Adverse events after naloxone treatment of episodes of suspected acute opioid overdose

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Objective: **An increasing and serious heroin overdose problem in Oslo has mandated the increasing out-of-hospital use of naloxone administered by paramedics. The aim of this study was to determine the frequencies and characteristics of adverse events related to this out-of-hospital administration by paramedics.**

Methods: **A one-year prospective observational study from February 1998 to January 1999 was performed in patients suspected to be acutely overdosed by an opioid. A total of 1192 episodes treated with naloxone administered by the Emergency Medical Service system in Oslo, were included. The main outcome variable was adverse events observed immediately after the administration of naloxone.**

Results: **The mean age of patients included was 32.6 years, and 77% were men. Adverse events suspected to be related to naloxone treatment were reported in 45% of episodes. The most common adverse events were related to opioid withdrawal (33%) such as gastrointestinal disorders, aggressiveness, tachycardia, shivering, sweating and tremor. Cases of confusion/restlessness (32%) might be related either to opioid withdrawal or to the effect of the heroin in combination with other drugs. Headache and seizures (25%) were probably related to hypoxia. Most events were non-serious. In three episodes (0.3%) the patients were hospitalized because of adverse events.**

Conclusion: **Although adverse events were common among patients treated for opioid overdose in an out-of-hospital setting, serious complications were rare. Out-of-hospital naloxone treatment by paramedics seems to save several lives a year without a high risk of serious complications.** ***European Journal of Emergency Medicine*** **11:19–23 © 2004 Lippincott Williams & Wilkins.**

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Keywords: adverse events, naloxone treatment, opioid overdose, out-of-hospital, paramedics

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Introduction

In 1980 the incidence of acute self-poisoning in Oslo was 2.8 per 1000 inhabitants, opioids being the main toxic agent in 182 of 1212 episodes studied [1]. The incidence of opioid overdose increased and was reported to be approximately 850 per year in the 1990s [2,3].

Initially, patients with life-threatening opioid overdose were artificially ventilated by ambulance personnel and brought to hospital for treatment in the emergency department, often leaving the hospital alone shortly after regaining consciousness and with a high risk of undiscovered relapse of intoxication. For this reason, treatment strategy has changed to outside-hospital treatment with assisted ventilation, the administration of naloxone, and observation of the patient until he/she has recovered sufficiently to be looked after by friends or relatives.

Some addicts have complained of adverse events associated with naloxone treatment. Several studies have reported on the efficacy and safety of out-of-hospital treatment of heroin overdoses with naloxone. Most studies have reported on paramedics treating overdosed patients alone or assisted by a physician [3–10]. Only a few studies have reported adverse effects or complications associated with the administration of the antidote [4,7,11,12].

The aim of this study was to determine the frequency and characteristics of adverse events related to the out-of-hospital administration of naloxone by paramedics in Oslo, Norway.

Materials and methods

The Emergency Medical Service (EMS) system in Oslo is a one-tiered centralized community-run system serving a population of approximately 500 000 inhabitants. There is no central registration of heroin addicts frequenting the central area of Oslo, although an estimate of some 6000 is given by the Oslo police. There is a tradition among drug abusers in Oslo to prefer injecting their drugs, and a hard-core injecting drug abuser milieu steadily recruits young people to extensive heroin abuse. One explanation for the high number of heroin abusers might be the low street

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price of heroin in Oslo compared with alcohol prices. The annual registered cases of overdose-related death in Oslo were 121 (range 115–134) in 1998–2001 [13]. This constitutes approximately a third of overdose fatalities in Norway [14]. Opioid overdose was the main cause of death in these cases.

There is no single law regulating the treatment of drug abusers in Norway. The treatment and rehabilitation of drug abusers is a responsibility of the individual counties, and has predominantly been based on principles of voluntary, drug-free rehabilitation. According to section 31 of the Social Services Act, drug abusers have been given help mainly by 'means of advice, guidance and practical assistance'. Assistance and treatment outside institutions must be proved to be insufficient before the drug abuser can be offered rehabilitation in a suitable institution. Compulsory treatment only includes pregnant drug abusers and drug abusers whose life and health could be proved to be in continuous danger.

