Journal of Forensic and Legal Medicine 31 (2015) 12–18

Contents lists available at ScienceDirect

Journal of Forensic and Legal Medicine

journal homepage: www.elsevier.com/locate/jflm

Original communication

Drug-related deaths between 2002 and 2013 with accent to methadone and benzodiazepines

Tatjana Petrushevska [a,*], Zlatko Jakovski [b], Verica Poposka [b], Vesna Velik Stefanovska [c]

[a] Ministry of Health, Head of Sector for Controlled Substances, National Focal Point for EMCDDA, Macedonia
[b] Institute of Forensic Medicine, Criminology and Medical Deontology at the Medical Faculty in Skopje, University "Sv.Kiril and Metodij", Skopje, Macedonia
[c] Institute for Epidemiology and Medical Biostatistics, Head of Cathedra, Medical Faculty "Ss. Cyril and Methodius" University of Skopje, Skopje, Macedonia

ARTICLE INFO

Article history:
Received 31 May 2014
Received in revised form
23 October 2014
Accepted 29 December 2014
Available online 7 January 2015

Keywords:
Methadone
Opioids
Overdose
Toxicity
Benzodiazepines
Drug-related deaths

ABSTRACT

Aim: The aim of the study is to assess the trends of overdose and drug related fatalities in the Republic of Macedonia during the 11 years.
Material and methods: Cross-sectional retrospective survey and reviewed of postmortem toxicological analyses which examined fatal poisonings with illegal drugs in years 2002–2013. Information about gender, age, drug consumption, reported years were analyzed. Narcotics were confirmed with toxicological semi quantitative fluorescence polarization immunoassay (FPIA) in urine (range 250–4000 ng/ml).
Results: Total of 165 deaths were observed. Out of them 145 (87.9%) were male. There is statistical significant differences between male and female DRD due to age (Mann–Whitney U Test = 925, Z = −2626, p = 0.0087). For $p < 0.05$ there is significant differences between genders due to cause of overdose (Pearson Chi-square = 9743, df = 4, p = 0.0449). DRD among male were mainly because of overdose due to heroin in 80 (51.17%) cases followed by DRD due to combination of methadone and BZD in 25 (11.72%) cases. Out of all DRD cases 50 (30.3%) are related to polydrug use. For $p < 0.01$ there is a significant differences between analyzed age groups due to cause of overdose (Pearson Chi-square = 33,886, df = 12, p = 0.0007).
Conclusions: Death cause analysis reveals the difficulties in determining the role of substitution drugs, as many other factors may be involved. The findings also highlight the importance of further enhancing treatment interventions for benzodiazepine misuse among patients on methadone substitution treatment.

1. Introduction

Drug addiction is a chronic, relapsing disease characterized by compulsive drug seeking and use despite harmful consequences as well as neurochemical and molecular changes in the brain.[1] Drug use can cause death directly by toxicity, either acute (e.g. overdoses) or chronic (e.g. cirrhoses or cardiovascular diseases), or by a variety of indirect effects including: facilitating the transmission of infectious diseases by certain patterns of use (e.g. sharing injection equipment); by circumstances surrounding drug dealing and social context (e.g. crime, violence); or by affecting the mental state (e.g. suicide) or psychomotor responses of the user (traffic accidents).[2] Liver disease is also likely to account for considerable numbers of deaths among drug users, mainly due to Hepatitis C Virus (HCV) infection, and often worsened by heavy alcohol use, though European figures are not available.

Using drugs in excessive quantities in an attempt to produce euphoria can result in misuse, leading to overdose. Many drug overdoses are accidental. Usage of illicit drugs of unexpected purity, in large quantities, or after a period of drug abstinence can also induce overdose, as well as the periods following release from prison[3] and dropping out of opioid substitution treatment are times of particularly high overdose mortality risk for drug users. Mortality among opioid-dependent users varies across countries and populations. Treatment is very needed to prevent Drug-Related Deaths (DRD).[4]Retrospective analysis of data of 2708 heroin-related deaths in north-eastern Italy indicated that to be female

* Corresponding author. "Dimo H. Dimov" No3 1000, Skopje, Macedonia. Tel.: +389 75 26 86 89.
E-mail address: tanja.petrusevska@gmail.com.mk (T. Petrushevska).

http://dx.doi.org/10.1016/j.jflm.2014.12.013
1752-928X/

and to have dropped out of any kind of treatment proved an important risk factor for overdose.[5]

Drug use is one of the major causes of mortality among young people in Europe, both directly through overdose (drug-induced deaths) and indirectly through drug-related diseases. Recent European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) analysis illustrates 6500 overdose deaths in 2011, and more than 70,000 overdose deaths during the first decade of the twenty-first century.[6] United Nations Office for Drugs and Crime (UNODC) estimates that there were between 102,000 and 247,000 drug-related deaths in 2011, corresponding to mortality rate of between 22.3 and 54.0 deaths per million population aged 15–64. This represents between 0.54 per cent and 1.3 per cent of mortality from all causes globally among those aged 15–64.20. The extent of drug-related deaths has essentially remained unchanged globally and within regions.[7]

The risk factors for heroin overdose are known and include the demographics of heroin users, the simultaneous use of other drugs, changes in tolerance, the amount of heroin used and injection as the route of administration.[8]

