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Fatal Poisoning in Methadone and Buprenorphine Treated Patients – Are there Differences?

Background: Some recent studies have suggested a lower risk of fatal intoxications in drug-dependent patients under buprenorphine compared to methadone treatment. **Methods:** Epidemiological reference data for the Munich region suggest that in 2003 approximately 10% of all substitution patients were treated with buprenorphine, and 87% with methadone. We studied the proportion of patients under methadone and buprenorphine substi-

tution among drug-related deaths. Data from forensic post-mortem and toxicological analysis were analyzed. **Results:** Data indicate that in 96 (35%) of all 272 so-called drug deaths, methadone was involved compared to a single case of buprenorphine, possibly indicating a relatively better risk profile of buprenorphine. **Discussion:** More prospective studies are necessary to assess the risk of fatal intoxications under different substitution regimens.

Introduction

There is broad evidence that the introduction of methadone substitution programs (MMP) in drug dependence has decreased the high mortality of intravenous heroin addicts up to 30% [22]. In Germany, the number of deaths attributed to drugs has increased in recent decades with a decline over the past ten years from 1624 in 1994 to 1477 in 2003 [19], probably due to the increased implementation of substitution treatment. Still a substantial number of deaths in drug dependence are attributed to fatal poisoning with methadone, mostly in combination with other drugs. A systematic review by Vormfelde and Poser [22] indicated that two thirds of all deaths attributed to methadone have occurred in subjects not on a MMP program and attributed to diverted methadone. A number of other studies also indicate a decrease of methadone-induced overdose mortality [5,16] over the years while Bryant et al. [6] reported an increase for New York for the years 1990–1998 parallel to an increase of prescriptions during that period.

Due to its safety profile buprenorphine has been considered as a possible alternative to methadone to lower the death rate in drug

dependence [22]. Buprenorphine is a low efficacy, partial mu-opioid agonist which has been introduced into clinical practice as an alternative to methadone for treatment of drug dependence. Its unique profile includes a ceiling on agonist activity that decreases toxicity and risk for overdose. Its slow dissociation from the mu-opioid receptor results in a long duration of action which offers the possibility of alternate-day dosing schedules. Several studies have shown encouraging clinical results [1,3,4]. Davids and Gastpar [8] concluded that buprenorphine is an effective, well-tolerated and – due to its pharmacological profile – very safe drug. There is also some evidence for buprenorphine to have less effect on cognitive functioning compared to methadone [17,18,20,21].

Buprenorphine has most frequently been used in France. For the period of 1994–1998, Auriacombe et al. [2] had already estimated a three times higher death rate from overdose of methadone compared to buprenorphine. In 2001, 74300 French heroin addicts were treated with buprenorphine compared to only 9600 with methadone. Surprisingly, the number of deaths with positive detection of methadone and buprenorphine over the same period was equal [13]. Other data indicate that fatalities associat-

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Received 18.4.2005 · Revised 25.7.2005 · Accepted 21.12.2005

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Pharmacopsychiatry 2006; 39: 85–87 © Georg Thieme Verlag KG Stuttgart · New York
DOI 10.1055/s-2006-941482
ISSN 0176-3679

ed to buprenorphine are linked to i. v. route and concomitant intake of other psychotropic agents [11,14]. Recent data from the UK indicate that there are few cases of buprenorphine-related deaths despite increasing sales, in most cases linked to intoxication with other compounds [15].

The present study was performed to further examine the safety profile of different substitution treatments with respect to fatal overdose.

Materials and Methods

We studied the relation of drugs to deaths associated with methadone or buprenorphine intake in the Munich and upper Bavarian area by comparing results from forensic post-mortem examinations with epidemiological reference data.

Epidemiological reference data

The relation of the methadone to buprenorphine substituted patients in the Munich region can be estimated by reference data provided by the national substitution register of the 'Bundesopiumstelle' which is located at the National Institute for Pharmaceutical Drugs and Medical Products (BfArM) in Bonn. All patients under substitution treatment must be named by their physician to avoid double treatments. According to this register, in 2003 in the greater Munich area 3401 patients were treated with substitution drugs. A total of 2950 (86.74%) patients were treated with methadone or levo-methadone, 337 (9.91%) with buprenorphine, and 114 (3.3%) with codeine or other drugs.

Forensic post-mortem examinations

Suspected non-natural deaths in the Munich and upper Bavaria region are autopsied at the Institute of Legal Medicine of the Munich University, including the vast majority (>>90%) of suspected drug-related deaths. Also, all toxicological analyses of death cases are performed at this institute (for methods, see [12]). The corresponding police records were evaluated, including all data on MMP (as far as reported to police authorities), personal circumstances and the known period of drug abuse and drug-free therapies. In any case of suspected non-natural death, police try to collect all data relevant to a possible cause of death from treating physicians, relatives or friends. All data available were examined in our retrospective study. The following parameters were collected: age, sex, antemortem drug-associated pathologies and circumstances of death. In all cases based on the clinical and toxicological findings an individual decision was made concerning causes of death and substances being involved.

Results

In 2002, 126 drug-related lethal intoxications were autopsied, 146 in 2003, among which 18% were female, including 14% of heroin-associated cases and 27% of MMP-associated cases. The mean age was 31 years vs. 30 years.

