Unexpected "Gas" Casualties in Moscow: A Medical Toxicology Perspective

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In October 2002, the Russian military used a mysterious "gas" to incapacitate Chechen rebels at a Moscow theater. Despite increased interest in the potential use of lethal chemical weapons in recent years, the medical community has paid little attention to the development of incapacitating, calmative, and "less than lethal" technologies. In this analysis, we review the events surrounding the use of a calmative "gas" during the Russian military action and discuss what is currently known about fentanyl derivatives, their aerosolization, and the rationale for their use as incapacitating agents. Collectively, the available evidence strongly suggests that a combination of a potent aerosolized fentanyl derivative, such as carfentanil, and an inhalational anesthetic, such as halothane, was used. The paper also assesses potential errors leading to the loss of a substantial number of hostages. Several lessons can be learned from this surprising and novel use of an incapacitating gas.

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INTRODUCTION

On October 26, 2002, more than 120 hostages held at the Moscow Dubrovka Theater Center by Chechen rebels died during a rescue attempt by Russian military special forces. First reports suggested that a "poison" gas had been used by the elite spotznaz in order to subdue the rebels and rescue the hostages. But what gas was it? According to press reports, Russian physicians were told that an anesthetic gas had been pumped into the theater, but the gas was not identified.[1] Perhaps concerns regarding the restrictions in the recently ratified Chemical Weapons Convention contributed to the cloak of secrecy surrounding the identity of the toxic agent.[2]

Medical toxicologists are familiar with many of the toxicologic issues surrounding chemical warfare agents; however, our assumption about which agents were used during this daring hostage rescue did not fit with the reported clinical effects. In this age of terrorism, the element of surprise is an important tool. Just as few people expected that hijacked jet aircraft would be transformed into offensive missiles of mass destruction, medical providers likely expected to receive victims suffering from bullet wounds, not a mysterious intoxication. Despite visits by military medics to some Moscow hospitals several hours before the raid, advising health care providers to increase their supplies of naloxone,[3] the emergency medical system was not adequately prepared to receive hundreds of casualties suffering from opioid intoxication.

WHAT HAPPENED?

On October 23, 2002, more than 800 people attending a stage show were taken captive by some 50 Chechen rebels. The rebels repeatedly threatened to blow up the theater if their political demands were not met. The Russian military stormed the theater early in the morning of October 26. An unidentified "gas" was introduced into the theater through the ventilation system approximately 15 minutes before the military offensive.[4] Hundreds of hostages were taken to local hospitals suffering from "sleeping gas" poisoning. According to local reports, "doctors spent the first few hours testing various antidotes before they found something that worked."[5] Some of the medical personnel may have assumed that the victims had been exposed to conventional chemical agents, such as the nerve agents sarin or VX. Some of the first victims were treated with atropine, an intervention that proved ineffective.[6] The finding of miosis may have added to the initial confusion. Other experts speculated that the gas might have been BZ, an incapacitating agent that produces anticholinergic delirium.[7] Western embassy physicians examined some of the hostages and concluded, "the agent they were exposed to appears consistent with an opiate rather than a nerve agent."[1] According to 2 Moscow physicians, "many patients had classic signs of opioid intoxication: pinpoint pupils, unconsciousness, [and] depressed breathing."[8] The opioid hypothesis was supported by reports from Russian physicians that naloxone was successful in reversing the effects of the intoxication.[9]

The Russian Health Minister announced 4 days after the event that, "a fentanyl derivative was used to neutralize the terrorists." He went on to state that the gas "cannot by itself be called lethal."[10] Despite this claim, 127 (16%) of the 800 hostages in the theater died, and more than 650 of the survivors required hospitalization.[11] The Russian Health Minister attributed the deaths of the hostages to their poor condition from limited food and water and immobility during 3 days of captivity. By 12 days after the rescue, 67 hostages and 9 rescuers remained hospitalized, 5 in critical condition.[11]

