

Department of Energy National Nuclear Security Administration Service Center



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RETURN RECEIPT REQUESTED

Mr. Edward Hammond The Sunshine Project 101 West 6th St., Suite 607 Austin, TX 78701

Subject: Freedom of Information Act Request - #2003-OK-18

Dear Mr. Hammond:

This office is in receipt of your May 20, 2003, Electronic Freedom of Information Act (FOIA) request. You requested Brian Andresen and Patrick Grant's "Dose Safety Margin Enhancement for Chemical Incapacitation and Less-Than-Lethal Targeting", Forensic Science Center at LLNL, January 1997 and the contract under which the report was produced.

The document is released in its entirety. Also, I am providing you the home page for the National Institute of Justice where you may request under the FOIA a copy of their contract which produced this report.

There is no charge for this service.

If you have any questions, please contact RoseAnn Pelzner, the FOIA Officer at (510) 637-3195.

Sincerely,

Douglas A. Ash Chief of Staff

FOIA Authorizing Official

Enclosures

Dose Safety Margin Enhancement for Chemical Incapacitation and Less-Than-Lethal Targeting

NIJ Final Report and Recommendations January 1997

Brian D. Andresen and Patrick M. Grant



Forensic Science Center
R-Division
Nonproliferation, Arms Control, and International Security Directorate
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Dose Safety Margin Enhancement for Chemical Incapacitation and Less-Than-Lethal Targeting

Final Report Executive Summary

Over the past three years we have been investigating the feasibility of implementing a new approach to support less-than-lethal technologies. The uses of extremely potent pharmacological agents have been investigated, as well as their delivery to the target under prison disruption crises, hostage situations, law enforcement needs, special military operations, and low intensity conflict.

A review of the most potent and commercially available pharmaceutical compounds was undertaken. Various classes of chemical anesthetic agents were studied, and existing data concerning their potency were compared. Experiments also centered on modes of delivery of the pharmaceutical agent to the target and the stability of these compounds in a weapon system. From this data review, a new combination of pharmaceutical agents and materials was selected for a new pharmaceutical-based less-than-lethal technology. The design of a novel, nonlethal system integrated highly potent fentanyl-based anesthetic compounds, skin penetrating solvents, and timed-release antidotes, all delivered with a small felt pad projectile. It was determined that very small solvent-soaked projectiles could be accurately delivered to a human target using either an air gun or a blank 38caliber cartridge, fired only with a primer for projectile delivery. A solvent, containing the anesthetic drug and timed release antidote, facilitated absorption of the drugs through the skin and into the central nervous system. With these tactics, little sound is generated during the firing of the drug-soaked felt pad. Tests were performed to acquire initial data on non-lethal projectile range, type of weapon system required under different operational scenarios, accuracy, solvent/anesthetic skin coverage, and clothes penetrating ability. Antidotes to the anesthetic compounds and timed recoveries were also investigated. Recommendations concerning final design of the weapon system are presented.

Dose Safety Margin Enhancement for Chemical Incapacitation and Less-Than-Lethal Targeting

Introduction

The initial goals of this study were to investigate the possibility of utilizing anesthetic compounds in combination with antidotes to enhance the dose safety of chemical incapacitants incorporated into future less-than-lethal technologies. We were to investigate the feasibility of implementing a new approach to support less-than-lethal technologies. The uses of extremely potent pharmacological agents delivered to human targets during prison disruption crises, hostage situations, law enforcement needs, special military operations, and low intensity conflict were to be considered.

We were requested to investigate and compare the efficacy of the most potent pharmaceutical agents currently available that could incapacitate an individual. We were to perform a literature review and compare all of the potential less-than-lethal pharmaceutical agents. Finally, we were asked to recommend future research concerning less-than-lethal delivery systems.

Background

The use of chemical incapacitating agents in humans must be carefully considered because of the potential danger of overdose. Most notably, anesthetic agents can cause respiratory depression, leading to death or permanent brain damage. Thus, such chemical agents must be safe, yet extremely fast acting, progressing to full strength followed by a rapid decrease in anesthetic effects with no long-term effects.

Clinical applications of anesthetic and neuromuscular blocking agents have a long and scientifically-based history. Following intentional exposure to either an intravenous (IV) or inhaled anesthetic, a patient is immmobilized and incapacitated, yet allowed to maintain reasonably stable metabolic pathways, with no long-term residual adverse effects following removal of the anesthetic. For law enforcement and other applications, in contrast to a clinical setting, the controls over the subject are minimal; therefore, safety margins, with respect to the dose of the drug, must be greater.

