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CASE REPORT

Buprenorphine-related deaths: unusual forensic situations

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Abstract The success of high-dose buprenorphine (HDB) as substitution therapy for major opioid dependence is related to its partial agonist effect on opioid receptors, which in theory makes it very safe to use. However, numerous deaths directly attributable to buprenorphine have been described in the literature. These deaths are generally related to misuse of HDB with intravenous administration and/or concomitant use of benzodiazepines, and they usually occur in patients on HDB substitution therapy for opioid dependence. We present three deaths attributed to HDB which arose from uncommon mechanisms and led to unusual forensic situations. The first death was that of a patient admitted to hospital after simultaneous prescription of HDB, clonazepam, oxazepam, and cyamemazine. The second death followed forcible administration of a very low dose of HDB to a patient with post-hepatitis C cirrhosis and heart failure. The third death was subsequent to an HDB overdose, probably with suicidal intent, in a young woman who had not been prescribed the drug as opiate substitute. Such deaths raise the question of the mechanisms involved and draw attention to the resulting unusual forensic situations.

Keywords High-dose buprenorphine · Death · Benzodiazepines · Liver failure · Non-substitutive use

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Introduction

Buprenorphine, an opioid derived from thebaine, has been used since the 1980s originally in the treatment of postoperative and cancer pain in injections of 0.2 mg [1, 2]. In July 1995, high-dose buprenorphine (HDB) received marketing authorization in France in the form of 0.4, 2, and 8 mg sublingual capsules as substitution treatment for major opioid dependence, under the trade-name Subutex® [3]. Prescription of HDB in this indication then became widespread in all European countries, as well as in the United States. Due to its properties as a partial opioid mu-agonist, theoretically HDB has little respiratory depression effect, which makes it safer to use than methadone [4]. In view of this, the prescription modalities of HDB have been considerably simplified compared with methadone and, in particular, it can be delivered by a dispensing chemist [3]. Prescription of HDB has increased in France in recent years: in 2008, 20,000 patients were recorded as treated with methadone compared with 97,000 treated with BHD [5]. However, in spite of its theoretically low toxicity, for several years, deaths have occurred that were directly attributable to intake of HDB [6–9]. The circumstances observed in the literature are misuse with intravenous injection of BHD [10] and/or the combination,

Table 1 Results of toxicological analysis of postmortem samples, case 1

	Peripheral blood (therapeutic range)
Δ9-THC	<0.2 ng/ml
11-OH-Δ-9-THC	<0.2 ng/ml
THC-COOH	1.4 ng/ml
Buprenorphine	2.1 ng/ml (1 to 5 ng/ml)
Norbuprenorphine	2.5 ng/ml (1 to 5 ng/ml)
Cyamemazine	110 ng/ml (50 to 400 ng/ml)
Oxazepam	120 ng/ml (20 to 2000 ng/ml)
7-aminoclonazepam	42 ng/ml (10 to 80 ng/ml)
Salbutamol	0.8 ng/ml (< 20 ng/ml, nasal route)

even within the therapeutic range, with benzodiazepines [11], likely to cause respiratory depression. The majority of victims are patients receiving HDB as substitution treatment, who secondarily use this drug for purposes other than medicinal ones [6–9]. The buprenorphine-related deaths that we report here demonstrate mechanisms and unusual forensic situations which we consider necessary to report. All toxicological investigations were carried out in conformity with the French Ministry of Justice guidelines [12], and notably included immunological screening for drugs, narcotics and buprenorphine, as well as measurement of drugs, prescription narcotics and psychoactive drugs by gas chromatography or liquid chromatography, and detection by mass or mass tandem spectrometry.

Case reports

Case 1

A 28-year-old man hospitalized in a psychiatric unit was found unconscious on his bed at 0045 hours by the nursing staff. He had last been seen alive the previous evening at 2145 hours. The patient had been admitted to the unit 72 h earlier for a depressive syndrome with episodes of delirium. He had previously been treated as an outpatient for chronic alcoholism and drug abuse. The treatment started on admission included high-dose buprenorphine (Subutex®), cyamemazine (Tercian®), clonazepam (Rivotril®), oxazepam (Seresta®), and salbutamol (Ventolin®). The autopsy performed the next day concluded on tracheobronchial flooding by fluid gastric content. Toxicological analyses were carried out on peripheral blood and urine. The results (Table 1) were in accordance with the patient's treatment and confirmed the presence of buprenorphine and its metabolite, norbuprenorphine, at levels which were within the therapeutic range, as were those of cyamemazine, oxazepam, 7-aminoclonazepam (an active clonazepam metabolite), and salbutamol. The low concentrations of Δ9-THC and 11-OH-Δ9-THC probably indicate that the cannabis intake was prior to the admission to hospital. The results of the other investigations were unremarkable. Death was attributed to asphyxia by inhalation of gastric contents.

