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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