Previously, the National Institute of Justice (NIJ) sponsored research (inhalation and IV animal dose studies) on fentanyl-related anesthetic agents (namely alfentanil) as potential incapacitating agents. In both cases, the dose safety margin was not sufficient for deployment in law enforcement situations. There has been a small amount of research on the potential for mixing selective antidotes with alfentanil so as to retain the incapacitating effect while restraining the respiratory depressing influence. Combining a narcotic antagonist with a powerful, narcotic-based anesthetic was the major theme of the research. The potential benefit to law enforcement operations and the personnel safety issues associated with the use of chemical incapacitants are extremely large. The operational considerations surrounding the use of highly potent, controlled substances are numerous and will require considerable policy assessment and mandated requirements.

In addition to developing new less-than-lethal technology concepts, the Forensic Science Center at the Lawrence Livermore National Laboratory has provided technical support to local law enforcement agencies. These activities have typically taken the form of analyses of evidentiary materials. Since these analyses have been more complete than those readily available to local law enforcement, they have been of significant value in pursuing a number of trial cases.

Utilizing this experience base, expert scientific and technical support to NIJ plenary sessions were provided to address the critical concerns associated with application of less-than-lethal systems. In addition, the accomplished support interactions were to be documented to illustrate the capabilities of the FSC. Issues and requirements that arose were identified in order to recommend specific methods whereby new forensic and scientific research technologies could be transferred to enhance law enforcement operations.

Anesthetics Overview

The history of the discoveries surrounding anesthetics is as colorful as any in medical science. Controlled surgical procedures were uncommon before 1846. Drugs such as alcohol, hashish, and opium derivatives taken by mouth were historically used for a variety of painful conditions. Other techniques, such a blow to the head or strangulation, did provide temporary relief from pain. However, the most common method to achieve a controlled surgical field was to simply restrain the patient by force. Understandably, surgery was the last resort until anesthetics were readily available.

The history of modern day anesthesia begins with the discovery and use of "the first anesthetic", diethyl ether, in 1842 by Crowford Long and the application of nitrous oxide by Horace Wells in dentistry in 1845. In 1847, James Simpson discovered the use of chloroform, which experienced sustained use for nearly 100 years. In 1929, the first respiratory gases -- cyclopropane, ethylene, and other hydrocarbon gases -- were introduced into surgery. In 1935, sodium pentothal and other barbiturates were first used. In 1942, curare was used for complete skeletal paralysis, and in 1956, halothane and other fluorinated and chlorinated gases were adopted into surgery. Modern surgery now utilizes a combination of solid dosage forms and mixed gases for well-controlled anesthesia in patients.

From the beginning, it was appreciated that anesthetics were the most dangerous drugs approved for general use because the margin of safety was so small. Typically, in a clinical setting, the lethal dose of an anesthetic is only 2-4 times the therapeutic dose. In contrast, the safety margins of other therapeutic modalities are typically 100-1,000 times greater.

Stages of Anesthesia

Before a new, less-than-lethal technology based on pharmaceutical agents can be selected, it is important to understand the effects that anesthetics have on the human body. The introduction of increasing amounts of an anesthetic causes a series of well-categorized levels of anesthesia to be observed. These are summarized below:

Stage 1 (minor surgery)

- a. There is analgesia without loss of consciousness
- b. There is only minor muscle relaxation
- c. There is retention of the swallowing reflexes
- d. There is some dizziness
- e. The patient can reply when spoken to
- f. The patient is conscious and progresses to unconsciousness

Stage 2 (not desired in surgery)

- a. Stage between conscious and unconsciousness
- b. Purposeless muscular activity
- c. Excited state, laughing, shouting, thrashing about
- d. Pupils are dilated
- e. Hypertension and tachycardia are marked
- f. Irregular deep respiration

Stage 3 (desired for most surgeries)

- a. Complete anesthesia and full muscle relaxation
- b. Surgical state for most parts of the body

Plane One

- a. Deep regular respiration
- b. Roving or eccentrically placed eyeballs
- c. Extremities are moderately relaxed
- d. Abdominal muscles are not relaxed

Plane Two

- a. Machine-like respiration
- b. Depth and length of inspiration and expiration are equal
- c. Eyes are centrally fixed

Plane Three

a. Irregular respiration

Plane Four

- a. Shallow respiration
- b. Jaw fully moveable during inspiration

Stage 4

- a. No respiratory effort because all respiratory muscles are paralyzed
- b. Pupils excessively dilated and edges are irregular
- c. Asphyxia obvious, progressing rapidly without external support
- d. Circulatory failure

Graphically, these stages of anesthesia can be seen in Figure 1. With any type of anesthetic, it is observed that muscular tone is elevated in Stage 2 anesthesia, yet decreases significantly in a Stage 3 state. In Stage 3, respiration is still maintained. However, Stage 4 should be avoided without mechanical respiratory support and consequently should be avoided in the field where cardiopulmonary equipment is not immediately available.