Entry criteria

The present study includes prospectively all episodes of suspected acute opioid overdose treated with naloxone out-of-hospital during the period 1 February 1998 to 31 January 1999. Opioid overdose was diagnosed on site by the ambulance personnel based on clinical observation (e.g. miosis, respiratory insufficiency, unconsciousness), the observation of user equipment on site and by information from bystanders. No blood analysis was available for toxicological screening to confirm or refute the presumed overdose agents.

Treatment procedures, collection of data and evaluation procedure

Paramedics in Oslo have 2 years of training followed by a final certification examination. They are specially trained in treating suspected opioid overdose with respiratory assistance and naloxone. A routine treatment regimen established by the EMS senior physician was followed during the study period: An initial dose of naloxone 0.4–0.8 mg was given intramuscularly, depending on body size, combined with an intravenous dose of 0.4 mg naloxone. If the patient did not respond satisfactorily, the intravenous dose could be repeated up to a maximum of 1.6 mg or a total dose of 2.4 mg naloxone. The paramedics should observe the patient until he/she was found to be alert with adequate respiration and pulse rate and capable of standing. The patient was taken to hospital for observation or further treatment if he/she was still intoxicated or otherwise ill after treatment. There was no system for the long-term follow-up of patients in the present study. Paramedics reported on overdose agent(s), patient's sex and age, symptoms of overdose, date and hour of administering naloxone, the dose and route given, and events observed until the patient left or was left by the paramedics. A specially designed reporting chart was used, including some predefined events: severe headache, confusion/restlessness, aggressiveness, tachycardia and seizures. Patient charts were collected daily by the authors. Serious events were those that resulted in death, were life-threatening or required hospital admission. All other events were defined as non-serious. According to observations reported by paramedics, each overdose episode was classified according to severity in the following way: Severe poisoning: life-threatening complications or cyanosis, e.g. respiratory arrest or severe cyanosis. Moderate poisoning: moderate respiratory depression, but without life-threatening complications. Mild poisoning: somnolence, confusion and miosis. All episodes were included in the study if naloxone treatment was given.

Results

During the study period 2172 emergency calls for the ambulance service to patients with suspected overdoses were received in the EMS. The criteria for out-of-hospital naloxone treatment was fulfilled in 1192 of these(55%). The mean age was 32 years (range 17–88). Men (mean age 33 years, range 17–56) were involved in 945 (79%) of the episodes. Women had a mean age of 30 years (range 18–88). Most patients were in their twenties (27%) or thirties (51%). In 183 episodes (15%) patients were referred to outpatient clinics or hospitals after treatment. In 43 of these episodes (23%) the patient did not respond satisfactorily on naloxone treatment. Others were taken care of because they had problems unrelated to naloxone treatment, e.g. fall injuries observed before naloxone treatment. The agents causing overdoses are listed, as reported by the paramedics (Table 1). Women were more frequently overdosed with heroin in combination with drugs than in combination with alcohol ($P = 0.001$), whereas men were more frequently overdosed with heroin in combination with alcohol than in combination with drugs ($P < 0.0001$). Eighty-seven per cent of all episodes were classified as severe poisoning. Mild or moderate poisoning was significantly more frequent in women than in men (19 versus 11%, $P = 0.0003$), as shown in Table 2. The total naloxone dose given for severe poisoning varied from 0.2 to 2.8 mg (mean 1.2 mg); for moderate poisoning from 0.4 to 1.6 mg (mean 0.8 mg) and for mild poisoning from 0.4 to 1.2 mg (mean 0.6 mg).

Table 1. Assumed overdose agents in the 1192 episodes as reported by paramedics.

Overdose agents	Men $N=945$ (%)	Women $N=247$ (%)
Heroin	482 (51)	134 (54)
Heroin + alcohol	221 (23)	29 (12)
Heroin + drugs	150 (16)	56 (23)
Heroin + drugs + alcohol	57 (6)	13 (5)
Others, e.g. amphetamine and ecstacy, benzodiazepines or unknown toxic agents	35 (4)	15 (6)

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Table 2. Episodes of poisoning treated in the out-of-hospital setting and events in relation to the seriousness of poisoning.

	Serious poisonings $n=1036$ (%)	Moderate or mild poisonings $n=156$ (%)	All $N=1192$
Number of episodes according to sex:			
Men	837 (89)	108 (11)	945
Women	199 (81)	48 (19)	247
Number of episodes with events (%)	503 (49)	35 (22)	538 (45)
Total number of events	683 (94)	42 (6)	726

Table 3. Events reported after naloxone treatment.

