A critical review of the causes of death among post-mortem toxicological investigations: analysis of 34 buprenorphine-associated and 35 methadone-associated deaths

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ABSTRACT

Aims To assess the trends in the number, mortality and the nature of forensic cases involving toxicological detection of buprenorphine or methadone among toxicological investigations performed in Paris from June 1997 to June 2002.

Design Retrospective, 5 year study with review of premortem data, autopsy, police reports, hospital data, and post-mortem toxicological analyses.

Setting and participants 34 forensic cases of buprenorphine and 35 forensic cases of methadone detection among 1600 toxicological investigations performed at the Laboratory of Toxicology in the Medical Examiner’s Office in Paris.

Measurements and results Therapeutic, toxic or lethal drug concentrations were defined based upon the results of blood analyses and the published literature. Drug concentrations were cross-referenced with other available ante- and post-mortem data. Subsequently, we classified a ‘clear responsibility’, ‘possible responsibility’ or ‘not causative’ role for buprenorphine or methadone in the death process, or ‘no explanation of death’. Buprenorphine and methadone can be regarded as being directly implicated in, respectively, four of 34 death cases (12%) and three of 35 death cases (9%), and their participation in the lethal process is strongly plausible in eight (buprenorphine) and 11 (methadone) additional deaths.

Conclusions Analysis of causes of death reveals the difficulties in determining the role of substitution drugs in the death process, as many other factors may be involved, including circumstances surrounding death, past history, differential selection of subjects into either substitution modality and concomitant intake of other drugs (especially benzodiazepines and neuroleptics). The potential for synergistic or additive actions by other isolated molecules—particularly opioids, benzodiazepines, other psychotropes and alcohol—must be also considered.

KEYWORDS Benzodiazepines, buprenorphine, cause of death, forensic sciences, gas chromatography, mass spectrometry, methadone, poisoning.

INTRODUCTION

Methadone was developed in Germany during the Second World War at a time when the country was unable to procure opiates for medical use from the Orient. Methadone is an effective analgesic and suppresses withdrawal symptoms from other opiates. This latter property has led to its usage for the treatment of
heroin-addicted persons in methadone maintenance programs since the 1960s. In these programs, orally administered methadone is provided as a substitute for injected heroin. Methadone does not provide a ‘high’ as such, but ideally prevents withdrawal and reduces the craving for heroin.

Buprenorphine is a partial agonist to opioid receptors derived from thebaine. At low dosage (0.3–0.6 mg intravenous or intramuscular), buprenorphine is a strong analgesic drug, 25–40 times more powerful than morphine. Buprenorphine is widely prescribed in a dose of 0.2 mg for the treatment of medium to high painful symptoms and also for premedication in anaesthesiology. In 1996, high-dosage buprenorphine was made available on the French market as a substitution treatment for heroin addicts. Three dosages exist: 0.4 mg, 2 mg and 8 mg.

In France, 74 300 heroin addicts were treated daily with buprenorphine in 2001, while only 9600 people were treated with methadone. A report in 2000 described the success of this heroin substitution program, since fatal heroin overdoses fell from 500 a few years ago to 100 in 1999. Another recent report suggests that high-dose buprenorphine, like high-dose methadone and levomethadyl acetate, substantially reduces the use of illicit opioids [1].

However, deaths have been reported during substitution with buprenorphine in humans [2,3]. Deaths may result from either misuse or overdose during buprenorphine substitution treatment [4,5]. More recently, a retrospective study was published of fatalities linked to buprenorphine in France from mid-1996 to March 2000 [6]. These reports show evidence that buprenorphine is misused and administered by the intravenous route [5]. The authors highlighted the association of substitution products (methadone or buprenorphine) with psychotropic drugs as a major factor in fatalities among heroin addicts. Moreover, buprenorphine is widely associated with benzodiazepine use in heroin addicts, and this combination is considered as a risk factor for lethal outcomes [2,4,7–10]. Fatal intoxications with methadone have also been reported [11–14].

While buprenorphine and methadone may be differentially employed according to the patient’s unique clinical condition, it is vital for clinicians to understand the circumstances in which each drug may be implicated in patient deaths, as this may impact on the choice of substitution product. Thus, the aim of this retrospective study was to assess the cause of death in 60 consecutive fatalities in which buprenorphine (n = 34), methadone (n = 35) or both (n = 9) were analytically detected from June 1997 to June 2002 at the Laboratory of Toxicology of the Paris Police Department.