Stage		ration	Eye	Eye	Pharynco-	Muscular	
	Inspiration	Expiration	Movement	Reflexes	Laryngeal	Tone	
One			}		Vocal		
Two	1			Lid Responds	Highly Excited		
Three Plane 1		/	M		Swallowing, Retching Emesis		
Three Plane 2				Corneal Responds		STATE OF THE PARTY	
Three Plane 3				Light Reflex Only			
Three Plane 4					Collapsible		
Four				Fixed and Dilated Pupils			

Selection of the Anesthetic Agent

Figure 1. Stages of Anesthesia

There are typically only three possible routes for the administration of anesthetic agents to a subject. One can apply inhalation gases, inject a solid dosage form, or be subjected to either IV or intramuscular (IM) injections. All modalities must allow the anesthetic agent to enter the blood stream in a timely manner, upon which it is carried to the central nervous system to render the subject either manageable or unconscious. For the present study, inhalation anesthetics were not addressed because of the lack of focus and control that would be associated with the administration of inhaled compounds in the field. Similarly, swallowing a solid dosage form is not realistic for law enforcement scenarios. Therefore, we primarily considered injectable anesthetic compounds that are currently utilized in surgery. All of the following anesthetics have been utilized, or are currently being utilized, for a variety of conditions in surgery or to render a patient semiconscious during heightened pain episodes (e.g., burn victims).

The injectable dosage forms currently utilized in surgery are grouped into the six categories. A brief description of each class of compounds is presented, and various attributes of the most promising candidate from each group are discussed in more detail.

Barbiturates

Barbiturates have a long history in anesthesia. Pentobarbital, amobarbital, and secobarbital are the barbituric acid derivatives used most frequently to provide sedation and to relieve apprehension before an operation. Tolerance to barbiturates is observed in individuals who have been taking various types of drugs, including barbiturates, alcohol, and even aspirin. Sulfur-containing barbiturate analogs are noted for their ability to rapidly cross the blood-brain barrier. In particular, sodium pentothal (thiopental), an ultrafast-acting arbiturate, is highly efficient and has a high affinity for specific brain receptors. It is typically utilized to rapidly induce Stage 3 anesthesia so that an inhalation gas can be subsequently used to maintain a controlled level of anesthesia. The typical anesthetic dose of pentothal is 100-500 mg (depending upon body size). It will produce an anesthetic effect in 10-20 seconds after a single injection. Although very potent, sodium thiopental can produce a dose-related depression of respiration as well as hypotension, both of which can be profound. This compound, under controlled conditions, could be utilized in less-than-lethal technologies at dose levels of 200-500 mg. However, it would have to be delivered IV for maximum effect at these quantities.

Tranquilizers

Benzodiazepines, such as Librium, Valium, and Serex, serve as anesthetics when sedation is needed to reduce anxiety prior to minor surgical procedures.

These compounds are potent when taken orally or injected IV. Following a single injection of 0.2-1.5 mg/kg (typically 20 mg), full sedation can be realized in 1-2 minutes. The drug of choice in this class is diazepam (Valium), which is often substituted for sodium pentothal in selected patients at risk for cardio-pulmonary depression. It is also noted that flunitrazepam (Rohypnol), is presently being abused and associated with date-rape. The victim's memory is significantly impaired following moderate alcohol/drug exposure.

In well-controlled settings, a benzodiazepine dose of 25 mg could be utilized in a less-than-lethal technology. However, if the concentration administered is not high enough for some target subjects, an increase in hostility

can result. However, the drug would have to be delivered IV for maximum effect, and the onset of action is slow because blood/brain passage is limited.

Opioids

A single IV injection of morphine (1-2 mg), meperidine (10-25 mg), fentanyl (0.05-0.1 mg), and other similar narcotic analogs is frequently employed to alleviate pain and are used in conjunction with inhalation anesthetics. At higher doses (e.g., morphine, 3 mg/kg over 15 minutes), narcotics can induce complete anesthesia. However, respiratory depression is severe, and an antidote (such as naloxone) with mechanical ventilation is critically necessary in all cases.

If the individual is also taking other narcotics such as codeine, heroin, meperidine (Demerol), methadone, or other opioids, the effects of an additional narcotic can overwhelm any supportive treatments. Although the amount of drug is small, the added risk associated with utilizing morphine alone in a less-than-lethal technology appears problematic. Other narcotics appear to be similarly dangerous if used in pure forms.

Neuroleptic-Opioid Combinations

In humans, neuroleptic compounds, such as butyrophenone (Droperidol), produce a state of quiescence with reduced motor activity, reduced anxiety, and indifference to the surroundings. At moderately low doses of 1-3 mg, the compound does not elicit narcotic-like symptoms, and the subject is responsive to commands. The only side effects is reported to be muscle twitching. However, research has shown that Droperidol enhances the effects of other central nervous system (CNS) depressants. In fact, when Droperidol and fentanyl are mixed, a new formulation (Innovar) is produced that appears to be especially effective as an injectable anesthetic.