Case 2

A 45-year-old man was found unconscious at home by the emergency services, alerted by his niece who was present. Resuscitation was unsuccessful and death was pronounced 15 min later. Examination of the body showed bruising and hematomas of varying age (1 to 4 days) as well as deep and superficial second-degree burns 2 to 3 days old. A Subutex® tablet was also found under the victim's body. His family stated that he had chronic hepatitis C and had undergone cardiac surgery several years previously. He had never been treated with buprenorphine. The autopsy performed the next day showed multiple contusions of the head, trunk, and limbs without apparent gravity, deep and superficial second-degree burns of about 6% of body area, signs of former cardiac surgery, and internal organ congestion with pulmonary edema. Pathological examination showed, in addition to skin lesions suggesting burns caused by a caustic substance, focal bronchopneumonia with the presence of food particles, as well as numerous bacilli suggesting inhalation lung disease. Examination of the liver revealed microvesicular cirrhosis and hemorrhage of the centrolobular veins and prenecrotic lesions of the hepatocytes, suggesting long-standing heart failure. Lastly, cardiomegaly with aortic and mitral valve calcification was observed. Toxicological examination revealed therapeutic blood levels of buprenorphine and trace levels of 7-aminoclonazepam (Table 2). The inquiry revealed that the victim had been confined against his will and tortured for 72 h by his niece and her partner with the aim of extorting money. The aggressors, who were also drug abusers treated with benzodiazepines and Subutex®, confessed that they had given the victim half a tablet of Subutex® and half a tablet of clonazepam (Rivotril®) at an undetermined time. They stated that the victim had rapidly presented disturbed consciousness after intake of these medications, and the respiratory difficulties had appeared secondarily. The aggressors also confessed that they had sprayed the victim with sodium hydroxide, an oven cleaner (Decapfour®), and

Table 2 Results of toxicological analysis of postmortem samples, case 2

	Peripheral blood
Buprenorphine	3 ng/ml (1 to 5 ng/ml)
7-aminoclonazepam	Presence

had hit him several times during 72 h. They received a 15-year prison sentence for extortion with violence and manslaughter.

Case 3

A 30-year-old woman was discovered unconscious in the living room at about 0800 hours by her husband, who had spent the night in the adjoining room with their two children. He stated that he had seen her alive the previous evening. Investigators found in the letterbox a stick of cannabis, a plaquette of flunitrazepam (Rohypnol®) 1 mg and a plaquette of Subutex® 8 mg. The autopsy 48 h later showed only massive acute pulmonary edema. The usual samples were taken with the exception of urine, as the bladder was empty. Toxicological analysis showed lethal levels of buprenorphine and norbuprenorphine, therapeutic level of bromazepam, trace level of 7-aminoflunitrazepam, an active metabolite of flunitrazepam, below the limit of quantification of the technique used, and therapeutic levels of paroxetine. Lastly, 11-hydroxy-Δ9-THC and its carboxylic derivative were found, indicating recent exposure to cannabis (Table 3). The inquiry showed that the victim, who had suffered from depression for several years, was treated with paroxetine and bromazepam. Her family also revealed that the victim, who had never previously taken psychoactive substances or presented any addictive behavior, had been consuming cannabis and Subutex® at regularly increasing doses for several months. She was also reported to have expressed suicidal intentions. Finally, death was attributed to suicide by massive intake of buprenorphine. It is not known how the victim obtained Subutex® and cannabis.

Discussion

Published reports of deaths attributed to buprenorphine are relatively numerous. The large majority of these deaths are related to misuse with intravenous administration and/or combination with psychotropic medications, mostly benzodiazepines. The benzodiazepines most often involved in these deaths are diazepam and nordiazepam [8, 13]. Neuroleptics are also quite regularly cited, in particular cyamemazine [13]. When these drugs are misused, therapeutic doses can be fatal, as shown by the fact that postmortem blood concentrations of buprenorphine and norbuprenorphine, as well as benzodiazepines or neuroleptics when present, often remain in the therapeutic range. Autopsy reports almost constantly mention marked asphyxia syndrome, even for postmortem buprenorphine and norbuprenorphine blood concentrations in the therapeutic range, as well as frequent inhalation of gastric content, in particular if benzodiazepines had also been taken. The mechanism leading to these deaths is still unclear, and the explanations that have been suggested generally relate to pharmacodynamics. Buprenorphine is a partial mu-receptor agonist and a kappa-1 and delta-2 receptor antagonist, resulting in a ceiling effect which makes it very safe to use even at high doses [4, 14]. Norbuprenorphine, on the other hand, has powerful respiratory depressive effects, more than ten times greater than those of buprenorphine [15, 16], and then may be responsible for the respiratory depressive effects of buprenorphine. These respiratory depressive effects may be mediated by opioid receptors in the lung rather than in the brain [15].