MATERIALS AND METHODS

Subjects
The population served by the coroner’s office includes all of Paris and part of the adjacent suburbs. However, not all fatal opioid-related deaths are likely to be referred to the medical examiner. Only a subset of cases is referred to the coroner’s office, this decision depending on the officials of the judiciary. The decision to recommend a post-mortem toxicological analysis can be made by a police officer, the examining physician, the prosecutor or the instructing judge. Obviously, there is a possibility at any stage of the investigation that the need for toxicological investigation could be overlooked.

All toxicological analyses of death cases performed at the Laboratory of Toxicology of the Paris Police Department from June 1997 to June 2002 that demonstrated the presence of buprenorphine or methadone, in whole blood and/or urine, were reviewed. Each toxicological case was requested by police services or magistrates, depending on the chronology of the case, in relation to a suspicious death, as defined by Article 74 of the French Penal Procedure Code.

All data reported by the forensic specialist, as well as police reports, were examined in our retrospective study. The following parameters were collected: age, sex, ante-mortem associated pathologies and circumstances of death.

Toxicological analyses
The research for and quantification of drug substances were carried out systematically in blood and urine. In the case of associated substances (other than buprenorphine or methadone), we also performed qualitative toxicological analyses in internal organs, hair and bile. A complete screening of post-mortem biological samples was performed in all subjects for carbon monoxide (using infrared spectrophotometry), for benzodiazepines by immunoassay (EMIT DAA of Microgenics Laboratories, Passau, Germany) on a COBAS MIRA analyser (Roche, Saint-Fons, France), for usual organic solvents, including ethanol (using head space gas chromatography-mass spectrometry (GC-MS)), and for pharmaceuticals and drugs of abuse (using liquid chromatography-diode array detector (LC-DAD) and GC-MS) [15]. The methods employed were gas chromatography coupled with mass spectrometry (HP 6890/5973 using Agilent® (Massy, France) technology for simple quadruple mass spectrometer and Varian® 2000 (Les Ulis, France) for ion trap), as well as high-performance liquid chromatography coupled with molecular absorption spectrometry with diode array detection (Alliance, Milford, MA, USA).
For quantitation, all analytical conditions were adapted and deuterated standards were added according to each identified drug.

**Definitions of drug concentration levels**

Generally, when interpreting a blood concentration from a post-mortem case, the toxicologist can find helpful information in databases presenting therapeutic, toxic and lethal concentrations. However, it should be noted that generally the ranges of both therapeutic and toxic concentrations have been determined empirically. Furthermore, it is noteworthy that the therapeutic, toxic and even lethal concentrations as defined in the literature do not take into account the role of tolerance. Therapeutic, toxic or lethal drug concentrations were defined based upon blood analyses. We defined ‘high concentration’ for ranges, where they exist, as those between therapeutic and toxic blood concentrations.

Unfortunately, the data available for buprenorphine therapeutic and toxic ranges is limited. We used the published therapeutic concentrations of buprenorphine and methadone published by Repetto et al. [16] and the toxic concentrations of buprenorphine and methadone published by Kintz et al. [17]. For buprenorphine, therapeutic blood concentrations were defined as less than 5 ng/mL, and toxic concentrations were defined as greater than or equal to 5 ng/mL. The limit of detection of buprenorphine by GC-MS is 0.5 ng/mL and the limit of quantitation by GC-MS is 1 ng/mL.

For methadone, therapeutic concentrations were defined as lower than 500 ng/mL. ‘High concentration levels’ were 500–1000 ng/mL. Toxic concentrations were defined as 1000–2000 ng/mL and lethal concentrations were greater than 2000 ng/mL.

Similar methodology was applied for determining concentration ranges for all other associated drugs.