A useful drug regime for humans is to administer a mixture of 0.1 ml/kg of Innovar (0.05 mg fentanyl and 2.5 mg of droperidol) in 250 ml of dextrose, infused over a period of 5-10 minutes. After 3-4 minutes the patient falls asleep and can stop breathing unless startled into taking a breath. Naloxone quickly reverses the effects of fentanyl. All other circulatory and biochemical pathways are less affected, and few side effects are observed with a combination of fentanyl and droperidol. Recovery is rapid, while nausea and vomiting are observed in only 5-10% of surgical patients.

Fentanyl Analogues

From the above review of injectable anesthetics, it became apparent that fentanyl (Janssen Pharmaceuticals) is an uncommon and very powerful drug. Whereas other compounds, such as sodium pentothal, benzodiazepines, and morphine, elicit an anesthetic response at dosage levels of 3-200 mg, fentanyl is highly effective in humans at microgram levels. Therefore, a literature review was undertaken to investigate the possibility of utilizing fentanyl or one of its analogues as less-than-lethal technology.

The piperidinyl family of opioids include Fentanyl, Alfentanil, Sufentanil, Lofentanil and Carfentanil. Because this class of drugs is very lipophilic, they cross the blood-brain barrier quickly and induce an extremely rapid onset of anesthetic action. Alfentanil may be classified as an ultrashort-acting drug, fentanyl and Sufentanil as short-acting, and Lofentanil as long-duration anesthetic. The analgesic doses of piperidinyl opioid drugs are not large (typically 0.3-44 µ/kg), and the typical analgesic plasma concentrations are very low (1-30 ng/ml). Anesthetic effects are observed at 30-100 ng/ml. Because so little quantity of the drug needs to be introduced into the patient, it is cleared quickly following a single IV injection. Anesthetic effects can be further maintained by continuing a dilute IV drip of the anesthetic agent.

Adverse effects following a single dose of $100 \,\mu g$ IV include bardycardia or tachycardia, hypotention, chest wall rigidity, seizures, and respiratory depression and collapse (in proportion to the overdose).

1. <u>Fentanyl (Sublimaze)</u> - Fentanyl is the oldest of the class of piperidinyl opioids. In contrast to other injectable anesthetics, it is an extremely powerful anesthetic and analgesic. Fentanyl was first synthesized in 1960 and is 100 times more potent than morphine.

- 2. <u>Sufentanil (Sufenta)</u> Sufentanil was first synthesized in 1974 and is approximately 1,000 times more potent than morphine. It is often utilized for certain types of surgeries because it has lesser of an impact on cardiac stability.
- 3. <u>Alfentanil (Alfenta)</u> Alfentanil was first synthesized in 1978 and is approximately 5-8 times less potent than fentanyl, yet it reaches blood/brain equilibrium in only 1.1 minutes. Consequently, Alfentanil induces its anesthetic effect very rapidly.

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- 4. <u>Lofentanil</u> Lofentanil was first prepared in 1976. Because this compound possesses 20-30 times the potency of fentanyl (2,000-3,000 times more potent than morphine), it has yet to find a clinical role.
- 5. <u>Carfentanil</u> Carfentanil was also first synthesized in the 1970s. It, too, is 20-30 times more potent than fentanyl and has yet to find a clinical role.

Pharmacological Comparisons of Fentanyl Analogs

Comparison of pharmacological data between fentanyl, its analogues, and other narcotic agents is most interesting. Mather (1983) presented data on the effects of opioids in dogs and rats for both analgesia and anesthetic potency. The data (Table 1) clearly reveal the potency of fentanyl and its synthetic analogues compared to morphine and pethidine (Demerol).

Table 1. Pharmacological data for fentanyl and its analogs compared to standard opiates*

	Analgesic Potency ^a			Acute Toxicity ^b	Therapeutic Index	Anesthetic Potency ^c		
	MED ₅₀ (mg/kg)	TMED ₅₀ (h)	Potency Ratio ^e	MLD ₅₀ (mg/kg)	MLD ₅₀ / MED ₅₀	MED ₅₀ (mg/kg)	Potency Ratio ^e	Safety Margin ^d
Opiate								
Fentanyl	0.011	0.093	292	3.5	323	0.0012	125	60
Alfentanil	0.044	0.03	73	47.5	1080	0.005	30	50
Sufentanil	0.00071	0.14	4521	17.9	25211	0.00025	625	800
Lofentanil	0.00070	0.55	4586	0.20	286	0.000025	6250	10000 •
Carfentanil	0.00032	0.29	10031	3.39	10594	na	na	na
Pethidine (HCl)	6.04	0.11	0.53	29	4.8	0.45	0.3	0
Morphine (SO ₄ H ⁻)	3.21	0.31	1	223	69	0.15	1	33

Abbreviations: LD_{50} = lethal dose; ED_{50} = effective does; MED_{50} = minimum ED_{50} by intravenous administration; $TMED_{50}$ = time of maximum effect after single intravenous (5 sec) bolus dose; MLD = mean value of LD_{50} ; na = not available.