In 169 (62%) of the 272 cases, heroin was detected at the time of death, usually as the main cause of death (= the substance most likely to cause death in mixed intoxications, according to blood levels), although only in 22 (8%) of the cases heroin was found

without any other substance of abuse; in 77 cases (28%) the combination heroin/ethanol proved to be fatal.

Methadone was found in 96 cases (35%). A total of 53 of those (55%) were linked to MMP according to police data, including 35 (62%) with marks of recent i. v. drug abuse including methadone. Sixteen of 53 MMP-associated cases (30%) occurred during the first days of adaptation or after discontinuation of methadone.

During 2002 and 2003 only one buprenorphine-related death was found: A 33-year old female, buprenorphine-maintenance therapy for 4 weeks, death due to i. v. – injection of dissolved buprenorphine. As buprenorphine can only be detected by special testing and not by a routine immunochemical drug screening, it cannot be ruled out strictly that additional buprenorphine-related deaths were not detected. This is unlikely, though, as in our experience toxicological analyses in most cases confirm police data concerning the substances of abuse, and all hints for buprenorphine (ab)use were controlled (Tables 1 and 2).

Discussion

The results from this observational study may indicate a lower risk of fatal intoxications in buprenorphine-treated compared to methadone-treated patients. Data from forensic post-mortem examinations from the Munich Institute of Legal Medicine suggest that 96 (35.2%) of 272 cases of so-called drug deaths (only lethal intoxications) were methadone-associated (Table 1).

About the half of the patient with methadone-associated deaths had not been treated in an MMP according to all available data (Table 2).

Still the number of methadone-associated deaths was considerably higher than those with buprenorphine. While in the upper Bavarian region approximately 10% of substitution patients are currently treated with buprenorphine, only a single case of fatal

Table 1 Drug-abuse associated deaths caused by intoxications, autopsied at the Munich Institute of Legal Medicine, 2002 and 2003

Lethal intoxications	n = 272	
female	n = 49	(18%)
Detection of heroin	n = 169	(62%)
heroin alone	n = 22	(8%)
heroin + etha NOL	n = 77	(28%)
Detection of methadone	n = 96	(35%)
Detection of buprenorphine	n = 1	

Table 2 Drug-abuse associated deaths by intoxication with detection of methadone, Munich Institute of Legal Medicine, 2002 and 2003

Methadone-associated deaths	n = 96	
MMP-associated deaths	n = 53	(55% of 96)
MMP + i. v. injection marks	n = 35	(62% of 53)
death during adaptation	n = 16	(30% of 53)

intoxication associated with buprenorphine (1%) was found in 2002 and 2003 compared to 96 methadone deaths.

These findings are basically in line with recent findings from France where buprenorphine is far more frequently used than methadone, while the number of deaths associated with buprenorphine and methadone are fairly equal [13].

Recent data from another major German city, Hamburg, indicate a mortality of patients in MMP to have decreased to 0.7% in 2001 compared to 1.3% in 1992 [9]. Corresponding to our data, in this study 71% of those who died by methadone had not been in MMP indicating the fatal role of methadone on the black market.

These data may indicate a possibly lower risk of fatal intoxications in buprenorphine compared to methadone patients but a number of methodological problems must be taken into account. The apparent differences between methadone and buprenorphine with respect to fatal poisoning may be explained by different sample characteristics. For example, methadone may be more frequently used in patients with higher intensity of dependence or craving. Comorbid drug and alcohol consumption must also be taken into account, as well as the availability of different substitution treatments on the 'black market'. There are also different legal restrictions concerning different substitution treatments, as in France. It may also be speculated that MMP is more often associated with bad compliance than BMT as shown by 62% i.v. injection marks in MMP-associated deaths. Additionally, buprenorphine shows the highest opiate-receptor affinity of all opiates/opioids. Therefore additional heroine abuse should not cause significant respiratory depression in buprenorphine users. The differences may indicate a potentially lower risk of buprenorphine due to its unique pharmacological profile including the 'ceiling effect' at the opioid receptor [8]. Also, there is no evidence that buprenorphine causes a highly increased number of deaths during the first days of a maintenance therapy or after a discontinuation (as 30% of MMP-associated deaths!).

Clinically, there is some corresponding evidence for buprenorphine to have less impact on cognitive function compared to methadone [10,17,18]. Clearly more longitudinal and comparative studies are necessary to answer these questions. Matching and allocating patients with substance used to different treatment settings and pharmacological regimens remains one of the challenging new topics in therapy of drug dependence [7].

Recently, the COBRA study was initiated, a nationally representative evaluation study based on a nationwide survey of substitution physicians in Germany [23,24] which is currently conducted and funded by the German Ministry of Science and Technology within the Bavarian-Saxonian ASAT research network [7]. The study gives detailed information on patient characteristics including the use of different substitution drugs in various regions and may also provide additional data on safety issues.

Acknowledgement

This paper has been prepared in the context of the collaborative COBRA study (www.cobra-studie.de) as part of the Addiction Re-

search Network ASAT (Allocating Substance Abuse Treatments to Patient Heterogeneity). Contact information: E-mail: asatkoordination@mpipsykl.mpg.de (www.asat-verbund.de) ASAT is sponsored by a federal grant of the Federal Ministry of Education and Research (01 EB 0440).

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