**Determination of the cause of death**

The cause of death was determined by either I.R. or J.T., both experts at the Laboratory of Toxicology of the Paris Police Department, from June 1997 to June 2002 in a non-blinded manner. Thereafter, S.P. reviewed all toxicological analyses, as well as data reported by forensic specialists, police reports and, when it existed, ante-mortem clinic background. Thus, using the various sources of data, we a posteriori defined ‘clear responsibility’ of buprenorphine or methadone in the death process when the case was free of other pathology or violent death, and when buprenorphine and/or methadone was found at toxic or lethal levels in blood, with associated drugs at therapeutic levels or less. A ‘possible responsibility’ of buprenorphine or methadone in the death process was defined when buprenorphine and/or methadone was found at toxic levels but other associated factors existed, such as previous illness or associated drugs at toxic or lethal levels. Buprenorphine or methadone were defined as ‘not causative’ in the death process when they were found at therapeutic levels or lower and associated factors existed, such as previous illness, evidence of violent death or the presence of associated drugs at toxic or lethal levels. ‘No explanation of death’ was defined when the case was free of pathology or violent death and when buprenorphine or methadone, as well as associated drugs, were found at therapeutic levels or less.

**Sales figures for high doses of buprenorphine and methadone in France during the same period (1996–2001)**

These data were drawn from the annual report of the Observatoire Français des Drogues et des Toxicomanies (OFDT) [18]. We compared the annual number of fatalities associated with buprenorphine and methadone to the annual sales figures.

**RESULTS**

From June 1997 to June 2002, at the Laboratory of Toxicology of the Paris Police Department, 34 post-mortem examinations were positive for buprenorphine and 35 others were positive for methadone in biological samples. In nine of them, buprenorphine and methadone were detected simultaneously. Over the 5 year period, there were progressive increases in buprenorphine- and methadone-associated deaths that parallel the increase in sales figures of both drugs (Fig. 1 a,b).

Buprenorphine was detected in 24 men and seven women, aged from 20 to 48 years, the median age being 33 years. The gender was unknown in three cases. Buprenorphine administration by the intravenous route was known or suspected in seven cases. Methadone was isolated in 26 men and eight women, aged from 23 to 47 years; the median age was likewise 33 years. The gender was unknown in one case.

Buprenorphine was quantitated in blood in a range of concentrations between 1 and 46.1 ng/mL, including 12 cases at toxic concentrations (more than 5 ng/mL) and in six cases within the therapeutic range (below 5 ng/mL). It was detected only in urine in 16 cases. Methadone was quantitated in the blood in a range of concentrations between 70 and 1960 ng/mL, including five cases within the toxic range (more than 1000 ng/mL) and 17 cases within the therapeutic range (below 500 ng/mL). It was detected only in urine in two cases.

Nine cases are listed in Table 1, where buprenorphine and methadone were both quantitated in biological
Figure 1 (a) Number of forensic cases (Paris) related to buprenorphine versus number of treatments (France), 1996-2002. (b) Number of forensic cases (Paris) related to methadone versus number of treatments (France), 1996-2002.

Table 1 Nine cases of simultaneous detection of buprenorphine and methadone.

<table>
<thead>
<tr>
<th>Common cases of buprenorphine and methadone</th>
<th>Buprenorphine in blood (ng/mL)</th>
<th>Buprenorphine in urine (ng/mL)</th>
<th>Methadone in blood (ng/mL)</th>
<th>Methadone in urine (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt; LQ*</td>
<td>12</td>
<td>251</td>
<td>1270</td>
</tr>
<tr>
<td>2</td>
<td>&lt; LQ</td>
<td>&lt; LQ</td>
<td>460</td>
<td>&lt; LQ</td>
</tr>
<tr>
<td>3</td>
<td>&lt; LQ</td>
<td>11.8</td>
<td>360</td>
<td>14620</td>
</tr>
<tr>
<td>4</td>
<td>12.2**</td>
<td>33.8</td>
<td>600</td>
<td>9200</td>
</tr>
<tr>
<td>5</td>
<td>&lt; LQ</td>
<td>5.6</td>
<td>351.5</td>
<td>3900</td>
</tr>
<tr>
<td>6</td>
<td>&lt; LQ</td>
<td>30.5</td>
<td>804</td>
<td>16.5</td>
</tr>
<tr>
<td>7</td>
<td>&lt; LQ</td>
<td>19.7</td>
<td>208</td>
<td>265</td>
</tr>
<tr>
<td>8</td>
<td>&lt; LQ</td>
<td>15.1</td>
<td>526</td>
<td>1159</td>
</tr>
<tr>
<td>9</td>
<td>&lt; LQ</td>
<td>15</td>
<td>1035**</td>
<td>7000</td>
</tr>
</tbody>
</table>

*LQ (limit of quantification) < 1 ng/mL.
**Toxic concentrations.
samples. This table shows that there was only one case of buprenorphine with a toxic concentration and a concomitant non-toxic concentration of methadone. Another case showed a toxic concentration of methadone with a non-toxic concentration of buprenorphine. The other seven cases shared non-toxic concentrations of buprenorphine and methadone.

