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Parenteral buprenorphine–naloxone abuse is a major cause of fatal buprenorphine-related poisoning

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ABSTRACT

Buprenorphine (BPN) medication for opioid maintenance treatment in Finland consists predominantly of buprenorphine–naloxone (BNX). Both BPN and BNX are associated with diversion, abuse and non-medically supervised use worldwide. Our purpose was to estimate the proportion of BNX to all BPN-related fatalities. The material consisted of 225 deceased drug abusers in Finland from January 2010 to June 2011 with a positive BPN and/or norbuprenorphine (NOR) and/or naloxone (NX) finding in urine. The data were divided into three groups based on the urine NX and BPN concentrations. The "Parenteral BNX" group (>100 μg/l NX) was presumed to consist of injecting or snorting BNX abusers and the "Parenteral BPN" group (>50 μg/l BPN, 0 μg/l NX) of injecting or snorting BPN abusers, while the "Other BNX or BPN" group (≤100 μg/l NX, or ≤50 μg/l BPN combined with 0 μg/l NX) was presumed to consist of mainly sublingual BNX or BPN users. In 12.4% of cases the NX urine concentration was higher than the threshold 100 μg/l. In fatal BPN poisonings, the proportion of parenteral BNX was 28.4%. In the "Parenteral BNX", "Parenteral BPN" and "Other BNX or BPN" groups, the proportion of fatal BPN poisonings was 67.9, 31.0 and 22.6%, respectively. BNX abuse can be fatal. Among the 225 BPN-related fatalities, parenteral abuse of BNX was shown to be common (12.4%) and BNX poisoning was the underlying cause of death in 8.4%. Parenteral BNX caused fatal BPN poisoning proportionally more often than parenteral BPN.

1. Introduction

Buprenorphine (BPN) is a semisynthetic opiate originally developed as an analgesic and used at low doses in post-operative and cancer patients [1,2]. BPN is a relatively long-acting partial mu agonist and full kappa antagonist. It is metabolised to norbuprenorphine (NOR) and the respective glucuronide conjugates [3]. In the late 1970s, BPN was proposed as a treatment for opiate dependence [4]. As a partial agonist it exhibits a ceiling effect at high doses, which means that there is a plateau for opioid agonist effects such as sedation and respiratory depression. Single doses of BPN up to 70 times the recommended analgesic dose were well tolerated by nondependent humans [5]. To discourage parenteral abuse of BPN, a co-formulation of BPN and the opioid antagonist naloxone (NX) was developed. When taken sublingually as prescribed, the therapeutic efficacy and safety of the buprenorphine–naloxone coformulation (BNX) are similar to those of BPN alone. Both medicines reduce the use of opiates and the craving for opiates among opiate-addicted persons who receive these medications in an office-based setting [6]. The advantage of BNX in preventing abuse is due to the fact that while the sublingual bioavailability of BPN is relatively high, that of NX is low [7]. Furthermore, if BNX is taken parenterally, the bioavailability of NX is high, which should precipitate withdrawal and attenuation of the pleasurable effects in opioid-dependent subjects [8].

Despite the indisputable benefits of both BPN and BNX in the maintenance treatment of opioid-dependent patients, these drugs are associated with a considerable amount of diversion, abuse and non-medically supervised use [9,10]. Fatal BPN poisonings have been reported, especially from France [11], Finland [12] and Sweden [13]. In New Zealand, BNX was introduced in 1991 following considerable intravenous abuse of BPN tablets. Although less abuse was associated with BNX and a reduction in the street price of BNX was noticed, the co-formulation still remained a drug of intravenous abuse [14]. Since then, many studies have proven that the abuse potential of BNX is less than that of BPN but still considerable in both opioid-dependent and non-dependent abusers [15–22]. However, until recently there has been no established laboratory urine assay to positively differentiate abuse between BPN alone and BNX in a clinical or forensic context. Furthermore, it has not been verified whether BNX can cause fatal poisonings at all.

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In our recent study, we measured total concentrations of NX, BPN and NOR in urine samples from opioid-dependent patients before and during the stable and unstable phases of substitution treatment with BNX [23]. Parenteral use of BNX was thought to be associated with a high NX/BPN concentration ratio in urine, while negative NX with a positive BPN finding suggested use/abuse of BPN alone [23].

