RESEARCH REPORT

Six deaths linked to concomitant use of buprenorphine and benzodiazepines

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Abstract

Aims. Buprenorphine at high dosage became available in 1996 for substitution treatment in France. This drug is considered particularly safe and has become widely available in general medical practice. We investigated the possible implication of a buprenorphine-benzodiazepine association in six deaths of known abusers. Design. Full investigation of cause of death was conducted for six drug abusers. Setting. The deaths occurred in two regions of France (Auvergne and Lorraine). Assays were carried out by the Institut de Medecine Legale at Strasbourg, France, one of the few French laboratories equipped to assay buprenorphine. Measurement. First, the blood and urine underwent triple exhaustive screening. Secondly, buprenorphine and norbuprenorphine were analysed in all the autopsy samples by HPLC/MS. Findings. Benzodiazepine-buprenorphine associations were found in every case; no other substances that could account for the death were found. The tissue concentrations were markedly higher than the blood levels. Conclusion. If the number of deaths linked to such drug misuse proves high, it may be necessary to review how buprenorphine is dispensed.

Introduction

The treatment of opiate abusers by substitution was introduced fairly late in France. Methadone, already widely used in other countries, became available in January 1995. The risk of overdose when this substitute drug is misused is well known, causing the public authorities to control its dispensing very strictly.

Buprenorphine high dosage became available in 1996. This synthetic morphinomimetic is a partial mu receptor agonist and a kappa receptor antagonist. It binds to morphine receptors, and has a duration of action of at least 24 hours. It is dispensed as a sublingual tablet to be taken once a day. It has been reported to have no euphoric effects and display an agonist activity ceiling, with no increased benefit on increasing the dosage. The withdrawal syndrome produced if the treatment is suddenly discontinued appears to be less rapid and less intense than with a pure agonist such as morphine or methadone.

In France it is used as an analgesic under the trade name Temgesic at dosages of 0.2 mg. For substitution treatment, a high dosage form is...
used, marketed under the trade name Subutex. The dosages for substitution are between 2 mg and 8 mg.

Because of the ceiling effect this drug is considered particularly safe and has therefore become widely available in general medical practice. It is dispensed at a “moderate level of control”. Any physician may prescribe buprenorphine in a counterfoil book for up to 28 days. Any pharmacist may supply it. Urine assays are not mandatory. However, it is recommended that the prescribing physician seek the advice of physicians in specialized drug abuse treatment centres, and experienced general physicians, via a collaborative network. In December 1996, 29,000 patients were being treated with buprenorphine.

Some drug abusers, and indeed some physicians, have not been complying with the approved practice for prescribing and using this drug. This paper reports the implication of a buprenorphine–benzodiazepine association in six deaths of known abusers.

**Methods**

**Subjects**

Six suspect deaths among abusers were reported in the period between November 1996 and March 1997 (three of them in Auvergne and three in Alsace). As very few laboratories are able to assay buprenorphine, analyses have not been conducted on all the overdoses of this period.

Six autopsies were ordered for legal purposes to establish cause of death. The observations comprise the information in the police report and information obtained, when available, from drug abuse care workers. None of these cases was being followed regularly, and none had an organized care programme.

**Case 1.** Male, aged 26 years, known heroin addict, found dead on his bed. Near the body were found a used insulin syringe, an empty blister pack of Subutex 8 mg and a teaspoon containing a white residue. Numerous other psychotrophic drugs (benzodiazepines) were found in the flat. Post-mortem examination showed no signs of violence, numerous venous injection points inside the left elbow, signs of severe asphyxia (cyanosis, multivisceral congestion, pulmonary oedema, Tardieu’s spots).

The evidence suggested that buprenorphine had been injected intravenously from crushed Subutex tablets; injection mark inside the elbow, syringe, spoon, Subutex blister pack close to the body, very low level of buprenorphine in the stomach contents, white residue shown to contain a high concentration of buprenorphine with no associated drug.