Except for one case of methadone detection, buprenorphine and methadone were uniformly detected in association with other drugs. The median number of drugs associated with buprenorphine was 4.5 (range 1–10), while the median number of drugs associated with methadone detection was 5.0 (range 0–10). The number of associated drugs wasdispersed randomly through the cases from 1997 to 2002. There did not seem to be any modal effect over 5 years (Figs 2 and 3, Table 2).

Among buprenorphine cases, one subject had one associated drug, four subjects had two associated drugs, eight subjects had three associated drugs, four subjects had four associated drugs, five subjects had five
associated drugs, seven subjects had six associated drugs, one subject had seven associated drugs, two subjects had eight associated drugs, one subject had nine associated drugs and one subject had 10 associated drugs.

Among methadone cases, one subject had no associated drugs, one subject had one associated drug, four subjects had two associated drugs, four subjects had three associated drugs, five subjects had four associated drugs, eight subjects had five associated drugs, six subjects had six associated drugs, three subjects had seven associated drugs, one subject had eight associated drugs, one subject had nine associated drugs and one subject had 10 associated drugs (Table 3).

For opiates and opioids, among buprenorphine cases, 18 subjects had one associated opioid, three subjects had two associated opioids and two subjects had three associated opioids. Among methadone cases, 12 subjects had one associated opioid, six subjects had two associated opioids and four subjects had three associated opioids (Table 4).

Concerning benzodiazepine use among buprenorphine cases, 16 subjects had one benzodiazepine, four subjects had two benzodiazepines, one subject had three benzodiazepines and one subject had four benzodiazepines. Among methadone cases, 18 subjects had one associated benzodiazepine, seven subjects had two associated benzodiazepines and one subject had three associated benzodiazepines.

The most frequently associated benzodiazepines were nordiazepam (buprenorphine: 13; methadone: nine), bromazepam (buprenorphine: six; methadone: eight) and diazepam (buprenorphine: four; methadone: 10). Other associated benzodiazepines (less than three times) were flunitrazepam, oxazepam and temazepam. Lorazepam was found in association with buprenorphine only once and midazolam was found with methadone only once. Concerning flunitrazepam, it is possible that it was underestimated because of its fragility in putrid medium (Table 5).

Very few subjects had co-ingested psychotropic drugs other than benzodiazepines with buprenorphine or methadone (less than four), except for cyamemazine (a neuroleptic similar in action to chlorpromazine), which 10 subjects had taken with buprenorphine and eight with methadone (Table 6).

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**Table 2** Number of positive drug detections in blood and/or urine in association with buprenorphine or methadone.

<table>
<thead>
<tr>
<th>Year</th>
<th>Methadone</th>
<th>Buprenorphine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median number of other associated drugs</td>
<td>Number of methadone cases during the year</td>
</tr>
<tr>
<td>1997</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>1998</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>1999</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>2000</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>2001</td>
<td>6.5</td>
<td>8</td>
</tr>
<tr>
<td>2002</td>
<td>6</td>
<td>3</td>
</tr>
</tbody>
</table>

**Table 3** Other substances associated with the finding of buprenorphine or methadone in the blood and/or urine.

<table>
<thead>
<tr>
<th>Substance</th>
<th>Buprenorphine</th>
<th>Methadone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioids/opiates</td>
<td>30 (12*)</td>
<td>36 (13)</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>31 (2)</td>
<td>35 (4)</td>
</tr>
<tr>
<td>Cocaine</td>
<td>11 (3)</td>
<td>7</td>
</tr>
<tr>
<td>Cannabis</td>
<td>14</td>
<td>18</td>
</tr>
<tr>
<td>Phenothiazines and antipsychotics</td>
<td>16 (8)</td>
<td>14 (5)</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>8 (1)</td>
<td>11 (2)</td>
</tr>
<tr>
<td>Other anxiolytics</td>
<td>9 (2)</td>
<td>9</td>
</tr>
<tr>
<td>Ethanol</td>
<td>16 (1)</td>
<td>19</td>
</tr>
<tr>
<td>Amphetamines</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Paracetamol (acetaminophen)</td>
<td>14 (1)</td>
<td>9</td>
</tr>
<tr>
<td>Carbon monoxide</td>
<td>0</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Others**</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>154</td>
<td>165</td>
</tr>
</tbody>
</table>