Events	No. of events (%) $n=726$
Confusion[a]	235 (32)
Headache[a]	157 (22)
Nausea/vomiting[a]	66 (9)
Aggressiveness[a]	62 (8)
Tachycardia[a]	47 (6)
Shivering	33 (5)
Seizures[a]	27 (4)
Sweating	24 (3)
Tremor	9 (1)
Miscellaneous	66 (9)

[a]Predefined events noted in the reporting charts used by the paramedics.

Frequency and characteristics of reported adverse events

Most patients were observed by ambulance personnel for only a short time after recovery. The observation time was, however, recorded in only 104 of the episodes (9%; mean observation time was 8 min with a range of 1–30 min).

Adverse events were reported in 538 of the 1192 episodes (45%), presenting a total of 726 events. Adverse events were significantly more often seen in cases of severe poisoning than in episodes with mild to moderate poisoning (49 versus 22%, $P < 0.00006$; Table 2).

Table 3 lists the most frequent adverse events, of which confusion/restlessness and headache dominated. Other events were aggressiveness, gastrointestinal complaints, tachycardia (range 80–180 beats per minute), shivering, seizures, sweating and tremor. These features were independent of whether the toxic agent(s) were heroin only or heroin in combination with other drugs or alcohol, and whether the poisoning was severe or not. Most events were considered to be non-serious, but were experienced as unpleasant for the patient. The episodes of tachycardia and seizures may be characterized as high-risk clinical conditions. Adverse events led to hospitalization in three episodes (0.3%), and they were therefore considered serious. These were one episode of confusion, headache and vision disorder, one episode of nausea and vomiting and one episode of confusion, tremor and 'feeling bad'.

Discussion

The present study was designed to investigate the safety of treating heroin overdoses in an out-of-hospital setting without further hospitalization. The paramedics based the recording of adverse events on observations of patients' complaints immediately after recovering from an opioid overdose. Others have earlier reported that data collected by ambulance personnel on non-fatal overdoses are an underutilized source of information [6].

The frequency of adverse events in the present study was higher than previously reported [4,7,11,12]. To our knowledge, only Yealy *et al.* [4] have systematically investigated the adverse events of naloxone treatment based on observations by paramedics on site, describing only six adverse events in the 813 patients studied. Their data were based on reviewing the charts of all patients who received out-of-hospital treatment with naloxone. The much higher frequency seen in our study is probably related to our method of prospectively observing the patients by using a reporting chart with a predefined list of expected events. The reporting of events is considered more complete when the patients are interviewed according to predefined lists of possible events, than when relying on spontaneous reporting [15,16].

Another reason for the high frequency of events seen in our study may be related to the rapid injection of naloxone, which is assumed to be necessary to avoid problems with patients resisting treatment when regaining consciousness. An unknown number of the adverse events may be related to the speed of the naloxone injection. A slower titration of naloxone according to the patient's needs might have led to fewer and less pronounced adverse events [12].

Osterwalder [11] suggested that complications can be reduced by using artificial respiration with a bag valve device as well as by administering naloxone in minimal divided doses, injected slowly. It could be argued that it would be safer to bring the unconscious patient to hospital intubated and with controlled ventilation or with ongoing bag–mask ventilation, than treating them outside hospital and leaving them without further contact. Ongoing bag–mask ventilation or intubation under

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unstable conditions outside hospital is always a threat to a patient's airways and oxygenation. As there is no legal way to keep a patient in hospital after recovery, it would not be safer to transport a patient to hospital before treating them. Leaving the treated patient together with a specialized team or friends and relatives outside the hospital seems a much safer procedure.

The events reported were mainly classified as non-serious, which is in agreement with observations by Yearly *et al.* [4]. However, serious events were observed in 0.3% of the episodes in addition to some events of high-risk clinical conditions such as tachycardia and seizures. Osterwalder [11], who studied naloxone treatment in overdosed patients after hospital admission, reported a frequency of 1.3% of severe adverse effects such as asystole, convulsions, pulmonary oedema and violent behaviour. These were all observed within 10 min after naloxone administration. He did not report on non-serious events, and therefore a comparison with our study is not possible.