- a. Rat: tail withdrawal from 55°C water.
- b. Rat: intravenous bolus.
- c. Dog: begins to go unconscious, intubated with no increase in blood pressure.
- d. Dog: ratio of single intravenous dose for surgical anesthesia (20 x MED) to dose producing severe cardiovascular side effects (alternating hyperactivity and depression) together with acidosis and hypermetabolism, convulsions and EEG exhaustion.
- e. Normalized to morphine.

^{*}L. E. Mather, Clinical Pharmacokinetics of Fentanyl and its Newer Derivatives, Clinical Pharmacokinetics 8: 422-446 (1983).

From Table 1, it can be seen that minimum effective anesthetic doses (MED₅₀) for the fentanyl class of drugs are considerably less than that for morphine. Whereas morphine elicits its effects at 150 µg/kg, Fentanyl, Alfentanil, Sufentanil, and Lofentanil produce anesthesia at 1.2µg, 5.0µg, 0.25µg, and 0.025 µg per kg, respectively. In this study, anesthetic levels for Carfentanil were not determined. However, from studies of the analgesic potency of this drug, we surmise that this compound also possesses extraordinary anesthetic potency.

From this initial study it was apparent that these newer anesthetic agents were not only potent, but that their anesthetic safety margin also appeared to be quite high. Fentanyl and Alfentanil have significant safety margins compared to Demerol. However, Lofentanil and Sufentanil appear to have exceptional safety margins when compared to both morphine and Demerol. This observation is due mainly to (1) the very high specific activity of these drugs for specific opioid brain-receptors, (2) ultralow blood/brain concentrations, (3) rapid redistribution following the initial anesthetic effect, (4) metabolic inactivation, and (5) efficient clearance from the plasma following an initial bolus dose. All pharmacologic and pharmacokinetic parameters point to this class of drugs as an ideal candidate for less-than-lethal technology.

Getting the Drug to the Target

An initial requirement of NIJ from the beginning of this study was that injectable anesthetic dosage forms, including darts or syringes, not be considered. A visit to the San Francisco Zoo revealed that current primate immobilizing systems are only available with injecting darts, syringes on poles, or exploding projectiles with anesthetizing delivery injectors. Upon viewing and evaluating these devices, it became clear that present veterinary control systems would be unacceptable for less-than-lethal technologies for a variety of social and logistical reasons. Therefore, an alternative drug-delivery system was investigated that could humanely deliver a less-than-lethal drug system to an individual without requiring a needle, dart, or cartridge-fired injector.

Transdermal Solvent Delivery Systems

Transdermal patches have been well studied, and preparations for motion sickness (Transdermal Scop®), nicotine withdrawal (Nicoderm®), and severely burned patients (Fentanyl patch) are commercially available. The patches contain

a polymeric reservoir of the drug dissolved in a solvent that carries the drug through the skin in a well-controlled, time-release manner. Unique solvents that penetrate the skin easily are utilized to carry the drug directly through the epidermal layer (Figure 2). Once through the upper skin, the drug is absorbed into the capillary bed from which it is rapidly transported to the target tissues. The main advantages of transdermal patches are that (1) a sustained blood-level concentration can be maintained over extended periods of time, and (2) only a single patch is needed to maintain the therapeutic dose.

The solvents utilized for transdermal patch systems include ethanol, glycerol, and dimethylsulfoxide (DMSO). Ethanol and glycerol deliver the pharmaceutic preparation slowly, whereas the latter solvent facilitates a transfer of drugs very rapidly through the skin. Dimethylsulfoxide is approved for use in veterinary medicine and also has some limited medical uses in human disease (e.g., interstitial cystitis). The solvent is often used in sports medicine in an "unofficial" manner as a topical liniment for arthritic conditions, joint pain, and soft-tissue injuries. This solvent has not exhibited significant toxicology when used correctly. Therefore, it would appear that DMSO could be utilized as an inert carrier to rapidly transfer a fentanyl-based anesthetic into a target, without need of a dart-based injection system.

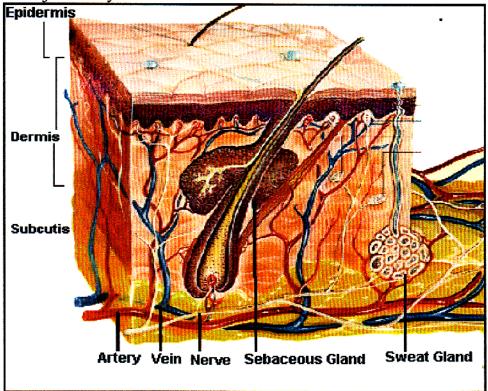


Figure 2. Blood supply to the different layers of the skin.