Our objective in the present study is to estimate the proportion of BNX abuse to all BPN-related fatalities in Finland during an 18-month period in 2010–2011. Following urine analysis of postmortem cases associated with BPN or BNX abuse, we elaborate the material based on BPN, NOR and NX urine concentrations and case background information and evaluate the results in terms of the role of BNX in the cause and manner of death. We also present a case report describing a typical BNX associated death in which the cause of death was classified as BPN poisoning.

2. Methods

2.1. Data sources

Our primary data consisted of all deaths in Finland in which a case was registered and a comprehensive postmortem toxicological analysis was performed between 1/1/2010 and 6/30/2011 at Hjelt Institute, Department of Forensic Medicine. The total number of postmortem toxicology cases investigated during that time period was 10,464. From this material, all the cases with a confirmed positive BPN and/or NOR and/or NX finding in urine were included. Those cases were excluded in which BPN or BNX had been used as a prescribed analgesic without reference to drug abuse, according to a forensic pathologist's referral or death certificate.

The postmortem database included a forensic pathologist's referral, laboratory analysis results, and information extracted from the death certificate issued by a forensic pathologist. The referral contained a brief description of the circumstances of death and the main autopsy findings. The laboratory data included BPN, NOR and NX concentrations in urine. Information from the final death certificate included the age and gender of the deceased, the cause of death with contributing factors according to the International Classification of Diseases (ICD-10), and the manner of death (World Health Organisation, WHO).

The data were divided into three groups, "Parenteral BNX", "Parenteral BPN" and "Other BNX or BPN", based on concentration data. The "Parenteral BNX" group consists of cases in which the NX urine concentration was above 100 μg/l. In the group "Parenteral BPN", the BPN urine concentration was above 50 μg/l and no NX was found. The "Parenteral BNX" group was presumed to consist of injecting or snorting BNX users and the "Parenteral BPN" of injecting or snorting BPN users, while the "Other BNX or BPN" group (≤100 μg/l NX, or ≤50 μg/l BPN combined with 0 μg/l NX) was presumed to consist of sublingual BNX or BPN users and unclear cases. We also tested the results with higher concentration thresholds, NX of 200 μg/l for the "Parenteral BNX" group and BPN of 100 μg/l for the "Parenteral BPN" group.

A BPN-related death was classified as a fatal BPN poisoning, if a forensic pathologist had determined in the death certificate the cause of death as poisoning and highlighted BPN as the most important finding.

2.2. Laboratory methods

The analysis method for BPN, NOR and NX has been described and validated in detail elsewhere [23]. The method for 1-ml urine samples involved enzymatic hydrolysis by β-glucuronidase and liquid–liquid extraction followed by liquid chromatography–tandem mass spectrometry in multiple reaction monitoring mode. Dedicated deuterated internal standards were used for calibration and analysis. A lower limit of quantification of 1.0 μg/l was established for each of the three compounds in urine. Ethanol was analysed in blood samples by headspace gas chromatography. Cases with blood ethanol concentration higher than 0.5‰ were classified as positive for alcohol.

Table 1
Frequency of postmortem cases in "Parenteral BNX"[a], "Parenteral BPN"[b] and "Other BNX or BPN"[c] groups divided according to the cause of death into fatal BPN poisonings and other causes of death.

Cause of death	Parenteral BNX[a]	Parenteral BPN[b]	Other BNX or BPN[c]	Total
BPN poisoning	19	13	35	67
Other	9	29	120	158
Total	28	42	155	225

[a] "Parenteral BNX", based on naloxone (NX) urine concentration > 100 μg/l, is presumed to consist of injecting or snorting buprenorphine–naloxone (BNX) users.
[b] "Parenteral BPN", based on buprenorphine (BPN) urine concentration >50 μg/l with NX 0 μg/l, is presumed to consist of injecting or snorting BPN users.
[c] "Other BNX or BPN", based on NX urine concentration ≤100 μg/l, or BPN urine concentration ≤50 μg/l with NX 0 μg/l, is presumed to consist of sublingual BNX and BPN users.