Little information is available about the dose of the chemicals used. One Russian physician stated that toxicology testing to identify the exposure was not performed because "to conduct such tests we have to know approximately what we're looking for, and we didn't know what to look for. Besides, we didn't have the technical means to conduct such tests."[8] Preliminary analyses of blood and urine specimens from 2 survivors who returned to Germany detected traces of halothane, no fentanyl, and no evidence of nerve agents.[12]

Although one of these patients had been on a ventilator, a possible source of halothane contamination, the

other patient had not been ventilated. These early analytic findings and the reports from Russian health officials suggest that the toxic gas was some sort of combination agent. News reports suggested that the most likely combination of agents was a highly potent fentanyl derivative used in conjunction with an inhalational anesthetic agent, such as halothane.[8]

AEROSOLS OF FENTANYL AND FENTANYL DERIVATIVES

A large number of fentanyl derivatives have been developed. Many are more potent than fentanyl. Like fentanyl and meperidine, these agents all have a phenylpiperidine structure, are structurally dissimilar to natural opiates, and are potent agonists at μ opioid receptors. Depending on the dose, fentanyl and its derivatives produce analgesia, respiratory depression, central nervous system depression, and miosis.

The Russian acknowledgment that the gas was a fentanyl derivative raised a number of issues regarding the use of such an agent in this situation. Many observers were unaware that an aerosolized fentanyl preparation was even available. However, investigations into the utility of administering fentanyl as a nebulized aerosol were first reported more than a decade ago.[13,14] A "gas" of fentanyl or one of its derivatives is not a gas per se, but an aerosol of fine particles. The physical behavior of an aerosol differs considerably from that of a true gas. Particle size may influence the distribution of such an aerosol. The more potent the drug, the less needed to aerosolize to obtain the same effect. Conditions favoring aerosolubility may be influenced by the potency of the specific agent.

In a 1998 study,[15] the delivery of 100 to 300 μg of aerosolized fentanyl base was shown to have comparable bioavailability to intravenous administration at the same dosage. Worsley et al[14] had noted earlier wide variation in blood levels after patients were given aerosolized fentanyl for postoperative anesthesia and suggested that this unpredictability in fentanyl pharmacokinetics was a result of its high lipid solubility and high volume of distribution. Another challenge is the short duration of action of fentanyl. Researchers have developed a liposome-encapsulated drug carrier system to provide a more controlled and sustained release of aerosolized fentanyl.[15] A 1999 paper[16] concluded, "inhalation of fentanyl offers an easy, noninvasive route of administration … [although] additional study is required to determine the safety and efficacy."

Identifying the exact fentanyl derivative that was used in the Moscow incident is difficult without definitive analytic confirmation. Sufentanil is shorter acting, is much more potent than fentanyl, and is available as a nasal spray. Its lipid solubility is much greater than fentanyl or morphine (Table). Alfentanil is a ultra–short-acting analgesic agent that has a more rapid onset of action and shorter duration of action than fentanyl and sufentanil.[17] Another fentanyl derivative, remifentanil, is 20 to 50 times more potent than alfentanil and has a ultra-short duration of action. Remifentanil is mainly used for brief procedures.

Another characteristic of sufentanil, alfentanil, and remifentanil is their wide therapeutic index (Table). A wide therapeutic index implies a greater safety margin between the effective dose and the lethal dose.The therapeutic index is derived from animal studies, not human studies, and may be based on only one animal species.

The administration of sufentanil by aerosol has been investigated. Jaffe et al[18] created sufentanil citrate

Table.
Characteristics of opioids including fentanyl derivatives.[25,34-36]

Opioid	Potency (Compared With Morphine)	Lipid Solubility*	Therapeutic Index†
Morphine	1	1.4	70
Meperidine	0.5	40	5
Methadone	4	120	12
Fentanyl	300	800	300
Sufentanil	4500	1800	25,000
Alfentanil	75	150	1100
Remifentanil	220	18	33,000
Carfentanil	10,000		10,600

*Lipid solubility=octanol/water distribution coefficient.
†Therapeutic index=median lethal dose (LD_{50})/lowest median effective dose (ED_{50}).

aerosols from solutions ranging in concentration from 10 to 75 μg/mL. As observed with opioids delivered by other routes of administration, the effect of aerosolized sufentanil was dose dependent in this rat model.