Delivery System for Less-than-Lethal Technology

To effectively deliver an anesthetic dose of a fentanyl-based/DMSO mixture for less-than-lethal technology, a mechanism to transport the drug to the target must be developed. The most direct application would be simply a solvent/drug-soaked sponge pressed against the subject. However, if the individual is brandishing a weapon, close contact with the target could be problematic. We therefore investigated a novel possibility for the delivery of the anesthetic compound to the target. We designed and tested a small felt pad soaked with solvent as a method for remotely delivering the drug/DMSO mixture to the skin of an individual. The main advantage of a solvent/drug delivery system is that the anesthetic drug formulation need only pass through the epidermis layer of the skin to reach the blood vessels. If the drug is so absorbed, it will elicit identical rapid anesthetic effects identical to any drug injection approach.

Proof of Concept - An Airgun Delivered Systems

Modern pellet pistols and pellet rifles are highly sophisticated and accurate weapons. They are capable of firing a variety of caliber pellet-projectiles at considerable velocities (e.g., 400-1,000 feet/second). They also have the capability of shooting felt cleaning pads. This possibility allowed us to test the concept of delivering a solvent-soaked felt pad to a target. We performed experiments to determine whether solvent would indeed be deposited on a target, how dangerous felt impact might be, and whether felt pads could be accurately carried to a target.

To demonstrate proof of concept, we initially considered the Beeman Sports Air Rifle or pellet pistol (Figure 3). Because samples could be more easily loaded into the breach of a pistol, experiments were performed with the Beeman Hurricane® pellet pistol. This 22-caliber weapon is capable of delivering a pellet at 400 feet/second and was found to easily launch a 22-caliber felt cleaning pad (see Figure 4). The pads were soaked with 0.5 ml DMSO and fired at various targets (Figure 5). These results were encouraging. At a distance of 15 feet, a tight pattern (approximately 2 inches) was generated by the experimenter. Although a sheet of standard notebook-paper could be penetrated at this distance, the solvent-soaked pads could not penetrate thick cardboard. The rifling of the pistol barrel allowed the solvent-soaked felt cleaning pads to accurately hit the target. The solvent was also evenly distributed upon impact, indicating a

controlled and uniform delivery of the solvent to the test surface. This fact is important in order to obtain consistent results with any drug delivery projectile.

Figure 3. Beeman air rifle and pistol.



At a distance of 23 feet, the felt pads would not penetrate the paper target, yet still deposited a uniform solvent residue. At this distance or greater, the impact of the solvent soaked felt pad would probably not be harmful, even if it impacted a sensitive area of the skin (e.g., eyes, ear, lips, etc.). If clothing were hit (instead of bare skin), the solvent could still penetrate a single layer of thin fabric (e.g., cotton shirt). However, any type of thick cloth material would not be efficiently permeated by the DMSO solvent system.

The ease with which a DMSO soaked felt pad delivery system could be carried efficiently to a target was encouraging. However, loading such a projectile

would require that a felt pad with DMSO/drug formulation be inserted in an open environment, potentially exposing the law enforcement office to the effects of the drug. A fully encapsulated solvent/drug delivery package would be needed. Future system developments should include small (22-caliber), paintball-type, fully encapsulated delivery projectiles, containing a sealed solvent and drug formulation.

1 inch 22 Cal Felt Pads

Figure 4. 22-caliber felt pads to deliver DMSO soaked formulation

38-Caliber Cartridge DMSO/Drug Delivery Package

In order to test a fully encapsulated system, a blank 38-caliber cartridge was utilized to deliver a DMSO/drug-soaked felt projectile to the target. This system was investigated because many law enforcement officials possess 38-caliber weapons, the weapon need not be modified, and the sealed cartridge could allow for a long shelf-life of a DMSO/drug formulation.

We initially investigated the powder charge of a normal 38-caliber handgun. A fully loaded blank cartridge proved to be totally unacceptable. However, projectiles launched with only the 38-caliber primer caps performed well and did not destroy the felt ball. Of several systems considered, acceptable launch velocities were generated with Speer's 38-caliber plastic cartridge cases and

Omark Industries CCI-350 "Magnum" primers (Figure 6). Projectile configurations were prepared and tested in the laboratory using these components.

Figure 5. Target results for 22-caliber felt pad experiments show reasonably uniform distribution of solvent on the target.