2.3. Statistical analysis

Medians and their 95% confidence intervals were used as summary statistics of the drug concentrations since the drug concentration data were skewed. A Kruskall–Wallis test for unpaired data was performed when comparing the concentrations and differences in manners of death between the "Parenteral BNX", "Parenteral BPN" and "Other BNX or BPN" groups. A p value of <0.05 was considered to indicate a statistically significant difference. Statistical analyses were performed with SPSS 15.0.

3. Results

Among the 10,464 postmortem toxicology cases investigated during the 18-month period, 225 cases (2.2%) met the inclusion criteria of the study: a urine sample testing positive for one of the following compounds, BPN, NOR or NX, and background information supporting drug abuse. The mean and median age of the deceased was 33 and 30 years, respectively, and the range was 18–73 years. The proportion of men was 84.9% (191 cases).

Table 1 shows the number of cases in the "Parenteral BNX", "Parenteral BPN" and "Other BNX or BPN" groups divided according to the cause of death into fatal BPN poisonings and other causes of death, as indicated by forensic pathologists. In 12.4% of cases the NX urine concentration was higher than the threshold concentration of 100 μg/l, indicating parenteral abuse of BNX. The proportion of fatal BPN poisonings by parenteral BNX to all fatal BPN poisonings was 28.4%. In the "Parenteral BNX" group, 67.9% of cases were fatal BPN poisonings, while in the "Parenteral BPN" group this figure was 31.0% and in the "Other BNX or BPN" group 22.6%. There was a statistically significant difference in the frequency of fatal BPN poisonings between the "Parenteral BNX" and "Parenteral BPN" groups ($p = 0.003$), and between "Parenteral BNX" and "Other BNX or BPN" ($p < 0.001$). The proportions of BPN poisonings between the groups "Parenteral BPN" and "Other BNX or BPN" did not differ significantly. Table 2 shows the urine concentrations of NX, BPN and NOR in the "Parenteral BNX", "Parenteral BPN" and "Other BNX or BPN" groups.

Using a higher NX threshold of 200 μg/l for "Parenteral BNX", there would be 16 (7%) "Parenteral BNX" cases of which 10 (63%) BPN poisonings. The differences in NX/BPN and NOR/BPN

Table 2
Urine concentrations of NX, BPN and NOR in the "Parenteral BNX", "Parenteral BPN" and "Other BNX or BPN" groups.

	Parenteral BNX			Parenteral BPN			Other BNX or BPN		
	N	Median (95% CI)	Range	*N*	Median (95% CI)	Range	*N*	Median (95% CI)	Range
NX (μg/l)	28	225 (152–306)	110–647	0			65	25 (11–36)	1.0–98
BPN (μg/l)	28	133 (106–173)	51–708	42	106 (92–147)	51–614	141	18 (14–23)	1.2–678
NX/BPN	28	1.57 (1.07–2.14)	0.43–6.4				65	0.83 (0.52–0.97)	0.00–400
NOR (μg/l)	27	39 (8–73)	1.0–863	41	44 (14–85)	1.3–504	144	11 (7.4–17)	1.1–430
NOR/BPN	27	0.22 (0.07–0.48)	0.00–2.8	41	0.26 (0.16–0.55)	0.02–4.9	141	1.26 (0.89–1.63)	0.02–700

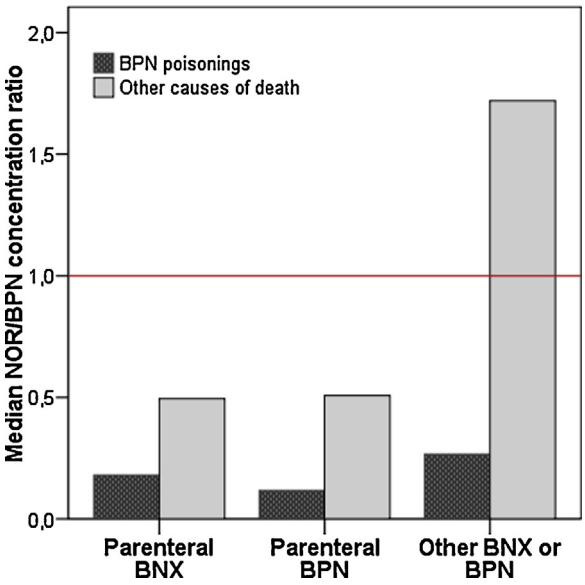

Fig. 1. Median urine NOR/BPN concentration ratios of the three groups in BPN poisonings and other causes of death.

