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Toxicological and pathological findings in a series of buprenorphine related deaths. Possible risk factors for fatal outcome

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ABSTRACT

Buprenorphine is considered to have little respiratory side effects at therapeutic doses and the partial agonistic properties should produce a "ceiling effect" for respiratory depression at higher doses. Still, there are several reports on buprenorphine related deaths. Most deaths involve drug users and the co-administration of other CNS depressant drugs as well as reduced tolerance have been suggested to be risk factors. The primary aims were to investigate if lack of tolerance and/or co-ingestion of other psychotropic drugs are significant risk factors in buprenorphine fatalities. From July 2005 to September 2009, all autopsy cases where buprenorphine or norbuprenorphine had been detected in femoral blood and where analysis of buprenorphine had been performed in urine were selected. Results from the postmortem examination and toxicology were compiled. Postmortem toxicology was performed using the routine methodology at the laboratory. In total, 97 subjects were included in the study. These were divided into four groups; Intoxication with buprenorphine ($N = 41$), Possible intoxication with buprenorphine ($N = 24$), Control cases where buprenorphine was not the cause of death ($N = 14$), and Unclear ($N = 18$). The metabolite to parent compound ratios in both blood and urine in the Intoxication group were significantly different from those in the Control and Unclear groups. An extensive poly-drug use was seen in all groups with several additional opioids in the Possible group (54%) and in the Unclear group (78%) and hypnotics or sedatives in more than 75% of the Intoxication, Possible, and Unclear cases. Illicit drugs were present in all groups but not to a great extent with amphetamine and tetrahydrocannabinol as the main findings. Interestingly, 4 cases in the Intoxication group presented with no other significant drugs in blood other than buprenorphine. We conclude that a lethal concentration of buprenorphine in blood cannot be defined. Instead the analysis of blood as well as urine can be an important tool to show that the drug was taken shortly before death and to rule out a continuous use of buprenorphine supporting the notion that abstinence is an important risk factor. The presence of alprazolam in more than 40% of the Intoxications and the presence of hypnotics and sedatives in 75% of the Intoxications suggests that these drugs interact with buprenorphine producing toxic effects that buprenorphine alone would not have produced. Still, in 10% of the Intoxications no other drugs were found indicating that under certain circumstances buprenorphine alone may produce respiratory depression resulting in death.

1. Introduction

Buprenorphine is a semi-synthetic opioid widely used in treatment of opioid addiction under the trade names Subutex® and Suboxone®. The doses range from 1 up to 32 mg/day but it is also used to treat moderate to severe chronic pain with therapeutic doses of 0.2–0.8 mg/day. Many of the opioids have severe adverse effects, respiratory depression being one of the more serious that can lead to coma and death. The respiratory depression is caused by a decreased sensitivity to carbon dioxide at chemoreceptors in the medulla oblongata and is thought to be mediated by the mu-receptor subtype [1]. There are three receptor subtypes, mu, kappa, and delta that all are G-protein coupled. Buprenorphine is a partial agonist at the mu-receptor and a weak antagonist at the kappa-receptor. At therapeutic doses buprenorphine is considered to have little respiratory side effects and the partial agonistic properties should

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produce a "ceiling effect" for respiratory depression even at higher doses. This has been shown in animal studies [2]. Still, there are several reports on buprenorphine related deaths that points in another direction and many of these cases present with buprenorphine concentrations in the therapeutic range [3–11]. A compilation of buprenorphine concentrations from earlier publications is presented in Table 1. The fatalities mainly involved drug users and the co-administration of other central depressant drugs was suggested as a risk factor [4–7,11]. In addition, many of the cases showed evidence of injection as mode of administration that might be important for the acute toxicity. The largest study to date, by Hakkinen et al. [4], involves 391 buprenorphine related deaths with almost half of them (182) classified as fatal buprenorphine poisonings. The study found significantly higher median buprenorphine concentration in the fatal poisonings than in cases with other causes of death (1.4 vs. 1.2 μg/L). However, this was not considered to be clinically significant. Instead the ratio of buprenorphine to the metabolite norbuprenorphine was proposed as a diagnostic tool, with a ratio >1 indicating a fatal buprenorphine overdose.

The clinical signs in non-fatal buprenorphine overdoses are very similar to those of heroin or methadone [12] however the mechanisms seem to be different as the subjects do not always respond to naloxone treatment. In cases of co-ingestion of bensodiazepines, treatment with flumazenil may reverse respiratory depression. These observations point towards a combined effect of buprenrophine and bensodiazepines. Bensodiazepines though, cannot be treated as a group because their interactions with buprenorphine vary as shown in several animal studies [13–15]. Among the evaluated substances flunitrazepam and midazolam were more likely to enhance the respiratory depressant effects.

