Deaths due to intravenous methadone use in Hamburg – using toxicological method to get information on the route of administration

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DRD longterm series:
Germany GMR (Destatis)/ SR (BKA)

DRD according to SR and GMR, Germany 1995-2013

ICD-9

ICD 10

SR (BKA)
GMR
Germany (SR): DRD, detection of opiates in monodrug/polydrug overdoses (%)
DRD in Hamburg

- Drug-related deaths declined considerably from 2000–2013
- MMT was introduced in Hamburg in 1990.
- Methadone was the most frequent cause of death for fatal poisonings among drug addicts in the city starting from 1998
- After a slight decline in methadone-related deaths in the following years, since 2010, they rised again and peak actually higher than before.
Development of overdoses in Hamburg from 1990 to 2012 (dotted line) and increase of the relative detection frequency of methadone (continuous line) and buprenorphine (broken line) (%)
Regional analysis across German Bundesländer: OST and methadone detection rate at Opiate-related Death

- Methadone detected in OD (%)
- Patients in OST/100,000, indexed
Methadone involved in opiate-related overdose (%)  

(mean Hamburg 2007-2013, others 2007-2011)
Toxicity and route of administration

• Drug users might administer substitutes intravenously
  – Patients in OMT
  – Diverted methadone
• Role as independent risk factor for DRD unclear

• Waldvogel et al. (2005) Illicit methadone injecting during MMT in Switzerland
• Iwersen et al. (2007), Musshoff et al. (2003): Frankfurt/Germany
• Judson et al. (2010): Injection trend in New Zealand
Classification problems

• Methadone-related fatalities are often classified as
  – Mono-intoxication
  – Directly methadone-related (major role in polydrug overdose)
  – Methadone-associated (minor role, sometimes in poly-opiate-overdoses)

• Important, but often missing or incomplete:
  – OMT status at time of death
  – Route of administration of substitute

• Problem refers to Single-case-analysis as well as for cross-sectional epidemiological data
MMT in Germany

- In Germany, all patients taking part in an OMT are registered by a medical board in order to avoid double treatment by multiple doctors.
- Data Protection Commissioner provided special permission for the Department of Legal Medicine
- Routine information about OMT status of DRD cases instantaneously available.
  - now on a regular basis, in earlier years exceptional allowance only for study reasons
Disaccharides as a marker for intravenous intake

• Recently, we developed a method for the detection of disaccharides (sucrose/lactose) in the urine of drug abusers.
• Disaccharides are split into the respective monosaccharides by carbolytic enzymes in the small intestine after oral intake.
• They cannot be split apart in the blood if substances containing disaccharides are injected intravenously.
• Therefore they are excreted unchanged in urine.
• It could be shown that disaccharides can be used as markers for the intravenous abuse of substitution medicines (Jungen et al. 2013 J Anal Toxicol 37, 652-58)
Sucrose and Lactose

- Sucrose is a typical viscosity enhancer in syrup-based methadone formulations
- Lactose and Sucrose are components of Methaddict®- tablets
- Lactose also component of market heroin/cocaine
- Unspecific detection in blood after oral intake only in rare cases of intestinal inflammation
Methods

- Material: Urine and venous blood samples from DRD in the Hamburg region from 2007-2012
- Methadone levels were determined by validated methods with GC-MS in the blood, brain and hair, and on various tissues, if available
- Limit of quantification (LOQ) for methadone: 0.007 mg/L, Limit of detection (LOD) 0.002 mg/L.
Analytical methods:
Urine and blood analysis

- Extraction of the benzoylated carbohydrates, chromatographic separation was performed by HPLC on a Varian Polaris 5 μm C18 250×4.0-mm column at a flow rate of 1.0 mL/min and detection wavelength of 230 nm.
- Mobile phase was composed of acetonitrile, water and tert-butyl methyl ether(60:24:8).
- LOD (LOQ) for lactose was 0.3 mg/L (0.6 mg/L) and for sucrose 0.3 mg/L (0.5 mg/L)
Classification Treatment Status