concentrations between the groups "Parenteral BNX" and "Other BNX or BPN" were even more clear. With a higher BPN threshold of 100 μg/l for "Parenteral BPN", there would be 22 "Parenteral BPN" cases of which 8 (36%) BPN poisonings. The difference in the median NOR/BPN concentration ratio between the groups "Parenteral BPN" and "Other BNX or BPN" were even more evident with this higher threshold.

Median urine NOR/BPN concentrations in BPN poisonings and in other causes of death are shown in Fig. 1. The NOR/BPN concentration ratio between fatal BPN poisonings and other causes of death was significantly different in the group "Other BNX or BPN" (0.267 in poisonings vs. 1.72 in other causes of death, $p = 0.005$). In the groups "Parenteral BNX" (0.180 in poisonings vs. 0.495 in other causes of death) and "Parenteral BPN" (0.117 vs. 0.507, respectively), the difference was not significant.

Fig. 2 shows the median urine NX/BPN concentration ratios in BPN poisonings and other causes of death. There was no difference

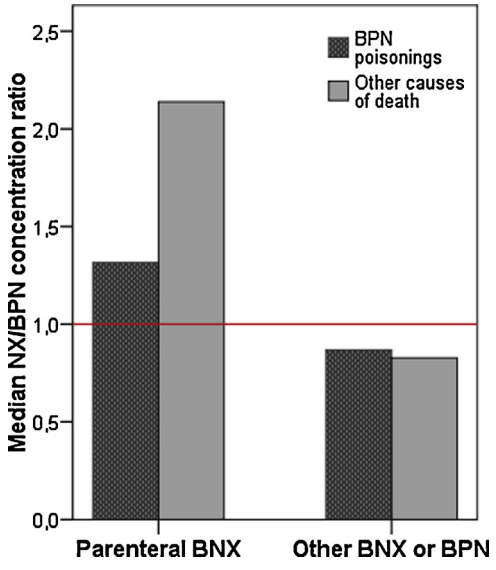

Fig. 2. Median urine NX/BPN concentration ratios in BPN poisonings and other causes of death.

in the NX/BPN ratio between BPN poisonings and other causes of death in either of the groups. In the "Parenteral BNX group", the median concentration ratios in BPN poisonings and other causes of death were 1.32 and 2.14, respectively, and in the "Other BNX or BPN" group 0.869 and 0.827, respectively.

Alcohol was found in 39.3% of the cases in the group "Parenteral BNX". The median blood alcohol concentration was 1.20‰ and the range was 0.58–2.10‰. In the group "Parenteral BPN" these figures were 28.6%, 1.65‰ and 0.69–2.50‰, and in the group "Other BNX or BPN" 38.1%, 1.40‰ and 0.52–3.20‰, respectively. The differences between the three groups were not statistically significant.

The manner of death did not differ significantly between the three groups. The proportion of accidents in the "Parenteral BNX", "Parenteral BPN" and "Other BNX or BPN" groups was 71.4%, 64.3% and 71.0%, respectively. The proportion of suicides was 10.7%, 14.3% and 12.0%, the proportion of diseases was 7.1%, 14.3% and 7.1%, the proportion of homicides was 3.6%, 4.8% and 3.2%, and the manner of death was unclear in 7.1%, 2.4% and 5.2% of cases, respectively.

The following case report depicts a typical account belonging to the group "Parenteral BNX": A 26-year-old male with hepatitis C and a history of BPN and alcohol abuse went to his friend's apartment at night after abusing drugs. The next day he was found dead. An injection mark was located in the inside of his elbow. Postmortem toxicology revealed blood alcohol concentration of 0.39‰ and urine alcohol of 1.5‰. The following drug substances were found in the postmortem femoral blood: BPN 2.7 μg/l, NOR 1.5 μg/l, alprazolam 0.031 mg/l, 1-hydroxyalprazolam 0.002 mg/l, diazepam 0.055 mg/l, and naproxen 17 mg/l. The concentration of nordazepam remained below the limit of quantification. The concentrations in urine were as follows: BPN 421 μg/l, NX 554 μg/l, and NOR 20.8 μg/l, resulting in the urine NX/BPN concentration ratio of 1.32 and NOR/BPN ratio of 0.05. A forensic pathologist determined the cause of death as buprenorphine, alprazolam and alcohol poisoning, with buprenorphine as the most important finding. The manner of death was classified as accident.