Another risk factor that has been suggested in opioid deaths is reduced tolerance due to a period of abstinence [16–21]. Even though there is no biomarker for tolerance, the investigation of abstinence might be used to evaluate this. Some research groups have used hair analysis to monitor drug use in the weeks or months prior to death concluding that abstinence from opioids is common in overdose deaths [17,19,21]. However, tolerance may be reduced within just a few days. Therefore the use of metabolite:parent compound ratios in both blood and urine has been suggested as a means to determine short time abstinence or to estimate the time of last intake [22–24]. The pharmacokinetics of buprenorphine has been described as a three-compartment model with long terminal half-lives for both buprenorphine and its metabolite norbuprenorphine [25,26]. In a study by Harris et al. [27] peak plasma concentrations of buprenorphine after single sublingual administration was reached after about 1 h (range 0.79–1.17 h) whereas the concentration of norbuprenorphine peaked at 2.6 h (range 0.98–4.81 h). The norbuprenorphine concentrations after a single dose were lower than those of buprenorphine during the first hours especially after iv injection [26,27]. Greenwald et al. [28] described the pharmacokinetics during treatment and presented data that showed comparable peak concentrations of buprenorphine and norbuprenorphine in plasma after different doses. The time to peak was about 1 h with only slightly longer time for the metabolite. These differences in plasma pharmacokinetics could be used to investigate to what extent a person has used buprenorphine recently. Before being excreted both buprenorphine and norbuprenorphine undergo conjugation and the primary excretion products in urine are the corresponding glucuronides. The mean times to peak were 2 h and 4 h for buprenorphine and norbuprenorphine after a single sublingual dose with the norbuprenorphine concentration exceeding that of buprenorphine after about 7 h [23]. Before dose during treatment the ratio between norbuprenorphine and buprenorphine is about 3 [29,30] similar to the pre-dose ratio in plasma reported by Harris et al. [27].

The primary aims of this study were to test the hypotheses that recent opioid abstinence and/or co-ingestion of other psychotropic drugs are significant risk factors in buprenorphine fatalities. Thus we compared the blood and urine buprenorphine and norbuprenorphine concentrations and calculated the metabolite/parent drug ratios, and assessed all other toxicological findings in cases where buprenorphine had been detected.

2. Materials and methods

2.1. Study population

This was a retrospective study. From July 2005 to September 2009, all forensic autopsy cases in Sweden where buprenorphine or norbuprenorphine had been detected in femoral blood and where analysis of buprenorphine and

Table 1
Previously reported data from overdose cases involving buprenorphine. Bup = buprenorphine, Nbup = norbuprenorphine, n.d. = not detected.

Reference	Year	*N*		Bup in blood (ng/mL)	Nbup in blood (ng/mL)	Bup in urine (ng/mL)	Nbup in urine (ng/mL)	Nbup/Bup in blood	Nbup/Bup in urine	Specimen
[11]	1998	20	Mean	8.4	2.6	172.1	67.3	0.5	0.8	Heart blood
			Median	5.2	1.6	46.9	31.0	0.3	0.7	
			Range	1.1–29	0.2–12.6	4.0–1033.0	6.6–230.0	0.03–2.0	0.1–2.6	
[9]	1998	6	Mean	7.4		103.6				Femoral blood
			Median	5.8		27.6				
			Range	1.1–17.7		15.0–344.1				
[5]	2001	39	Mean	10.2	8.2					Not specified
			Range	0.5–51.0	0.2–47.1					
[6]	2002	13	Mean	3.5	2.9			1.1		Not specified
			Median	2.2	1.5			0.7		
			Range	0.3–7.7	0.3–16.2			0.1–2.7		
[7]	2006	6	Mean	1.4	n.d.	2.5	1.7			Heart blood
Natural causes (*N* = 6)			Median	1.3	n.d.	1.1	1.7			
			Range	n.d.–3.2	n.d.	n.d.–7.8	n.d.–1.7			
Mixed drug		12	Mean	3.2	2.1	15.1	23.0			
reaction (*N* = 12)			Median	1.0	2.1	7.8	19.2			
			Range	n.d.–3.2	n.d.–3.4	n.d.–73.6	n.d.–49.8			
Other unnatural		3	Mean	24.5	23.7	8.3	359.0			
causes (*N* = 3)			Median	2.6	23.7	8.3	359.0			
			Range	2.4–68.6	n.d.–26.9	n.d.–8.3	n.d.–359.0			
[4]	2011	182	Median	1.4	0.8			0.56		Femoral blood
Buprenophine			Range	0.2–100	0.2–89			0.056–10		
poisoning (*N* = 182)										
Other causes of		209	Median	1.2	1.3			1.2		
death (*N* = 209)			Range	0.0020–74	0.14–200			0.030–100		