**Case 2.** Male, aged 20 years, multiple drug abuser (heroin, ecstasy, cocaine) under substitution treatment, found dead at the home of a friend, himself a drug abuser using Subutex 8 mg. His usual treatment consisted of Subutex, Visclargine (tiemornium), Lysanxia (prazepam), Nozinan (levomepromazine). Post-mortem examination showed probable asphyxia, no signs of violence, body already putrefied, time since death estimated at 48 hours. According to his friend, drug-induced suicide likely. Attempted drug-induced suicide previously recorded in July 1996.

**Case 3.** Male, aged 18 years, found dead in his room. Body in a state of putrefaction, time since death estimated at 5–8 days. In one pocket, an empty blister pack of Subutex. Post-mortem examination showed cyanosis of limb extremities, no sign of violence. The state of the body did not permit detection of any injection marks.

**Case 4.** Male, aged 35 years, prison inmate found dead in his cell. Previous treatment with Nozinan (levomepromazine), Prozal (fluoxetine), Lysanxia (prazepam) and Rohypnol (flunitrazepam). No prescription of Subutex. Post-mortem examination showed severe asphyxia with acute pulmonary oedema; no sign of violence or marks of injection.

**Case 5.** Male, aged 19 years, dead at home, known drug abuser (heroin, cocaine). Previous misuse of Subutex. Post-mortem examination showed asphyxia, no violence, no injection marks.

**Case 6.** Male, aged 18 years, very marginal and desocialized, living in a caravan. Known multiple drug abuser (heroin and benzodiazepines at high doses). No medical prescription. Subutex had been supplied to him by a fellow drug abuser. Intravenous use suspected for several months.
The death followed a group injection, acknowledged by the other people involved. Evidence of massive concomitant use of Tranxene (dipotassium chlorazepate) and Rohypnol (flunitrazepam) by oral route.

Toxicological analyses
The following post-mortem toxicological analyses were conducted on these six cases.

First, the blood and urine underwent triple exhaustive screening by immunochemical methods (EMIT on Syva ETS Plus, FPIA on Abbott TDx), high performance liquid chromatography with diode detection (HPLC/DAD) and gas phase chromatography coupled with mass spectrometry (GPC/MS). The combination of all these methods covers several thousand potentially toxic compounds, and allows identification and assay of narcotics (opiates and derivatives, cocaine, amphetamines and derivatives, etc.) together with all the psychotropes in the pharmacopeia (barbiturates, benzodiazepines, antidepressants, neuroleptics, carbamates, etc.). Other substances sought included ethanol, volatile solvents and cyanides by gas phase chromatography, carbon monoxide by carboxymetry, digitalis glycosides by high performance liquid chromatography coupled to mass spectrometry (HPLC/MS) and arsenic and thallium by atomic absorption spectrometry.

Secondly, buprenorphine and its main metabolite, norbuprenorphine, were analysed and quantified in all the autopsy samples (blood, urine, stomach contents, liver, brain, kidney, heart muscle, etc.) by means of an HPLC/MS method already described elsewhere. Unlike most opiates (morphine, codeine, etc.) and opiate-like agents (dextropropoxyphene, methadone), buprenorphine is particularly difficult to characterize in biological media, and so a large number of analytical procedures were used. Radio-immunological assay (RIA) is extremely sensitive, but it is difficult to use routinely and can be adversely affected by interference. Above all, it does not allow separate assay of buprenorphine and its metabolite (due to cross-reactivity). In addition, GPC/MS, although a favourite method in forensic toxicology, is inappropriate here due to the high thermal lability of buprenorphine. On the other hand, HPLC/MS offers a good compromise; simplicity and ease of use, and high sensitivity and absolute specificity. Our method was initially designed for biological fluids and hair, but proved suitable for homogenates of viscera after triple extraction, made necessary by the complexity of the tissues.

Assay of benzodiazepines in the post-mortem samples was carried out by HPLC/DAD as described previously elsewhere.

Results
Benzodiazepine–buprenorphine associations were found in every case (norbuprenorphine was found less systematically). No other substance that could account for the death was found (e.g. illicit poisons, psychotropics, other drugs).

