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Prescription opioid abuse based on representative postmortem toxicology

Margareeta Häkkinen *, Erkki Vuori, Ilkka Ojanperä

Hjelt Institute, Department of Forensic Medicine, University of Helsinki, Helsinki, Finland

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ABSTRACT

Opioids are important medications for pain and opioid maintenance treatment. Increasing use and abuse of prescription opioids has, however, caused worldwide concern. Our aim was to estimate the ratio between prescription opioid abuse and total use, based on representative postmortem toxicology. Our material included all the medico-legally examined deaths in Finland during 2010–2011 involving positive findings involving buprenorphine, codeine, fentanyl, methadone, oxycodone, or tramadol. We studied drug abuse by age group, with "abuse" meaning licit opioids used illicitly as narcotics. Drug-abuse history, drug injecting, or laboratory findings of illicit drugs defined an abuser case. We then compared abuser cases and other opioid-related cases between the opioids with the number of fatal poisonings, accidents, suicides, alcohol findings, concomitant opioid use, and median postmortem blood opioid concentrations. Opioid findings numbered 2499 in 2088 cases. Drug abuse involved 545 opioid-positive cases, which in Finland represented 0.5% of those deceased. The proportion of abuser cases among all opioid-related cases for buprenorphine was 85.5%, for methadone 82.4%, for tramadol 29.4%, for codeine 16.3%, for fentanyl 14.5%, and for oxycodone 6.9%. Abuse in age-groups >60 was rare. Concomitant other opioid findings were more frequent in abuser- than in other cases for codeine, oxycodone, and tramadol, whereas alcohol findings were more frequent in buprenorphine, codeine, and fentanyl abuse. Buprenorphine and methadone were most often related to drug abuse. Every other opioid studied involved some abuse, and especially tramadol. Abuse and fatal poisonings were concentrated in men aged 20–49.

1. Introduction

Opioids, although effective and important pain relievers and medications for opioid maintenance treatment, are abused as narcotics. Although illicit cocaine and heroin use has decreased, unintentional drug overdose deaths have increased, as has the consumption of opioid analgesics [1]. In the United States, prescription drug abuse is a major challenge in public health [2] and has become the fastest-growing drug problem [1]. Easy availability of prescription opioids maintains the abuse problem and has resulted in an opioid-abuse trend [3]. This increasing drug abuse contributes to more drug-related crimes, social and health problems, hospitalisation, and mortality. The abuse problem is worldwide, with South Asia, for example, confronting a struggle with inadequate treatment of pain, widespread opioid abuse, and insufficient access to opioid maintenance treatment [4].

Reporting opioid-related harm internationally is crucial for the monitoring and prevention of opioid epidemics in Europe [5]. Compared to North America, consumption of prescription opioids in Europe has been, thus far, considerably lower [2,5,6]. In France, prescription drug abuse especially concerns buprenorphine in connection with opioid maintenance treatment, morphine used as an analgesic, and to some degree, methadone and codeine [7]. In the United Kingdom, tramadol deaths have notably increased [8,9]. Deaths related to tramadol are often unintentional, and coadministration of psycholeptics or alcohol raises the risk for fatalities [9]. German researchers, in contrast, have concluded that risk for tramadol misuse or abuse and its prevalence in clinical practice is low, and they fear that strict restrictions for tramadol prescription would lead to inadequate treatment of pain [10]. Pain treatment in today's Europe seems, however, not to be inferior to that of North America, despite Europe's lower opioid consumption [2].

In Finland, nearly all opioid abuse during recent years has involved prescription opioids [11]. The one most abused is buprenorphine; heroin use is currently very rare. The latest estimate of problematic drug abuse in Finland dates back to 2005, when 0.52–0.69% of the population aged 15–55 faced social or

* Corresponding author at: PO Box 40 (Kytösuontie 11), FI-00014 University of Helsinki, Finland. Tel.: +358 414354313; fax: +358 919127518.
E-mail address: margareeta.hakkinen@helsinki.fi (M. Häkkinen).

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health problems due to drugs [11]. Problematic opioid abuse accounted for 0.13–0.18% [11]. The consumption of opioids has remained rather stable during recent years with only a slight increase from 15 defined daily doses (DDD)/1000 inhabitants/day in 2005 to 16.5 DDD/1000 inhabitants/day in 2010 and 2011 [12]. In 2005, fatal opioid poisonings numbered 126 [13], and in 2011, 189 [14]. No current estimate of the magnitude of opioid abuse exists, but in Finland, as well, abuse of prescription medications is increasing: during 2010–2011, 48% of the pregabalin and 19% of the gabapentin postmortem cases were attributable to drug abuse, and 90% of pregabalin and gabapentin abuse included concomitant opioids [15].

The purpose of this study is to evaluate the proportion of abuser cases to other opioid-related cases for the most common prescription opioids in Finland during 2010–2011, based on medico-legal cause-of-death investigations. The reason for our choosing autopsy cases as study material is Finland's high medico-legal autopsy rate; postmortem toxicology during the study years involved 13% of all deaths, giving a more representative sample of the population than in other countries. The comprehensive postmortem database allows distinctive epidemiological research, because it also includes individuals not usually participating in self-reporting surveys, and the results are based on actual laboratory analysis. We compare the differences between prescription opioids in terms of age, cause and manner of death, concomitant alcohol and other opioid use, and opioid concentration in postmortem femoral blood, to create an abuser profile for each drug.

