Acute pulmonary alveolitis in narcotics-related deaths

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Abstract: „Narcotic lung” is a term used to describe in one word the polymorphic changes of all pulmonary compartments following abuse and intoxication with opiates. These changes include non-cardiogenic pulmonary edema, congestion, hemorrhage, acute and chronic inflammation, macrophage accumulation and adulterant-related lesions like foreign body granulomas. Intravenous administration of narcotics produces an acute inflammatory reaction in the alveolar wall accompanied by an exudation of fluids and cells into the alveolar space. Acute alveolitis is less described in the literature, it frequently appears as a histopathological modification in heroin and methadone-related deaths.

We retrospectively analyzed 35 cases of drug-related deaths with the aim to describe alveolar changes in relation to drug type and concentration. Acute alveolitis occurred in 78% of the heroin-related deaths and in all deaths related to methadone. At morphine blood concentrations above 1000 ng/l the incidence of acute alveolitis was much higher than at lower concentrations (85.7% vs. 50%), on the other hand hemorrhagic and severe forms occurred more often. The total average lung weight was 1526 g, similar to other reports in the literature. Microthrombosis was a rare finding, in 2 cases of methadone and 3 (11%) cases of heroin-related deaths.

Key words: heroin lung, alveolitis, desquamated alveolocytes, hemorrhagic alveolitis

Heroin lung is the most frequent complication of heroin intoxication. In many ways the lung of the narcotic addict in the overdose resembles that of the shock lung [1, 2]. On the other hand, a category of chronic lung disease characterized by scarring and/or inflammation of the lungs called „stiff lung syndrome” has been described in heroin addiction. Bypassing the gut-liver-lung axis removes two important filtering and detoxifying mechanisms from the system and leaves the lung as the only primary filter mechanism for intravenous administrated drugs [3].

In deaths following narcotic injection several lung modifications have been described, such as congestion, edema and varying degrees of acute and chronic inflammation, intra-alveolar exudate or macrophage accumulation, foreign body granulomas and interstitial fibrosis. Aim of our study is to analyse the alveolar lining epithelium changes in heroin-addicts who died because of an overdose.

Material and methods

We performed a retrospective study on a group of 35 cases of autopsies from the Institute of Legal Medicine in Freiburg, Germany, in which cause of death was determined as heroin or methadon intoxication, sustained by toxicological analysis. In cases of polidrug...
intoxications, those with heroine as main cause of death were taken into consideration. We reviewed the autopsy protocols and re-examined the lung histological sections stained with hematoxiline-eosine.

Left and right lung weight was recorded for every case and we diagnosed microscopical lesions: edema, microtrombs, and presence of inflammatory cells in alveolar space; alveolar cell desquamation was described and graded (1 to 4) based on a combination of intensity and extent of the lesions.

Toxicological results of blood sampled from femoral vein were recorded and compared to the severity of the pulmonary modifications.

**Results**

Out of 35 cases studied 4 were women (11.4%) and 31 men (88.6%), ages between 17 and 45 years. Mean and median age was 29 years, with an interquartile range of 24 – 36 years.

In 8 cases (22.9%) methadone overdose was the cause of death and in 27 cases (77.1%) it was heroin intoxication. In the latter, morphine levels ranged between 800 and 3541 ng/l, with an average of 1563 ng/l and a median value of 1407 ng/l.

The descriptive parameters of the pulmonary weights, separate for left and right, are shown in table 1. The t – test for compare means showed no statistical significant difference between the methadone and heroin group (p>0.05).

<table>
<thead>
<tr>
<th>Heroin overdose</th>
<th>Statistical parameter</th>
<th>Methadone overdose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left lung (g)</td>
<td>Right lung (g)</td>
<td>Left lung (g)</td>
</tr>
<tr>
<td>706.74</td>
<td>820.93</td>
<td>638.38</td>
</tr>
<tr>
<td>175.2</td>
<td>155.58</td>
<td>161.47</td>
</tr>
<tr>
<td>460</td>
<td>587</td>
<td>530</td>
</tr>
<tr>
<td>1115</td>
<td>1130</td>
<td>1040</td>
</tr>
<tr>
<td>600 – 770</td>
<td>670 – 914</td>
<td>591 – 764</td>
</tr>
</tbody>
</table>

**Table 1** Lung weight in narcotics overdose

Circulatory modification markers observed were arteriolar and capillar hyperemia (in all cases), pulmonary edema and microtrombs. Acute pulmonary edema was noticed as microscopically diagnosis in 14 cases (40%) from both groups (but only one from the methadone group and 13 from the heroine group) and it was absent in 21 cases (60%), the absence percentage in methadone group reached 87.5%. We found microtrombs in only 5 cases (14.3%): 2 in methadone overdose (25% of the group) and 3 in heroine overdose (11%) cases.

Alveolitis was qualitatively assesed as simple (desquamative)(Fig. 1) or hemorrhagic (Fig. 2) and graded semiquantitatively from 1 to 4 (Fig. 3), depending on the number of alveolocytes exfoliated in the alveolar space and the number of involved alveoli on the slide. Alveolitis was present in 29 cases (82.85%) from both groups combined but in all 8 cases (100%) of the methadone group (table 2).