Opioids, particularly heroin, are by far the drugs most often implicated in overdoses. Heroin overdose is a serious consequence of heroin use and one of the leading causes of premature death and illness.[9] Alcohol and benzodiazepines are frequently associated with opioids in overdoses.[10] In addition to heroin, other opioids found in toxicological reports include methadone.[11]

Methadone is a synthetic opioid. Methadone is used for the treatment of opioid addiction and for treatment of chronic pain. Methadone works to treat pain by changing the way the brain and nervous system respond to pain. It also works as a substitute for opiate drugs of abuse by producing similar effects and preventing withdrawal symptoms in people who have stopped using opiate drugs.[2] Methadone is an effective maintenance therapy intervention for the treatment of heroin dependence as it retains patients in treatment and decreases heroin use better than treatments that do not utilise opioid replacement therapy. However, it does not show a statistically significant superior effect on criminal activity or mortality.[12] The use of methadone in opioid maintenance treatment is potentially associated with a number of adverse effects and the risk of fatal toxicity. Increased methadone availability may lead to an increase in methadone-related deaths.[13] Methadone replacement is the most widely used treatment for opioid addiction and reduces harm to patients. However, people enrolled in such programmes are at high risk if they relapse—the combination of methadone and heroin is often a deadly one. Indeed, the 2012 data in United Kingdom (UK) report 414 overdose deaths involving methadone—the third highest mortality in 20 years.[14] Methadone toxicity is enhanced by underlying disease, especially in individuals with underlying cardiac and pulmonary pathology.[15] The safety of methadone has been called into question by data indicating a large increase in the number of methadone-associated overdose deaths in recent years.[16] The use of methadone in opioid maintenance treatment is potentially associated with a number of adverse effects and the risk of fatal toxicity. Methadone-associated overdose deaths have dramatically increased.[17] There is a rising trend of fatal poisonings due to medicinal opioids in several countries. Methadone poisonings were associated with accidental overdoses with the drug concentration in blood remaining within a therapeutic range.[18] Mortalities attributed to methadone intoxication alone are rare. Noticeable in the studies is the high percentage of cases of combined drug intoxication (76%).[19]There is some evidence that recent initiation of methadone, psychiatric admissions, and concomitant use of benzodiazepines are associated with a higher risk for overdose. In the years 1997–2001, methadone was detected in the blood of 398 cases that were analyzed by the Institute of Legal Medicine, Bonn. Methadone was the only drug in only 18 cases. In most of the cases, up to five additional drugs were also being taken: benzodiazepines (61%), ethanol(40%), morphine (39%), cannabinoids (35%), cocaine (28%), anti-depressants (3%) and amphetamines (2%).[20]

Evidence on cardiac risks is primarily limited to case reports, primarily in patients on high doses of methadone, and to studies showing an association between methadone use and prolongation of QTc intervals. Research is needed to understand the effectiveness of dosing methods, electrocardiogram monitoring, and other risk in patients prescribed methadone.[21] The prevalence of any comorbid psychiatric disorder among Methadone Maintenance Treatment (MMT) patients is almost six times higher than the control group.[22]

The treatment of drug dependent users in the Republic of Macedonia (MKD) dates back to the late 1970s and the early 1980s, with the introduction of substitution treatment (methadone). Until adoption of the first National Drug Strategy this type of treatment was centralized. Within the implementation of the National Drug Strategy 2006–2012, the system of care which includes outpatient treatment, hospital treatment, detoxification and substitution treatment was developed and decentralized, with expansion of the network of services for treatment and harm reduction of drug abuse, including methadone maintenance treatment (11 centers were opened, as well as 3 programs in prison facilities). The introduction of new models for the treatment of dependent drug users was in place as well, with introduction of Buprenorphine, since 2009, for detoxification and substitution treatment.

In the MKD, drug-related deaths are registered by the General Mortality Register of the National Statistical Office and two countrywide documentation systems, special registers: the Police Register of the Ministry of Interior and Register of the Institutes for Forensic Medicine. However, National Focal Point (NFP) receives the latest data from four entities: the Institute of Forensic Medicine, Criminology and Medical Deontology at the Medical Faculty in Skopje; the Institute of Forensic Medicine Bitola, the Institute of Forensic Medicine Shtip and the Institute of Forensic Medicine Tetovo. Data from General Mortality Register of the National Statistical Office is statistically evaluated with 2–3 years of delay. It is also very hard to receive extracted data, only for DRD. Since 2007, MKD is applying EMCDDA methodology for key indicator “drug-related deaths”.

The aim of the study is to assess the trends in the number and nature of drug related fatalities in the MKD (2 million inhabitants) during the last 11 years with accent of methadone and benzodiazepines.

2. Material and methods

A cross-sectional retrospective survey, reviewed postmortem toxicological analyses, examined fatal poisonings with illegal drugs in years 2002–2013. Information about gender, age, drug consumption, reported year and place were analyzed. Narcotics were confirmed with toxicological semiquantitative fluorescence polarization immunoassay (FPIA) in urine (range 250–4000 ng/ml).

From the all registered deaths at the Forensic Institutes in 4 cities in the Republic of Macedonia, cases where drug consumption was the cause of death were selected. Additionally, the survey carried on retrospective analysis of the data collected by National Focal Point for cooperation with European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), related to: a. data for acute intoxication available from Toxicological Information Centre, for 2011 as well as b. seizures of heroin for the period 2002–2013.