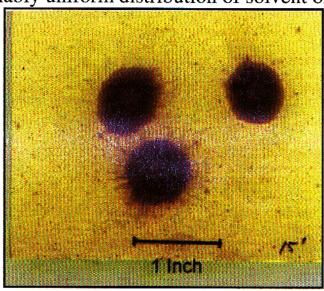
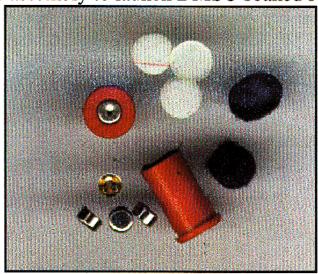


Figure 6. 38-Caliber plastic shell casing, felt-ball, and "Magnum" primers assembly to launch DMSO soaked formulation.



At ten feet, the hand-made felt cylinders impacted the target and delivered the DMSO solvent in a manner identical to the airgun experiments. This finding was very important because this 38-caliber system (1) allowed the DMSO/drug delivery system to be totally encapsulated, (2) did not expose law enforcement to

any open DMSO/drug formulation, (3) should allow for an extended formulation shelf-life, and (4) delivered the less-than-lethal projectile at a consistent and well controlled velocity to the target. All of these are significant attributes that would allow development of a pharmacology-based less-than-lethal technology.

Antidote Considerations

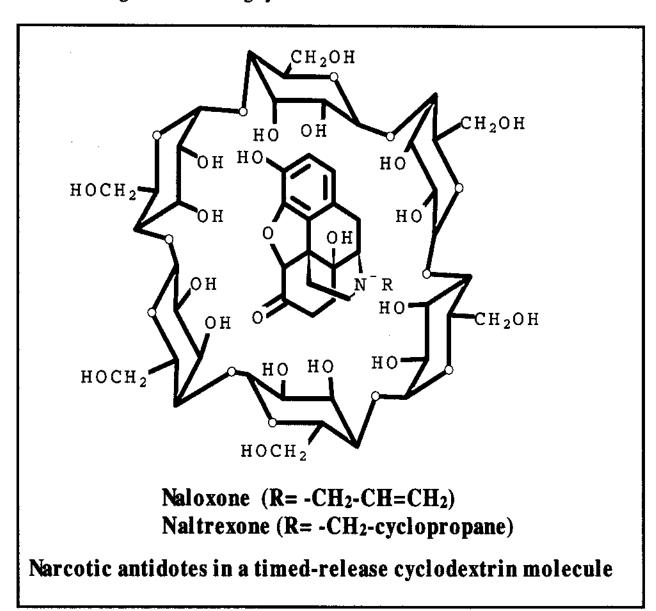
From this pharmacologic review, the most dangerous side effect from any of the narcotic-based anesthetics considered is respiratory depression. The use of less-than-lethal technology based on an anesthetic is made more problematic if the subject has recently injected other stimulants or narcotics. Therefore, an antidote should be added as an essential component of the drug-delivery formulation.

The antidote of choice for respiratory depression associated with narcotic toxicity is naloxone. Naloxone and related opioid antagonists typically have no side effects when administered intermittently. A small, 400µg-800µg dose of naloxone prevents or promptly reverses the effects of most opioid narcotics. Respiratory depression, low blood pressure, and sedative effects are returned to normal within 1-2 minutes. The antidote remains active for 1 to 4 hours, which affords ample time for all effects of the anesthetic drug-formulation to be eliminated.

Although opioid-antagonists might appear promising for a less-than-lethal technology, simply mixing naloxone with a fentanyl-based formulation would defeat the intent of the anesthetic. Therefore, it appears desirable to utilize a timed-release combination of naloxone with an ultrafast-acting fentanyl-based anesthetic formulation. After contacting the skin, the DMSO/drug formulation would be quickly absorbed to induce anesthesia. If the naloxone were delivered within a caged structure, such as a cyclodextrin, then a slower acting, timed-release antidote could be provided for the less-than-lethal technology. Cyclodextrin compounds are currently used in a variety of pharmaceutical and cosmetics industries for their ability to capture and slowly release selected compounds. The internal receptive structure of the cyclodextrin can be synthesized with different dimensions to control the timed-release aspects of the formulation. Private discussions with Fuisz Technologies (Chartilly, Virginia), a manufacturer of cyclodextrin, indicated that such a timed-release naloxone/cyclodextrin molecular structure could be easily prepared.

A major research issue will be to design a slowly released antidote that reaches its maximum effects only after the anesthetic has had sufficient time to render the subject amenable to capture or restraint. Future research should include studies of the size and solubility relationships of the cyclodextrin/naloxone complex necessary for optimum timed delivery of the antidote.

Meetings with Fuisz Technologies also produced another idea for placing a fentanyl-based/antidote system within a cyclodextrin 10-micron powder. The dry powder could be dispersed as a smoke during a hostage situation. Terrorists would be incapacitated by breathing anesthetic smoke injected into an air duct or office building air conditioning system.