CARFENTANIL

Carfentanil is another fentanyl derivative with very high potency and a high therapeutic index. It is a one of a series of N-4-substituted 1-(2-arylethyl)-4-piperidinyl-N-phenylpropanamide compounds. It is the only opioid approved in the United States for immobilizing large exotic animals; it is not approved for use in human beings.[19] Known as Wildnil, it is used primarily as an incapacitating agent for large animals, such as elephants, rhinoceroses, wolves,[20] seals,[21] and polar bears.[22] A typical dose to immobilize seals is 10 μg/kg.[21] It may also be administered intravenously, transmucosally,[23] or orally.[24]

Published reports on the analgesic activity and toxicity of carfentanil date to the 1970s. In a rat study, Van Bever et al[25] compared carfentanil and 3-methyl fentanyl with fentanyl, morphine, and meperidine. They found that carfentanil had the lowest median effective dose (0.00032 mg/kg), with a potency 10,000 times greater than morphine. Furthermore, they found that these 4-substituted fentanyl derivates had an unusually high safety margin (Table).

The narcotizing effects of carfentanil may recur 2 to 24 hours after treatment with an opioid antagonist.[19] In an investigation on carfentanil in Rocky Mountain elk, high-dose naltrexone (100 or 500 mg of naltrexone per mg of carfentanil) was an effective antagonist; however, renarcotization at 8 to 24 hours was common when only 25 or 50 mg of naltrexone per mg carfentanil was used.[26] "Narcotic recycling" also occurred in carfentanil-immobilized wood bison that were treated with naloxone.[27] Given the high lipophilicity of these fentanyl derivatives, redistribution from tissue stores to the central compartment may explain the recurrent opioid effect. Similar effects are known to occur with high-dose fentanyl anesthesia and may be potentiated by acidosis, hypothermia, and rewarming.[28]

In a recent report[29] prepared for the US government, entitled "The Advantages and Limitations of Calmatives for Use as a Non-Lethal Technique," the authors write that carfentanil "has gained new interest … because of the recent pursuit of novel calmative agents capable of unconventional administration." The report continues, "although not yet used in human populations, this drug offers the potential advantage of being administered to non-compliant or violent patients in situations requiring only indirect contact."[29] This report did not discuss aerosolization; however, aerosolized carfentanil is currently under study. The Web site of KROSS, Inc. states that it is monitoring a clinical study involving carfentanil aerosol.[30] A MEDLINE search from 1966 to November 2002 did not identify published studies on aerosolized carfentanil.

Another mystery surrounding the Russian event is whether it involved a single agent or a combination of agents. The early German analytic data[12] showing evidence of halothane plus the Russian admission to using a fentanyl derivative suggest that more than 1 agent was used. This may also explain the failure to fully obtain reversal with naloxone in some cases, although hypoxic brain injury also may have contributed.

It seems very possible that the Russians used a multiagent regimen consisting of a highly potent opioid and an inhalational anesthetic agent. For decades, the combination of an opioid with an inhalational anesthetic agent has been a mainstay of the balanced anesthesia approach. Fentanyl and its derivates are commonly used in conjunction with inhalational anesthetic agents.[31] Fentanyl, sufentanil, and alfentanil are routinely used with inhalational agents, such as nitrous oxide or isoflurane. A combination approach also may help prevent emergence reactions that may occur with opioids. Glenski et al[32] showed that low-dose sufentanil at a 0.5 μg/kg dose can be used successfully to supplement halothane/nitrous oxide anesthesia in infants and children. However, a slightly higher dose of sufentanil was associated with increased adverse events, such as hypotension, bradycardia, and respiratory depression. In one patient, reversal with an opioid antagonist was required.[32]

UNEXPECTED DEATHS

If carfentanil was used, why did more than 120 hostages die? Carfentanil has a therapeutic index of 10,600. Shortly after the tragedy, it was reported that the consensus of Russian health experts was that "this drug could not have caused death."[8] Given the extraordinarily high therapeutic index of carfentanil, reactions among Russian officials suggest that the large number of deaths from gas poisoning was not anticipated.