We considered two subgroups within the heroin overdose cases, under and above 1000 ng/ml morphine as determined by toxicological analysis.

Alveolitis was much more frequent in the high-level morphine group (90.46% vs. 33.33%) and it had more often a hemorrhagic character, the differences were statistical significant (Fischer’s exact test, p<0.05).
Fig. 1 Acute desquamative alveolitis with septal and intraalveolar inflammatory mononuclear cells

Fig. 2 Hemorrhagic alveolitis
Small amount of inflammatory cells in the alveolar space was found in 16 cases, in 14 (40%) the cells were mononuclear and in 2 cases (5.7%) polymorphonuclear.

<table>
<thead>
<tr>
<th>Alveolitis</th>
<th>Methadone group (n=8)</th>
<th>Heroin group (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤ 1000 ng/ml</td>
<td>&gt; 1000 ng/ml</td>
</tr>
<tr>
<td>- simple</td>
<td>6 (75%)</td>
<td>1 (16.66%)</td>
</tr>
<tr>
<td>- hemorrhagic</td>
<td>2 (25%)</td>
<td>1 (16.66%)</td>
</tr>
<tr>
<td>Total (simple+hemorrhagic)</td>
<td>8 (100%)</td>
<td>2 (33.33%)</td>
</tr>
<tr>
<td>Absent</td>
<td>--</td>
<td>4 (66.66%)</td>
</tr>
</tbody>
</table>

Table 2 Alveolitis type frequency

We graded alveolitis from 1 to 4 taking into consideration the intensity and the extent of the observed modifications. The frequency of evaluated lesions is shown in figure 4. Compared to the frequencies noticed in the entire group, in cases with low morphine concentration the alveolar lesions were less severe (2 cases with grade 1 and 1 case with grade 3).
Discussions

Heroin is a synthetic morphine derivative that was first sold by Bayer in 1898. Once in the body, it is very rapidly converted to 6-acetylmorphine and then to morphine. The first step takes about 10 – 15 minutes and the total conversion is completed within a few hours.

Measurements in a group of 40 cases of heroin-related deaths showed a median total morphine concentration of 1070 ng/l and a significant postmortem redistribution of morphine and its metabolites seemed unlikely [4]. In our group, the median concentration was 30% higher (1407 ng/l). According to other opinions, morphine redistributes postmortem from tissues to blood and this time-dependent process can easily double the measured blood morphine concentration; blood from peripheral veins is less subjected to this increase [5]. Body packers dying from ruptured drug packets may have morphine levels that exceed 100,000 ng/l [6].

Methadone continues to be the drug of choice for the treatment of heroin addicts and most methadone-related deaths occur during the first few weeks of maintenance therapy, as a result of quickly advancing the dosage [7].

Pulmonary edema was described for more than 150 years ago in narcotic-related deaths and it is presumed to be related to respiratory depression, although allergic or anaphylactic reaction theories still persist [8, 9]. Fulminant forms of edema are also reversible and treatment with adequate ventilation, good pulmonary toilet and naloxone is effective [10]. In one series the average weights of the right and left lungs were 830 and 790 g respectively [11], we found similar results for the right lung but lower average weight for the left lung (706 g).

Edema was identified microscopically in less than 50% of the heroin overdose cases, but hyperemia was a constant observed modification. Beside congestion and edema, acute and chronic inflammation and intra-alveolar exudates or macrophage accumulation, acute lobular pneumonia, aspiration, foreign body granulomas, needle emboli have been described [3, 12, 13, 14].

Evaluation of 8 cases of addicts dying from narcotism showed the 100% presence of alveolar wall inflammation, without a discernible regional distribution of the lesions; rather, there was an uneven pattern of involvement within each region and lung examined. The acute lesion was described as a collection of neutrophils with occasional eosinophils and mononuclear cells irregularly distributed in alveolar septal walls, sometimes with prominent margination of polymorphonuclear leukocytes within small arteries and septal capillaries with mild septum involvement [15].

Intravenous administration of narcotics produces an acute inflammatory reaction in the alveolar wall accompanied by an exudation of fluids and cells into the alveolar space; the extent, severity and duration of the response doubtlessly depends on the quantity and composition of the material injected. In our study we confirm the higher incidence of alveolar lesions (85%) in heroin-related deaths with total blood morphine level above 1000 ng/l, the more often hemorrhagic character of alveolitis and the higher severity grade.

Whether the acute inflammatory cell response is seen as margination in alveolar capillaries, as infiltration into the alveolar septae or as migration into the alveolar space probably depends on the time elapsed between injection and death. Pulmonary arteries showed no evidence of acute or chronic vasculitis, nor in our series neither in other studies; vascular wall measurements showed no difference in medial thickness between drug users and non-users [12, 16, 17].
Conclusions

Desquamation of alveolar cells into the alveolar space is a frequent appearance in the narcotic-related deaths. The extent and severity (including hemorrhagic forms) of the lesion depends on the quantity of substance injected.

Correlation with higher values of lung weights in suddenly died young adults and possible other microscopic changes like congestion, edema and foreign body granulomas should orientate the diagnosis towards investigation of narcotic drugs.

References