4. Discussion

We were able to show that parenteral BNX abuse poses a high risk of fatal poisoning. In our postmortem material, the proportion of parenteral BNX abuse was 12% of all buprenorphine-related abuser cases, while 68% of parenteral BNX cases were BPN poisonings. Of all the BPN poisonings, 28% were attributed to parenteral BNX use. The proportion of BPN poisonings was significantly higher in the "Parenteral BNX" group than in the "Parenteral BPN" or "Other BNX or BPN" groups. Parenteral BNX abuse has previously been studied with questionnaire surveys among injecting drug users or opioid substitution treatment clients. Regular or daily BNX injecting has been reported to be 5% [21], 3–7% [24], and 8.3% [16]. BNX injecting had occurred during the previous 6 months in 9–10% [24] and 13% [21]. These percentages are parallel to the parenteral BNX abuse of 12% in the present study of postmortem cases.

In this study, the NX/BPN concentration ratio was significantly higher in the "Parenteral BNX" group and lower in the "Other BNX or BPN" group. We have previously reported that a high NX/BPN ratio may indicate parenteral use of BNX among patients in opioid maintenance treatment [23]. Furthermore, the NOR/BPN concentration ratio was low in the parenteral groups and high in the "Other BNX or BPN" group. It has previously been found that a urine NOR/BPN concentration ratio of <0.5 indicates very recent use of BPN, and a ratio of 1 indicates use within the previous 7–10 h [25]. In our study, the median NOR/BPN ratios were <0.5 in the parenteral groups in both BPN poisonings and other causes of death and in BPN poisonings in the group "Other BNX and BPN",

and >1 in other causes of death in the "Other" group (Fig. 1). The present results indicate that in the parenteral cases and in BPN poisonings the use of BPN or BNX had been more recent.

Urine analysis for establishing the NX threshold concentration [23] was crucial for differentiating parenteral BNX use. The pharmacokinetics of BPN and NX has been studied in various settings [7,25–32]. The elimination half-life of NX is less than 2 h [7], while those of BPN and NOR are much longer and variable. Sublingually taken BPN half-lives of 20–32 h [7], and 41 and 44 h [26] have been reported. For NOR, a half-life of 34 h [7] and 40 and 73 h [26] in sublingual use have been reported. NX concentrations in plasma are low and detectable only for a few hours, making plasma less suitable for monitoring compliance. Interestingly, very little is known about the urinary pharmacokinetics of NX. An early paper reported that 24–37% of a labelled NX dose appeared in urine during the first 6 h and that very little radioactivity was measurable after 48 h [33]. Another study found about 55% of the daily NX dose excreted in 24-h urine as NX and metabolites [34]. Only one previous study utilised a urine NX assay for assessing the abuse potential of BNX in a clinical context, but no concentrations were reported [14]. Other studies dealing with urine NX concentrations have focused on detecting urine adulteration [35,36].

We tried to set our NX threshold concentration in urine high enough to avoid the possibility that sublingual BNX use would be considered parenteral BNX abuse. Hull et al. [35] took the view that NX would be undetectable in urine with a cut-off concentration of 100 μg/l if the BNX was taken sublingually. In our previous paper [23], we studied patients at different phases of opioid maintenance treatment. During the stable phase of treatment, urine NX was 5–200 μg/l and in 85% of the cases <100 μg/l. On the other hand, at the unstable phase of the treatment, in which parenteral BNX abuse was also suspected, urine NX was >100 μg/l in 33% of the cases and >200 μg/l in 22%. In the present study, we used the NX threshold of 100 μg/l but also tested a higher threshold of 200 μg/l for the group "Parenteral BNX". The results were rather similar with both thresholds.

