crushing the sublingual tablets
probably constitutes another risk factor of potentially fatal overdosage. According to the circumstances of death (presence of syringe(s), spoon(s), etc.) and autopsy findings (needle marks), the manner in which BUP was taken was ruled intravenous in 8 of our 20 subjects. Most of the clinical reports of BUP-induced respiratory depression concern intravenous administration (12,20-23,28,29,33,34), although the intraspinal (24,26,27,35) and intramuscular (36) routes have been sometimes implicated. These parenteral ways of administration involve a quasi-instantaneous saturation of the central opiate receptors and a maximization of BUP bioavailability, which is otherwise poor, especially if the drug is taken orally (20–30%). Finally, the high dosage of Subutex tablets is also likely to play a role in the occurrence of accidents, in spite of a theoretical “ceiling effect”, which is related to the agonist/antagonist duality of BUP pharmacodynamic activity, claimed to reduce this risk (8). By the intravenous route, severe respiratory depressions (requiring assisted ventilation) have been observed with dosages in the range of 2–10 µg/kg (12,20-22,33,34). A single 8-µg tablet of Subutex provides a dose of BUP 10 to 50 times greater.

Conclusion

This paper has presented an original series of 20 fatalities attributed to BUP overdosage that was recorded in France over a 16-month period and obviously linked to the recent introduction of a high-dosage formulation devoted to substitution for opiate addicts (no other deaths previously reported in France or anywhere else). Intravenous misuse and association to other psychotropics (especially BZDs) appear as major risk factors for such accidents. These observations clearly highlight some deficiencies of the substitution policy followed in France at present. BUP was proved amply useful for the treatment of opiate dependence; nevertheless, its delivery strategy should be improved to contend potentially hazardous misbehaviors.

References


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