2. Materials and methods

Our primary data included all cases with comprehensive toxicological postmortem analysis registered during 2010–2011 in the Hjelt Institute, Department of Forensic Medicine, University of Helsinki. This laboratory performs all postmortem toxicology for the Finnish population of 5.4 million inhabitants, utilising comprehensive laboratory methods covering toxicologically relevant drugs, alcohols and poisons [16]. During 2010–2011, deaths in Finland totalled 101,472 and medico-legal autopsies 22,421. Medico-legal death investigation in Finland concerns sudden or unexpected deaths, and always, deaths suspected to be related to accident, crime, suicide, poisoning, occupational disease, medical procedure, or war.

Our postmortem database included a forensic pathologist's referral, laboratory analysis results, and information from the death certificate completed by a forensic pathologist. The referral included a brief description of the circumstances of death, a brief medical history with medications used by the deceased, the main macroscopic autopsy findings, and preliminary laboratory analysis requests. From the death certificate, the database extracted information on age, gender, manner of death according to the World Health Organization, and cause of death and contributing factors according to the International Classification of Diseases (ICD-10).

We extracted all cases found positive for Finland's most prescribed opioids: buprenorphine, codeine, fentanyl, methadone, oxycodone, or tramadol. Morphine, although a widely used pain medication, was excluded because morphine is also a metabolic product of codeine, and distinguishing morphine from codeine use in laboratory findings is very difficult. A positive opioid finding represented a positive record of postmortem samples from any biological sample, such as blood, urine, liver, or muscle. Concentration data represented postmortem femoral blood concentrations. A blood alcohol concentration $\geq$0.5‰ indicated a positive alcohol record. Our definition of fatal opioid poisoning was drug poisoning as the cause of death and an opioid as the most important finding.

Abuse in our study meant use of opioids as narcotics, that is, their illicit and unprescribed use by drug addicts. To assess whether the drug use indicated abuse or other use, all documents concerning each case underwent individual investigation. One of the following defined the case as abuse: a known history of drug abuse, drug self-administration by intravenous or nasal route, new injection marks or injection equipment near the deceased, laboratory analysis results of illicit drugs such as amphetamine, cannabis, or designer drugs, and, in addition in every case, no indication for medical use of that opioid. The term "other use" referred to medical use as well as to non-medical misuse without intention to use drugs as narcotics, such as drug-induced suicides without evidence of drug addiction.

An independent samples Mann–Whitney *U*-test determined the statistical difference between the abuse and other user groups of each opioid. A $p < 0.05$ denoted the limit for statistical significance. The statistical analysis tool was IBM SPSS 21.0.

3. Results

The postmortem cases testing positive for opioids in medico-legal cause-of-death investigations in Finland during 2010–2011

Table 1
Comparison between abuser cases and other opioid-related deaths. Characteristics of all opioid-related cases according to known drug abuse, cause and manner of death, drug and alcohol findings, and blood opioid concentrations in medico-legal cause-of-death investigations in Finland during 2010–2011.

Opioid (N = 2499)	All cases %	Age, median (range)	Men %	Fatal opioid poisoning %	Accident %	Suicide %	Alcohol positive[a] %	Concomitant opioids positive %	Concentration, median (range)[b]
Known abuse (n = 716)									
Buprenorphine (307)	85.5	30 ↓ (18–69)	85.0 ↑	37.1 ↑	71.3 ↑	10.7	34.9 ↑	31.6	1.2 ↑ (0.2–99)
Codeine (123)	16.3	35 ↓ (19–73)	75.6	26.8 ↑	65.0 ↑	10.6	33.3 ↑	52.8 ↑	0.27 ↑ (0.02–7.9)
Fentanyl (32)	14.6	30 ↓ (22–49)	84.4 ↑	78.1 ↑	84.4 ↑	3.1	28.1 ↑	56.3	8.2 ↑ (0.2–45)
Methadone (70)	82.4	35 ↓ (18–58)	87.1	47.1 ↑	72.9 ↑	5.7	17.1	48.6	0.40 (0.10–3.6)
Oxycodone (41)	6.9	35 ↓ (23–74)	85.4 ↑	39.0 ↑	68.3 ↑	9.8	12.2	56.1 ↑	0.24 ↑ (0.02–1.5)
Tramadol (143)	29.4	32 ↓ (18–70)	84.6 ↑	39.2 ↑	66.4 ↑	17.5	25.2	50.3 ↑	3.1 ↑ (0.10–61)
Other use (n = 1783)									
Buprenorphine (52)	14.5	75 ↑ (20–95)	53.8 ↓	5.8 ↓	19.2 ↓	19.2	5.8 ↓	40.4	0.8 ↓ (0.20–6.8)
Codeine (628)	83.7	61 ↑ (7–100)	69.0	8.6 ↓	17.3 ↓	12.7	22.2 ↓	15.4 ↓	0.12 ↓ (0.02–130)
Fentanyl (187)	85.4	72 ↑ (0–98)	56.7 ↓	1.6 ↓	25.7 ↓	9.6	2.7 ↓	51.3	3.3 ↓ (0.01–49)
Methadone (15)	17.6	47 ↑ (26–76)	66.7	6.7 ↓	20.0 ↓	20.0	20.0	40.0	0.35 (0.07–3.0)
Oxycodone (557)	93.1	71 ↑ (1–102)	62.5 ↓	3.1 ↓	33.6 ↓	7.5	5.0	25.9 ↓	0.08 ↓ (0.01–10)
Tramadol (344)	70.6	58 ↑ (19–98)	68.0 ↓	8.7 ↓	20.1 ↓	15.4	21.2	26.5 ↓	0.9 ↓ (0.03–79)

↑ or ↓ significantly ($p < 0.05$) higher or lower value between abuser cases and other cases.
[a] Blood alcohol $\geq$0.5‰.
[b] Postmortem femoral blood concentration, μg/l for buprenorphine and fentanyl, mg/l for other opioids.