In our study the majority of patients were severely cyanotic and hypoxic before the naloxone treatment. This may explain the high frequency of severe headache and seizures reported. The mechanisms by which naloxone may induce seizures is uncertain. Mariani *et al.* [17] reported experimental studies that gave evidence of a receptor-independent γ-aminobutyric acid antagonism as the most likely mechanism. Seizures may therefore be a symptom of the opioid withdrawal syndrome. However, seizures are also well-known complications after severe cerebral hypoxia, as might have been the case in comatose patients. Other events are probably related to opioid withdrawal effects, which are characterized by agitation, nausea, vomiting, diarrhoea, piloerection, yawning, lacrimation and rhinorrhea, mild shivering and restlessness. Opioid abstinence may also be characterized by sweating, light tremor, cardiovascular symptoms and signs, muscle pain, bone pain, sleep disorders, abdominal pain and seizures.

Extreme agitation and combative behaviour have also been reported after administering naloxone [18,19]. According to Gaddis and Watson [19] the mechanisms involved may be related to the physical discomfort of withdrawal, the confusion of awakening in an unexpected setting, anger at losing the altered mental status 'high', the effects of other concomitantly ingested medications no longer opposed by narcotics, underlying personality disorders or other causes. Osterwalder [11] suggested that violent behaviour might be explained as an acute withdrawal syndrome. Cuss *et al.* [20] suggested that naloxone antagonizes opioid suppression of the sympathomimetic system, resulting in a sudden increase in its activity, which may be the mechanism for the occurrence of tachycardia.

The most important limitation of the present study was the short time of observing the patients. The effect of naloxone is expected within one minute after intravenous administration and within 5–10 min after intramuscular administration. Accordingly, most adverse events should occur within few minutes after naloxone administration. This is also demonstrated in the study by Osterwalder [11], in which no further complications were observed after a 10 min period following naloxone administration. We therefore assume that most events were captured within the reported observation time. Watson *et al.* [21] suggested that the frequency of relapse of opioid toxicity is approximately 20–45% after the initial response to naloxone, most frequently with long-acting opioids, but also occurring with short-acting opioids such as heroin. To capture cases of reintoxication, Osterwalder [12] concluded that patients should be monitored for a period of at least 8 h, far longer than in our study. We may thus have lost cases with relapse of heroin intoxication.

The police investigate all sudden unexpected deaths outside hospital, therefore all overdoses that result in deaths are investigated. Previous contact with the ambulance service a short time before the patient dies will be discovered and investigated. We have not received any information that relapses are a problem. All overdose patients are registered in a patient database archive at the dispatch centre, and relapses in which the patient was unconscious would be discovered. We do from time to time see the same patient with a new overdose as a result of the injection of a new heroine dose, but this is not a major problem.

Another limitation in our study is that data concerning overdose agents were based on observations and information from bystanders or patients. It could be argued that ambulance personnel cannot trust information about the intoxication given by the patient or lay individuals. The drug abuser milieu in Oslo is well known to ambulance service personnel. The ambulance service has organized courses in basic life support for drug addicts for some years. Drug addicts know that they are treated with respect and that all information on drugs is kept confidential. Therefore we have no reason to believe that they do not cooperate or give false information about their intoxication. It is also well known that drug addicts usually combine opioids with other central nervous system depressants, particularly benzodiazepines or stimulants such as amphetamines [9,22–25], and exact information in each case is not to be expected at the time of antidote administration.

Media focus in Norway is still strongly directed towards the fact that the number of overdoses resulting in death has not been reduced on a nationwide basis, and towards the lack of better life-saving measures for the individual.

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More use of compulsory treatment is debated [14] as the legal framework very much prohibits the use of treatment and rehabilitation against the patient's will. New and debated methods such as low-threshold methadone distribution and public injection rooms are being used and tested. The nationwide number of clients receiving substitution treatment has increased dramatically. In spite of the large number of overdose-related deaths, it has been difficult to allocate resources for new applicants for treatment, particularly in Oslo.

Conclusion

A high incidence (45%) of adverse events was reported during out-of-hospital naloxone administration. It is likely that the observed events mainly represented opioid withdrawal effects caused by naloxone. They could also be related to hypoxia and to the extensive use of heroin in combination with other agents. Most events were non-serious. Events such as tachycardia and seizures could represent high-risk conditions and should initiate the follow-up of patients. The present practice of treating acute opioid overdose out-of-hospital seems to save several lives a year. However, the risk of relapse should be studied further.

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