• N=116 methadone overdoses

(1) never been in OMT (NOMT)
(2) in OMT at the time of death (A-OMT)
(3) formerly been in OMT (F-OMT) which was finished at least 2 weeks (but no more than 7 years) before death
Subdivision of methadone overdoses: OMT status (n=116, %)

- At time of death: 49%
- Formerly in OMT: 30%
- Never in OMT: 21%
Mean Age / Gender (n=116)

- At time of death: 41 years, 67% male
- Formerly in OMT: 38.3 years, 71% male
- Never in OMT: 37.1 years, 77% male
2007-2012: Concomitant Substance patterns in methadone-associated overdoses (n=116)
Substance patterns in methadone-associated overdoses

Never in OMT
At time of death in OMT
Formerly been in OMT

- Mono intoxication
- Alcohol
- Opiates
- Cocaine
- Benzodiazepines
Detection rate of disaccharides (n=116, %) in methadone-associated overdoses

- At time of death: 59%
- Formerly in OMT: 80%
- Never in OMT: 56%
Disaccharide distribution (%) in disaccharid- positive methadone- associated overdoses

- Sucrose only: 37.9%
- Sucrose and lactose: 10.3%
- Lactose only: 15.5%
Results

• Overall, 64% showed at least one disaccharid in urine
• 48% detection rate for sucrose

• Sucrose concentration ranges from 2 up to 1000 mg/l:
  ➢ Cut-off for „marker positive“ was set at 40 mg/l
• All **blood** samples of the cases with disaccharide-positive results in urine showed negative results (n=25).

- Post-mortem blood samples should not be taken for disaccharid analysis
## Methadone concentrations in venous blood (Mean/Median, n=116)

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Median</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All</strong></td>
<td>0.72</td>
<td>0.04</td>
<td>0.04</td>
<td>3.4</td>
</tr>
<tr>
<td>M- Monointox</td>
<td>0.88</td>
<td>0.55</td>
<td>0.08</td>
<td>3.4</td>
</tr>
<tr>
<td>A-OMT *</td>
<td>0.98</td>
<td>0.56</td>
<td>0.08</td>
<td>3.4</td>
</tr>
<tr>
<td>F-OMT *</td>
<td>0.64</td>
<td>0.47</td>
<td>0.05</td>
<td>2.1</td>
</tr>
<tr>
<td>N-OMT *</td>
<td>0.36</td>
<td>0.31</td>
<td>0.08</td>
<td>1</td>
</tr>
<tr>
<td><strong>All Disaccharides positive (DP)</strong></td>
<td>0.57</td>
<td>0.37</td>
<td>0.06</td>
<td>3.1</td>
</tr>
<tr>
<td>DP: A-OMT</td>
<td>0.82</td>
<td>0.56</td>
<td>0.1</td>
<td>3.1</td>
</tr>
<tr>
<td>DP: F-OMT</td>
<td>0.45</td>
<td>0.37</td>
<td>0.3</td>
<td>0.99</td>
</tr>
<tr>
<td>DP: N-OMT</td>
<td>0.28</td>
<td>0.3</td>
<td>0.06</td>
<td>0.79</td>
</tr>
</tbody>
</table>

_A-OMT: At time of death in OMT; F-OMT: Formerly in OMT; N-OMT: Never in OMT_  
_DP: Disaccharide- positive  
* = significant difference between groups
Conclusions

- Methadone-associated overdoses are a persistent phenomenon in the Hamburg region, dominating since years over other opiate-related fatalities.
- Intravenous route of administration of methadone substitute formulations is frequently found (around half of the cases).
- Methadone syrup formulations play a major role in this group.
- This refers to persons who stay away of treatment, but actually also to those in MMT at the time of death.
- Urine disaccharid analysis is a valuable tool for toxicological reanalysis of post mortem samples but could also serve as quality control in treatment.
- Blood analysis fails because of post mortem degradation of disaccharides.
Thank you for your attention!

Intravenous methadone application as a serious risk factor for an overdose death: methadone-related fatalities in Hamburg from 2007 to 2012

Stefanie Iwersen-Bergmann • Hilke Jungen • Hilke Andresen-Streichert • Alexander Müller • Sally Elakkary • Klaus Püschel • Axel Heinemann