*Number of cases where the drug was at toxic or lethal concentration.
**Others include: metoclopramide, hydroxyzine, buspirone, cetirizine, fluconazole, zidovudine and ephedrine.

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**Table 4** Other opioids associated with detection products of substitution.

<table>
<thead>
<tr>
<th>Substance</th>
<th>Buprenorphine</th>
<th>Methadone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heroin</td>
<td>5 (5*)</td>
<td>6 (6)</td>
</tr>
<tr>
<td>Morphine</td>
<td>2 (2)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Codeine</td>
<td>6 (2)</td>
<td>7 (3)</td>
</tr>
<tr>
<td>Dihydrocodeine</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Pethidine (meperidine)</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Pholcodine</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Propoxyphene</td>
<td>5 (1)</td>
<td>5</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>0</td>
<td>9 (3)</td>
</tr>
<tr>
<td>Methadone</td>
<td>9 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Total</td>
<td>30</td>
<td>36</td>
</tr>
</tbody>
</table>

*Number of cases where the drug was at toxic or lethal concentration.
In half the cases, ethanol was associated (similarly in both groups) with concentrations exceeding 1 g/L: in five cases in the buprenorphine group and in eight cases in the methadone group (Table 7). In one case, the concentration reached 3.54 g/L.

A cross-analysis of toxicological investigations data permits appreciation of the responsibility of the products of substitution.

Among people having consumed buprenorphine, two groups were distinguished, according to their blood concentrations:

- **For 12 cases**, the concentration was toxic. Among them, seven cases showed other drugs at lethal or toxic levels, capable in and of themselves of causing death. In the five other cases, buprenorphine may be considered as directly responsible for the death; however, four of the five had alcohol, cannabis and/or from one to eight other associated substances at non-toxic concentrations, which may have also played a role in the lethal process.

- **Among 22 other cases** for which buprenorphine was positive at non-toxic levels, 18 deaths can be explained by other associated drugs or violent causes. The remaining four cases cannot be explained by other drugs at toxic concentrations. However, it bears mention that there was concomitant absorption of three to five other drugs in these cases and absorption of ethanol among two (0.4 g/L and 1.3 g/L).

In summary, buprenorphine can be regarded as being directly implied in four of 34 death cases (12%) and its participation in the lethal process is plausible in eight others, as is the case for other associated toxicants. In 18 cases, it appears not to have been responsible and in four cases, no explanation was evident (Table 8).

- **For 19 cases**, methadone was quantitated at high toxic concentrations, but was considered responsible for death in only three cases, since the two other deaths involved violent circumstances (homicide by firearm, burns and carbon monoxide intoxication). For 11 other cases, methadone was associated with another substance at toxic concentration, or with another plausible cause of death.
Among 21 other cases for which methadone was positive at non-toxic levels, 13 deaths can be explained by other associated drugs or violent causes. For the remaining eight deaths, concentrations of methadone were low and none of the other identified substances reached a toxic concentration.

In summary, methadone can be regarded as implied directly in three of 35 deaths (9%), and its participation in the lethal process was plausible in 11, as was the case for other toxicants associated with its use. In 21 cases, it appears not to have been responsible and in eight cases, no explanation was evident.