Blood assays
The blood concentrations of buprenorphine were in the therapeutic range in observations 1, 2 and 6 (2.5, 1.1 and 1.7 ng/ml), and higher than therapeutic in the other three (9.0, 12.6, 17.7 ng/ml) relative to known values in non-abusers.

The exhaustive screening detected no traces of opiates (morphine, codeine, 6-monoacetylmorphine, etc.) in the post-mortem blood.

In contrast, all the subjects displayed benzodiazepine at therapeutic-range levels for both demethylflunitrazepam and 7-aminoflunitrazepam (metabolite of flunitrazepam, classically found alone in post-mortem examinations, as flunitrazepam cannot usually be assayed).

Finally, in subjects 2, 3 and 4, a moderate ethanol level was found (the ante-mortem origin of which is arguable in cases 2 and 3, given the state of putrefaction of the bodies).

Tissue assays
The levels of buprenorphine measured in the brain, kidney and liver were, respectively, 3–12 times, 1–33 times and 2–28 times higher than in the blood.

Discussion
The discussion will address two issues: (1) analysis of our data concerning blood and tissues concentrations; and (2) assessment of the risk of respiratory depression by overdose induced by buprenorphine, alone or associated with benzo-
Table 1. Post mortem concentrations of buprenorphine and norbuprenorphine (all values in ng/ml or ng/g)

<table>
<thead>
<tr>
<th></th>
<th>Subject 1</th>
<th>Subject 2</th>
<th>Subject 3</th>
<th>Subject 4</th>
<th>Subject 5</th>
<th>Subject 6</th>
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<tbody>
<tr>
<td><strong>BUP</strong></td>
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<tr>
<td>Blood</td>
<td>2.5</td>
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<td>9.0</td>
<td>12.6</td>
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<td>Urine</td>
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<td>–</td>
<td>–</td>
<td>30.5</td>
<td>344.1</td>
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<tr>
<td>Bile</td>
<td>–</td>
<td>–</td>
<td>&gt;1500</td>
<td>–</td>
<td>&gt;30 000</td>
<td>770</td>
</tr>
<tr>
<td>Stomach contents</td>
<td>1.5</td>
<td>2.8</td>
<td>5.2</td>
<td>877</td>
<td>8800</td>
<td>134.9</td>
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<tr>
<td>Liver</td>
<td>54.8</td>
<td>30.4</td>
<td>114.5</td>
<td>74.6</td>
<td>272.6</td>
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<td>Brain</td>
<td>7.1</td>
<td>12.9</td>
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<td>76.1</td>
<td>150.8</td>
<td>9.1</td>
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<td>Kidney</td>
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<td>14.5</td>
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<td>Heart muscle</td>
<td>4.6</td>
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<td>–</td>
<td>3.0</td>
<td>12.2</td>
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<td><strong>Other compounds (microg/ml in blood)</strong></td>
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<td>7-AF = 0.124</td>
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<td>EtOH = 200</td>
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BUP = buprenorphine; norBU = norbuprenorphine; DMD = demethyldiazepam; OXA = oxazepam; 7-AF = 7 aminoflunitrazepam; EtOH = ethanol = sample unavailable or not analysed; n.d. = not detected.
Buprenorphine and benzodiazepine-linked deaths

Diazepines, according to the administration route, and in relation to pharmacological, toxicological and narcotic parameters.

In all the cases the blood concentrations of buprenorphine were fairly low. In general, neither the efficiency nor the central depressor effects of buprenorphine are closely correlated with plasma levels. This is accounted for by the high lipophilicity of the molecule, and its strong persistent binding to opiate receptors. In the rare cases of side effects when assays were carried out, the plasma concentrations were in the therapeutic range.

Given its high lipophilicity, buprenorphine is distributed almost entirely in the extravascular volume, irrespective of its mode of administration. Consequently, its tissue concentrations were markedly higher than its blood levels. The levels found in the stomach contents in cases 4 and 5 suggest a massive sublingual or oral dose, although there has been no study of buprenorphine concentrations in stomach contents after oral, sublingual or parenteral administration. Similarly, the breakdown kinetics of buprenorphine in gastric acid medium are unknown.