With regard to the role of the combination of benzodiazepines with buprenorphine, it has been suggested that they may have an interactive effect on the central respiratory command and/or cumulative physiological effects, in particular relaxation of the dilator muscles of the pharynx and dysfunction of the diaphragm related to benzodiazepines associated with decreased ventilatory response to hypoxia and hypercapnia due to the opioids [14]. This mixed mechanism perhaps leads to the inhalation of gastric content that is very frequent in subjects exposed to both benzodiazepines and HDB. Pharmacokinetic hypotheses are now beginning to be explored, notably concerning buprenorphine and desmethylflunitrazepam [17].

While the exact mechanisms of these deaths remain unknown, the circumstances are fairly stereotyped. The classic pattern described [6–9] is that of a young man with long-standing opiate addiction and receiving HDB substitution therapy, who is found dead at his home or in the street, generally with a syringe and empty blister packs of HDB and other medications beside him. The socio-economic context, when known, is generally unfavorable. It is, however, difficult to determine whether these deaths were caused by accidents or suicides.

In the cases we present here, the circumstances and/or mechanisms of death show unusual features. Case 1 is a perfect illustration of the potential dangers of concomitant use of HDB and other psychoactive medications. The originality of this case lies in the fact that this combination

Table 3 Results of toxicological analysis of postmortem samples, case 3

	Peripheral blood (therapeutic range)
Buprenorphine	21.8 ng/ml (1 to 5 ng/ml)
Norbuprenorphine	30 ng/ml (1 to 5 ng/ml)
Bromazepam	190 ng/ml (80 to 170 ng/ml)
7-aminoflunitrazepam	< 1 ng/ml (5 to 15 ng/ml)
Paroxetine	220 ng/ml (70 to 200 ng/ml)
Δ9-THC	Undetected
11-OH-Δ9-THC	3.94 ng/ml
THC-COOH	60.3 ng/ml

of drugs can no longer be categorized as the misuse that is classically found in such deaths, but becomes a question of medical responsibility. This combination resulted from a prescription issued by a psychiatrist, in a hospital setting, where the patient was not closely monitored. Although concomitant use of HDB and benzodiazepines in particular—and psychotropic medications generally—is not formally contra-indicated, the summary of product characteristics clearly mentions in the sections 'Special warnings and precautions for use' and 'Interaction with other medicinal products and other forms of interaction' the risk of death from respiratory depression if buprenorphine is used in combination with benzodiazepines, and of increased central depression if it is used with other central nervous system depressors. The product summary also states that HDB must be used with caution in asthmatic subjects because of the risk of bronchospasm. The presence of salbutamol in the prescription implies that this patient may have had asthma or chronic obstructive bronchitis likely to hasten respiratory failure. Doctors and psychiatrists in particular should have their attention drawn to the therapeutic associations and necessity for close monitoring of these patients if such prescribing cannot be avoided.

Case 2 is more complex. Here again, autopsy revealed a very marked asphyxia syndrome and inhalation of gastric content, while toxicological analysis found buprenorphine in the therapeutic range. Levels of 7-aminoclonazepam were not measured because of its low toxicity. The absence of clonazepam is very probably due to the fact that nitrobenzodiazepines (clonazepam, nitrazepam, and flunitrazepam) degrade very rapidly in postmortem blood and are replaced by their 7-amino metabolite [18]. From a pharmacological viewpoint, the finding that buprenorphine levels were in the therapeutic range should be emphasized. The victim absorbed only half a tablet of HDB on the first day when he was held, or about 3 days before death. The two aggressors separately confirmed this version, which was corroborated, at least with regard to the quantity, by the investigators, who found, beneath the victim's body, a box of Subutex® in which only half a tablet was missing. Taking into account the fact that buprenorphine has a half-life of terminal elimination of about 20 to 25 h, and that it presents no particularities of postmortem redistribution, the presence of a therapeutic level of buprenorphine after administration of one half-tablet 3 days previously can only be explained by the victim's liver failure. This liver failure, demonstrated by the microvesicular cirrhosis observed on pathological examination, was very probably related to the hepatitis C reported by the family. Expression of CYP450 3A4, which converts buprenorphine into norbuprenorphine, is known to be greatly decreased in patients with a chronic liver disease [19, 20] thus increasing buprenorphine toxicity [21]. Very recent works have also suggested that even at therapeutic levels buprenorphine may induce severe hepatotoxicity in patients with hepatitis C [22, 23]. It is thus very probable that the hepatocellular insufficiency following chronic hepatitis C increased the toxicity of buprenorphine in this victim, and naturally also that of the benzodiazepines, causing respiratory depression even though the quantities absorbed were very low. The victim's heart disease also very probably hastened the terminal cardiorespiratory failure.