Several factors may explain the deaths. Unpredictable uptake of opioids after a given dose is one problem: up to fivefold variation in plasma concentration may occur after the administration of a standard dose. In addition, there may be a three- to fivefold variability in therapeutic plasma levels of opioids needed to effectively block a defined response. In the Moscow theater, a uniform dose of the carfentanil-halothane mixture would have been quite improbable. Air currents would be expected to disperse the aerosol unequally through the theater. For example, the physical positioning of each hostage in relationship to the ventilation system must have considerably influenced the individual's exposure dose.

Other variables may also influence the toxicity of opioids. Fentanyl and most of its derivatives are highly lipid soluble and have large volumes of distribution. Many patients remained in intensive care units for several days after the exposure. We can only speculate that hypoxic brain injury, as well as delayed redistribution of the fentanyl derivative to the central compartment, may have contributed to prolonged hemodynamic and respiratory instability. The wide therapeutic margin of drugs, such as carfentanil, may have lulled some scientists into believing that the poison gas could not have produced lethality. However, the lowest median effective dose (ED_{50}) in these studies was based on the tail-withdrawal test in rats.[25] As many researchers have learned over the years, animal data cannot be extrapolated directly to human beings.

LESSONS LEARNED

It seems likely that the 800 hostages were about to be killed by Chechen rebels. To rescue them, the Russian military used a calmative agent in an attempt to subdue the rebels. The intent was likely to win control of the theater with as little loss of life as possible. Given the large number of explosives in the hands of the hostage takers, a conventional assault or the use of more toxic chemical agents might have significantly increased the number of casualties. Although it may seem excessive that 16% of the 800 hostages may have died from the gas exposure, 84% survived. We do not know that a different tactic would have provided a better outcome.

The use of a "sleeping gas" or calmative agent in this setting is a novel attempt at saving the most lives. Medical attention to these approaches has been scanty. A MEDLINE search from 1966 to 2002 reveals few reports on calmative agents. Delivery of fentanyl as an aerosol has only been reported in a few pilot projects, and to our knowledge, information on the aerosolization of carfentanil is not reported at all in the public domain. Greater collaboration between clinicians and military planners is encouraged.

A better appreciation of some of the pharmacokinetic and toxicokinetic issues relating to carfentanil redistribution might have heightened concerns about recurrent toxicity. A therapeutic index of 10,600 (or 25,000 in the case of sufentanil) may inappropriately lessen anxiety about the potential lethality of these agents. Given some factors, such as the lipophilicity of the fentanyl derivatives and the health status of the exposed, as well as great uncertainty regarding the absorbed dose, the potential for inadvertent overdose should have been addressed more thoroughly. Ironically, opioid intoxication is a relatively simple poisoning to treat. Preparation of rescuers and medical teams with suitable stores of effective antidotes, such as naloxone, is essential. The Moscow event urgently prompts a reassessment of our antidote armamentarium. In the United States, naloxone, for a long time a critical antidote to treat heroin overdose and iatrogenic opioid toxicity, has now become a crucial component of our chemical warfare antidote repository.

Nine days after the Moscow theater incident, the US National Research Council issued a report entitled "Developing Effective Non-Lethal Weapon Options Is

Needed to Enhance Naval Force Capabilities."[33] This long-awaited study strongly recommended that the "US Department of the Navy should move toward integrating non-lethal weapons—designed to incapacitate people or material while minimizing unintended death and damage—into naval war fighting requirements, research and development programs, acquisition plans, and operations." The report states that one of the problems in the past was the "lack of new ideas" and "small budget" and that a greater emphasis is needed "on understanding the effects of non-lethal weapons on intended targets and whether those effects are useful for military operations and within the bounds of treaty constraints." In addition, the report adds that the "highest priority should be placed on four science and technology areas of non-lethal weapons," including the development of calmative agents. Medical toxicologists, emergency physicians, and physicians in general may have a constructive role in sharing expertise and staying current on these rapidly progressing technologies.

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