DISCUSSION

Surprisingly, in this retrospective study we found approximately as many deaths with positive detection of methadone as those with positive detection of buprenorphine over the same period of time in spite of a far greater number of prescriptions for buprenorphine. In the same vein, a recent retrospective study on severe opioid poisonings requiring intensive care admission from 1995 to 1999 in north-east Paris showed that buprenorphine was detected in 19 cases while methadone was detected in 12 patients [19]. In France, approximately 80 000 heroin addicts are treated daily by high-dose buprenorphine while 10 000 heroin addicts are treated by methadone. According to the sales of methadone and buprenorphine during this period of time, one might have anticipated a higher number of deaths associated with buprenorphine than with methadone if toxicity was similar. Our data do not allow us to form any firm conclusions regarding the potential toxicity of each substance, due to the large number of variables in terms of chronicity of treatment, associated drug use and other potential sources of bias. Indeed, different prescribing practices for each drug and differential patient selection criteria for opioid substitution may in part explain our findings. While methadone is delivered in specialized health centres every week—with urine drug testing—buprenorphine may be prescribed in France by any general practitioner for a 28 day period and delivered by any pharmacy without any requirement for drug testing. From the beginning, methadone appears to have had the image in France of ‘a drug of last resort’ for the most desperate cases (this is not the case in the majority of countries, which have employed only methadone substitution for many years). On the contrary, buprenorphine is perceived among users and care givers as a first-line treatment, more simple, more flexible and thus a priori destined for ‘less serious cases’. The differences in prescribing rules and the disparity with regard to access to the two products clearly have a strong influence on their reputations. Another reason for prescribing one drug versus the other may have to do with the perception that methadone, due to its pure μ agonist properties, has greater anxiolytic effects than buprenorphine. This would encourage use of the former in subjects presenting with psychopathology complicated by a greater degree of anxiety. These elements seem to be corroborated by a study that attempted to identify predictive factors for response to treatment by high-dose buprenorphine and that showed that social insertion and previous attempts at abstinence were favourable factors while, inversely, psychiatric disturbances that had not been treated previously were unfavourable factors [20]. However, authors are not unanimous in this regard. Certain consider that buprenorphine is a first-line substitution treatment, reserving methadone as a utilizable treatment in selected cases [21]. A similar point of view has been expressed by a Swiss group, who concluded that it is not appropriate to treat all patients with a pure agonist like methadone and that initial induction of treatment with buprenorphine is often preferable with the possibility to resort to methadone treatment [22]. It might thus be argued that the indications for buprenorphine and methadone are sufficiently different that comparison of mortality in their use serves little purpose. On the contrary, we find the comparison to be critical. In locations where both substitution products are available, this data may be used to determine more appropriate prescribing conditions for each drug. Conversely, in locales where only one of the drugs is available, this comparison should encourage a review of the existing formulary.

Tolerance to opioids and/or benzodiazepines would be expected to play a significant role in both their individual and combined toxicities. Tolerance has been reported with methadone as well as buprenorphine. In vivo behavioural studies showed that higher efficacy μ agonists appear more resistant to tolerance than do lower efficacy agonists. Treatment with escalating doses of morphine or buprenorphine produced greater tolerance to the lower efficacy buprenorphine than to the higher efficacy agonist, morphine [23]. Furthermore, repeated morphine treatment results in less cross-tolerance to higher efficacy agonist methadone than to morphine [24]. Unfortunately, in our forensic study, because the ante-mortem histories of drug use of the subjects were often unobtainable, we cannot comment on the role that tolerance, or lack thereof, may have played in these deaths.

On the contrary, comparison of the incidents caused by the abuse of each tends to suggest that the risk of deaths would be higher if methadone alone were available [25].

Tracqui described 20 deaths attributed to ‘intoxication’ by buprenorphine, despite blood concentrations close to the therapeutic range [3]. However, in five cases out of 20, there were additional associated opioids.
Only the study of Kintz [6] collected forensic cases, and is thus directly comparable with ours. In this series of 117 deaths, only one case involved buprenorphine taken alone, quantitated at 0.8 ng/mL, and death was listed as being caused by aspiration pneumonia. Furthermore, the author did not consider the lethal concentrations of various substances associated with buprenorphine.

Kintz recognized, like others, the determining role of benzodiazepines in the death process when they were employed with buprenorphine [19] or with methadone [14]. It is known both experimentally [26] and clinically [27] in anesthesiology that the respiratory depression induced by the opioids can be worsened by the addition of benzodiazepines.

Our discussion is based on analytical findings performed on very selective and sensitive analytical equipment. However, we did not quantify norbuprenorphine, the metabolite of buprenorphine, which was demonstrated by Ohtani and colleagues as a strong toxicant playing a predominant role in the respiratory depression associated with buprenorphine [28]. For methadone, our dosages did not distinguish D and L methadone since we did not use a chiral column on our chromatographs.