This case is also original from a judicial viewpoint. Although this was not chemical submission stricto sensu, since buprenorphine was not given without the victim's knowledge, but at knifepoint, there are similarities, as the aggressors confessed that they wished to weaken the victim in order to extort money. In all the literature we examined (Pubmed/EMBASE), a single case of chemical submission for sexual abuse is described [24]. This is very probably due to the fact that the pharmacokinetic and pharmacodynamic properties of buprenorphine are not those generally sought by aggressors aiming at chemical submission, for sexual abuse in particular (i.e., very rapid action, sedation, amnesia after the event). This case shows however that HDB can be used in this context to weaken potential victims.

In case 3, the mechanism of death is beyond doubt and appears clearly as a HDB overdose, shown by the massive postmortem blood concentrations of buprenorphine and norbuprenorphine. The benzodiazepines probably only played the role of cofactor in this case. The circumstances of death, however, are noteworthy as they raise a problem which is still little known, that of misuse of HDB, defined as use that is not subsequent to prescription as part of substitution treatment. Questioning of the family circle of the victim showed that she had no history of addictive behavior. She was thought to have begun this consumption de novo, a few months previously, in parallel to that of cannabis and flunitrazepam. Although we could not determine from the available information whether this was a true addictive behavior according to DSM-IV criteria [25]. All the persons questioned spoke of her depressive syndrome, demonstrated by postmortem blood presence of paroxetine and bromazepam, which was reported to have worsened recently with the onset of suicidal intent.

Primary consumption of HDB outside the setting of substitution therapy is increasing, but it is still only slightly taken into account by the health authorities. A study carried out by the French monitoring center of drugs and drug addiction (Observatoire Français des Drogues et Toxicomanies, OFDT) revealed that this behavior is more common in men than in women, in a social context that is generally more precarious (lack of income, imprisonment), where HDB appears as a safer alternative in terms of toxicity and above all much less costly than heroin [26]. Primary consumption of HDB in a festive environment is also mentioned. More rarely,

initiation takes place within an affective relationship, in a couple or between friends. The information available in the present case led us to think that the victim, who was not in difficult circumstances and did not have a high nightlife, may well have become a consumer through someone she knew. Primary consumers of HDB generally seek to « get high » and relieve inhibitions, and also, as was probably the case of our patient, to obtain a sedative and tranquilizing effect. Lastly, the drug is usually injected, and more rarely taken by the oral or nasal route (sniffing). In the present case, no needle marks were found at autopsy. As nasal swabs were not taken and gastric content was not analyzed, the route of administration of HDB remains unknown.

In conclusion, these cases highlight yet again the potentially dangerous nature of HDB, particularly if combined with other psychoactive drugs or if the victim also has lung or liver disease, and they draw attention to the unusual forensic situations resulting from misuse.