The interpretation of these blood concentrations must allow for the possibility of post-mortem redistribution processes. Such redistribution can be especially marked for lipophilic compounds with high distribution volumes (i.e. with strong tissue binding). Their massive release from visceria after death can cause a local rise in blood levels in the adjoining vessels. This can sometimes result in spuriously high values if assays are performed on samples taken from these areas. In our six observations, despite the appreciable lipophilicity of buprenorphine, any such redistribution could only have been at most of minor importance, because blood samples were taken not only from the heart, but also from the periphery (i.e. femoral artery) at a point not prone to redistribution effects, according to the consensus adopted by the French Association for Further Training in Forensic Medicine. The heart blood samples were used for the qualitative screening of drugs and narcotics, and the peripheral samples for quantification. These precautions ensured that the post-mortem blood levels were close to those in the blood stream at the time of death.

The risks incurred by the misuse of Subutex seem to arise through a combination of two practices: (1) improper use of the tablet form for intravenous administration or massive oral doses; and (2) association of other psychotropic agents, especially benzodiazepines.

The ceiling effect of buprenorphine is documented in clinical practice. However, the association of central nervous system depressants is liable to modify this property, especially as individual variations in sensitivity may be implicated.

The only case of buprenorphine overdose reported to date in the literature is consistent with this. A massive dose of 35–40 0.4 mg tablets by sublingual and/or oral route in a young man induced only minimal symptoms of drowsiness, with no respiratory or haemodynamic disturbances. In contrast, to our knowledge no study has explored the effect in humans of supratheraapeutic doses of buprenorphine administered by the parenteral route, e.g. intravenous bolus.

Concomitant use of benzodiazepines seems to be strongly implicated in buprenorphine overdose. This association has been reported in a large number of clinical observations of respiratory depression resulting from buprenorphine at therapeutic doses.

Although the intraspinal and intramuscular routes are sometimes involved, most of these cases concern intravenous administration. By this route, severe respiratory depression (requiring assisted ventilation) has been observed for dosages between 2 and 10 g/kg. A single tablet of Subutex 8 mg crushed in a spoon and injected affords a dose of buprenorphine 10–50 times greater.

Benzodiazepines have been found in over 50% of cases of death through overdose. The frequent implication of benzodiazepines in deaths by overdose is probably linked to its respiratory depressive potential at high doses, which seems similar to that of barbiturates. Flunitrazepam seems to be most often used, and also demethylidiazepam. In a series of 19 deaths directly or partly attributable to a dextropropoxyphene overdose (another opiate-like drug often misused by drug abusers), concomitant benzodiazepine use was found 13 times (of which demethylidiazepam 12 times).

Cases 4 and 5 suggest that in certain situations (associations with other CNS antidepressants, individual sensitivity) a massive dose of buprenorphine by sublingual and/or oral route may lead to a true overdose, despite the ceiling...
effect and the poor enteral bioavailability of this drug. The literature reports some cases of severe respiratory depression after proven absorption of buprenorphine by the sublingual route.\textsuperscript{15,36,54}

These pharmacological findings are to be interpreted with caution, since the pharmacological effects of morphine agonists are not the same in abusers and non-abusers.

The recording of six deaths linked to misuse of associations of benzodiazepines with high-dose buprenorphine prompts us to make a number of recommendations:

- It is important to evaluate risks as precisely as possible by carrying out systematic blood assays of buprenorphine in every case of death of a drug abuser when drug misuse can be suspected.
- There is a need to improve pharmacological knowledge concerning the effects of benzodiazepine–buprenorphine associations.
- Information for both prescribers and users needs to be updated.
- In the light of the above, it may be important to review the provisions for dispensing high dose buprenorphine.

These cases were drug abusers who were not included in well-organized care programmes, and who were deliberately misusing prescriptions (a relatively common occurrence). However, the demonstration of potentially lethal effects of the buprenorphine–benzodiazepine association challenges the purported harmlessness of buprenorphine.

References