Setting a BPN threshold concentration in urine for the group "Parenteral BPN" was challenging since there is little data to compare with. Only a few reports on postmortem cases have been published in which injection or snorting of BPN is known. Postmortem urine BPN concentrations in injecting cases were 15.0 μg/l and 344 μg/l [37], and 3.4 μg/l and 23 μg/l [38]. Postmortem urine BPN concentrations in snorting cases were as high as 193, 216 and 775 μg/l [39]. Interestingly, Seldén et al. found that the median postmortem urine BPN concentration was as low as 50.5 μg/l in fatal poisonings ($N = 41$) [13]. Data from 18 volunteers who received 0.4 mg Suboxone sublingually showed a median maximum BPN urine concentration of 9.0 μg/l at 2 h after receiving the dose, while the highest individual concentrations were 52.6 μg/l and 59.8 μg/l [25]. In our material, BPN-related deaths had usually been delayed so we set the threshold at 50 μg/l. There are certainly parenteral BPN cases under this limit, too, but the cases with low concentrations cannot be distinguished from sublingual use without more precise information on the circumstances of death. Conversely, in the "Parenteral BPN" group there might also be some sublingual cases. When testing our data with the higher BPN threshold of 100 μg/l, the results were rather similar to those obtained by the current threshold of 50 μg/l. The proportion of BPN abuse was 36% with the higher threshold and 31% with the lower one.

In our previous study, benzodiazepines were found in 82.4%, alcohol in 58.2%, and either benzodiazepines or alcohol in 94.0% of the BPN related deaths [12]. Furthermore, out of the 391 BPN-related deaths previously studied, there was only one case in which no other drugs than BPN was found [12]. Similarly in the present material, especially alcohol and/or sedative-hypnotics were frequently encountered in buprenorphine-related cases, as exemplified by the case note above. It is a generally accepted fact that co-abuse of benzodiazepines and opioids is substantial and has negative consequences for general health, overdose lethality, and treatment outcome [40]. The specific mechanism involving drug interactions in buprenorphine toxicity is under investigation [41].

This study involves some limitations. We divided the data into the three groups based on laboratory results and not on actual information on the route of drug administration or whether the deceased had used BPN or BNX. In most cases, the information on the administration route or drug product could not be obtained from the death certificates nor from the pathologists' referral, and consequently we had to set the threshold limits based on the few available previous publications. In only a few cases there was information on how the drug had been administered. In the death certificates the exact drug was seldom mentioned, and when it was, it was usually referred to as BPN, even if the drug had obviously been BNX. Further data on urine NX concentrations in parenteral and sublingual BNX use are needed.

In Finland, the disappearance of heroin from the drug scene after the outbreak of the Afghan war in 2001 and registration of BPN for use in opioid substitution treatment in 2002 resulted in a sharp increase in BPN abuse and fatal poisonings [42]. Contrary to most other countries, heroin never came back but the abuse of prescription opioids, especially BPN, has continued to escalate [43]. BPN abusers have risky abuse patterns, including intravenous administration and concomitant medication abuse [44]. BNX became available in Finland in late 2003 and many treatment centres rapidly transferred their BPN patients to BNX [45]. Currently all patients in BPN substitution treatment receive BNX, except for pregnant women, who receive BPN alone. Consequently, nearly all BPN without NX on the illicit market is imported. BPN is today the most important abused opioid causing fatal poisonings in Finland [12]. However, so far no data have been available to evaluate the respective roles of BPN and BNX in these deaths. The present study suggests that parenteral BNX abuse poses a similar or even higher potential for fatal poisoning than parenteral BPN.

5. Conclusions

It has been shown for the first time using laboratory methods that parenteral BNX abuse is responsible for a great proportion of fatal BPN poisonings. The percentage of BPN poisonings among the parenteral BNX abusers (68%) was twice as high as among the parenteral BPN abusers (31%). The proportion of parenteral BNX abuse (12%) of all BPN-related postmortem abuse cases was parallel to that found in clinical studies among intravenous abusers. The manner of death in fatal BPN poisonings was predominantly accidental and did not differ significantly between parenteral BNX, parenteral BPN and other BPN-related cases.

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