With regard to our blood and urine post-mortem samples, we noted that buprenorphine was detected only in the urine in 16 cases, and methadone was detected only in the urine in two cases. This could artificially increase the total number of buprenorphine overdoses. Thus, it would be logical to remove those buprenorphine and methadone cases detected in urine only. Even though the principal buprenorphine metabolite is active, and methadone metabolites are not active, if we remove those buprenorphine and methadone urine-only positive cases then the global number of deaths associated with methadone rises.

Our classification of ‘clear responsibility’, ‘possible responsibility’ or ‘not causative’ roles of buprenorphine and methadone in the death process, or ‘no explanation of death’, refers to the past history of the subjects, which often is not well known. Moreover, those data are only provided by officials in a retrospective context.

In order to appreciate the action of the various substances analysed, it is appropriate to consider the difficulty inherent in interpreting the concentrations found in the corpse using toxic concentrations measured in the living. Specific references for these situations are generally unavailable. For the living subject, the analyst uses serum or plasma for which effective therapeutic, toxic and lethal concentrations have been established. For the corpse, the use of lysed whole blood may explain the origin of dispersions from published data. One may add to these difficulties the variability of biological environments after death [22,29,30]: development of microbial flora able to produce or to consume alcohol; quick degradation of flunitrazepam (less than 24 hours) [22]; re-circulation of blood within the vessels under the action of gases of putrefaction [29,30]; exchanges between intra- and extracellular biological compartments; ‘exit’ of drugs from tissues; contamination of blood from the digestive tract; and external contamination. In summary, it is almost always difficult to determine the precise role of a drug in the death process.

In our studied series, buprenorphine and methadone were present at more or less elevated concentrations, sometimes clearly toxic, when compared with analytical data usually observed in the living subject. However, the imputability of the death to these two molecules can be established only rarely (less than 12% of the cases for buprenorphine and less than 9% for methadone) and must be really excluded in 64% of the cases of buprenorphine and 60% of the cases of methadone. For the remaining 24% of buprenorphine-associated and 31% of methadone-associated cases, the participation of these drugs in the process that caused death is plausible at best.

In four of the 34 deaths involving buprenorphine, no explanation was evident. We note that in three cases there were co-ingestions of buprenorphine and methadone and two to four other drugs [temazepam, cannabis, propranolol, cyamemazine, paracetamol, alcohol (0.3 g/L) and cocaine] at therapeutic blood concentrations. The fourth case had cocaine at therapeutic blood concentrations and alcohol at 1 g/L.

In eight of the 35 cases involving methadone, no cause of death was evident. Three of these cases involving both buprenorphine and methadone have just been described. Four other cases implicated methadone along with two to six associated drugs at therapeutic blood concentrations (bromazepam, codeine, morphine, cannabis, paracetamol, cocaine, diazepam, dicydrocodeine, cetirizine). The final case among them associated methadone and bromazepam at therapeutic concentrations, along with ethanol (0.27 g/L).

**CONCLUSIONS**

This paper reports a review of forensic cases involving 34 cases of buprenorphine detection and 35 cases of methadone detection among 1600 toxicological investigations performed at the Laboratory of Toxicology of the Paris Police Department within the period of June 1997 to June 2002.

Buprenorphine was detected in post-mortem whole blood by GC-MS in a range from 0.5 ng/mL to 46.1 ng/mL, while methadone was measured at 20 ng/mL to 1960 ng/mL.

The study of the role of each drug, based on total blood concentrations of these and associated substances and
the reported death circumstances, leads us to assess the clear responsibility of buprenorphine only in four cases (12%), and of methadone only in three cases (9%). The potential for synergistic or additive actions by other isolated molecules, particularly opioids, benzodiazepines, other psychotropic drugs and alcohol, must also be considered. Finally, even though both buprenorphine and methadone may be used as heroin substitution products, their precise roles may differ according to clinical circumstances. This should be taken into account in both the choice of prescription of these drugs and in any comparison of associated mortality.

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Conflict of interest statement

This work was supported by Schering-Plough, the distributor of buprenorphine in France.

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