References

1. Rolly G, Versichelen L (1976) Buprenorphine as postoperative analgesic. Acta Anaesthesiol Belg 27:183–186
2. Adriaensen H, Van De Walle J (1976) Clinical use of buprenorphine in chronic administration. Acta Anaesthesiol Belg 27:187–191
3. Auriacombe M, Fatseas M, Daulouede JP (2008) Therapeutiques de substitution aux opiacés: méthadone orale et buprénorphine sublinguale. In: Reynaud M (ed) Traité d'addictologie, 2nd edn. Medecine-Sciences Flammarion, Paris, pp 620–644
4. Walsh SL, Preston KL, Stitzer ML, Cone EJ, Bigelow GE (1994) Clinical pharmacology of buprenorphine: ceiling effects at high doses. Clin Pharmacol Ther 55:569–580
5. Obradovic I, Canarelli T (2008) The initial prescription of methadone in health establishments. An analysis of medical practices in hospital and penal environments since the introduction of the circular dated January 30, 2002. Tendances 60:1–4
6. Kintz P (2001) Deaths involving buprenorphine: a compendium of French cases. Forensic Sci Int 121:65–69
7. Kintz P (2002) A new series of 13 buprenorphine-related deaths. Clin Biochem 35:513–516
8. Lai SH, Yao YJ, Lo DS (2006) A survey of buprenorphine related deaths in Singapore. Forensic Sci Int 162:80–86
9. Tracqui A, Kintz P, Ludes B (1998) Buprenorphine-related deaths among drug addicts in France: a report on 20 fatalities. J Anal Toxicol 22:430–434
10. Valenciano M, Emmanuelli J, Lert F (2001) Unsafe injecting practices among attendees of syringe exchange programmes in France. Addiction 96:597–606
11. Reynaud M, Petit G, Potard D, Courty P (1998) Six deaths linked to concomitant use of buprenorphine and benzodiazepines. Addiction 93:1385–1392
12. Ministère de la Justice. Note SJ-06-240-AB3/04.08.06 relative à la tarification des analyses toxicologiques
13. Pirnay S, Borron SW, Giudicelli CP, Tourneau J, Baud FJ, Ricordel Y (2004) A critical review of the causes of death among post-mortem toxicological investigations: analysis of 34 buprenorphine-associated and 35 methadone-associated deaths. Addiction 99:978–988
14. Megarbane B, Deye N, Baud FJ (2004) Contribution of experimental data to respiratory depression induced by psychotropic drugs. Réanimation 13:334–342
15. Ohtani M, Kotaki H, Nishitateno K, Sawada Y, Iga T (1996) Kinetics of respiratory depression in rats induced by buprenorphine ans its metabolite, norbuprenorphine. J Pharmacol Exp Ther 281:428–433
16. Megarbane B, Hreiche R, Pirnay S, Marie N, Baud FJ (2006) Does high-dose buprenorphine cause respiratory depression? Possible mechanisms and therapeutic consequences. Toxicol Rev 25:79–85
17. Pirnay S, Megarbane B, Decleves X, Risede P, Borron SW, Bouchonnet S, Perrin B, Debray M, Milan N, Duarte T, Ricordel Y, Baud FJ (2008) Buprenorphine alters desmethylflunitrazepam disposition and flunitrazepam toxicity in rats. Toxicol Sci 106:64–73
18. Robertson MD, Drummer OH (1998) Stability of nitrobenzodiazepines in postmortem blood. Forensic Sci 43:5–8
19. Iribarne C, Picard D, Dreano Y, Bail JP, Berthou F (1997) Involvement of cytochrome P450 3A4 in *N*-dealkylation of buprenorphine in human liver microsomes. Life Sci 60:1953–1964
20. Kobayashi K, Yamamoto T, Chiba K, Tani M, Shimada N, Ishizaki T, Kuroiwa Y (1998) Human buprenorphine *N*-dealkylation is catalysed by cytochrome P450 3A4. Drug Metab Dispos 26:818–821
21. Tegeder I, Lötsch J, Geisslinger G (1999) Pharmacokinetics of opioids in liver disease. Clin Pharmacokinet 37:17–40
22. Peyriere H, Tatem L, Bories C, Pageaux GP, Blayac JP, Larrey D (2009) Hepatitis after intravenous injection of sublingual buprenorphine in acute hepatitis C carriers: report of two cases of disappearance of viral replication after acute hepatitis. Ann Pharmacother 43:973–977
23. Zuin M, Giorgini A, Selmi C, Battezzati PM, Cocchi CA, Crosignani A, Benetti A, Invernizzi P, Podda M (2009) Acute liver and renal failure during treatment with buprenorphine at therapeutic dose. Dig Liver Dis 41:e8–e10
24. Kintz P, Villain M, Tracqui A, Cirimele V, Ludes B (2003) Buprenorphine in drug-facilitated sexual abuse: a fatal case involving a 14-year-old boy. J Anal Toxicol 27:527–529
25. First MB, Tasman A (2004) DSM-IV-TR™ mental disorders. Diagnosis, etiology and treatment. Wiley, Chichester, pp 351–372
26. Escots S, Fahet G (2004) Usages non substitutifs de la buprenorphine haut dosage. Investigation menée en France en 2002–2003. Observatoire Français des Drogues et des Toxicomanies. http://www.ofdt.fr/BDD/publications/docs/epfxsek6.pdf