Proposed Testing of the New Less-Than-Lethal Technology

Because a pharmacologically-based, less-than-lethal technology possesses both projectile delivery and drug absorption requirements, an *in vitro* assay is necessary prior to animal and human tests to insure proper timed delivery of the anesthetic and antidote. A survey of the literature revealed that both the cosmetics and pharmaceutical industries employ many types of skin tests on a variety of products prior to general use. These biological assays are typically performed using animal and cadaver skin stretched over a small receptor chamber bathed in saline (Figure 7).

Cosmetics, drugs, pesticides, and industrial compounds are applied to prepared samples, and measurements are made to determine the passage of target compounds through skin. The temperature of the apparatus is controlled in order to more realistically obtain transdermal information. Pharmacokinetic data on cosmetics/drug formulations are obtained as a function of variations in skin temperature and blood perfusion.

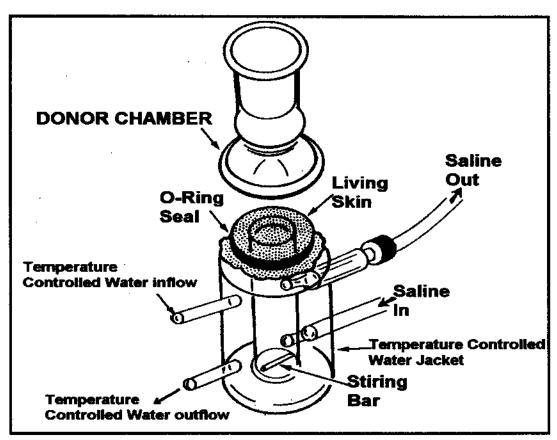


Figure 7. Test apparatus for less-than-lethal projectile

One company (Reifenrath Consulting and Research, Richmond, California) was consulted upon learning that they have utilized this type of apparatus extensively in a variety of studies for the Army. Our discussions elucidated the testing requirements needed to accurately determine the absorption fate of chemicals through human skin. In order to develop pharmaceutical-based less-than-lethal technologies, studies employing similar apparatus must be performed. Human skin samples would be impacted (shot) with a projectile laced with DMSO/fentanyl-related mixtures in order to measure (in nearly real time) the passage of the drugs through skin.

These *in vitro* experiments would be essential for understanding the dermal transport and pharmacokinetics of the solvent/drug/antidote formulation following an impulse impact of less-than-lethal projectiles on the skin. In contrast to simply painting an anesthetic formulation on the skin, our experimental design would have a projectile impact the skin with some concomitant erythema. Following impact, the dilated blood vessels beneath the site of projectile impact should cause an enhancement in the skin absorption of the anesthetic formulation. This, in turn, should accelerate the overall effect of the anesthetic. However, these types of *in vitro* studies should be performed in the laboratory first in order to study the effect of projectile velocity on drug absorption.

The dermal transport apparatus would be configured at the center of a target. An airgun or a 38-caliber DMSO/drug projectile would be fired at the target from a variety of distances. The saline outflow from the apparatus would be attached to a variety of highly sensitive experimental instruments (e.g., ultraviolet or mass spectrometer, or solid-phase microextraction (SPME), for timed isolation of drugs, etc.). These experiments would be used to measure the transport speed of the anesthetic across the skin under different conditions and variable drug concentrations. The skin-penetrating solvents will also carry the fentanyl-based anesthetic and cyclodextrin/naloxone. Measurements would be made to determine which of the fentanyl-based anesthetics was transported through the skin most quickly, as well as the effects obtained when a timed-release antidote is simultaneously carried across the dermal layer.

These initial *in vitro* studies would greatly facilitate the development of the pharmaceutical-based, less-than-lethal technology under conditions

that closely resemble human skin. These tests should clearly determine the feasibility of reaching specific concentrations of the anesthetic drug under a variety of conditions (e.g., drug concentration, solvents utilized, projectile speed, etc.). These investigations would optimally produce data that would guide future animal studies.

Conclusions and Future Recommendations

Safety

The purpose of this study was to identify a highly potent anesthetic that could be introduced into a subject and elicit its affects quickly, but for only a very short duration. Anesthesia was to be implemented to subsequently restrain target personnel in law enforcement or terrorist situations. In contrast to surgical anesthesia, unconsciousness may only be required for 15 seconds to 1 minute; i.e., as short a period as necessary to place restraints or remove a person from a regulated situation.

The results of this study point to a possibility that pharmaceutical-based, less-than-lethal technologies could be developed. This new approach would implement anesthetic drugs to briefly reach the blood-brain concentration necessary for unconsciousness. Fortunately, under these circumstances, short duration anesthetic excursions are induced by highly potent, low-concentration drugs. They quickly cross the blood-brain barrier, impact opioid brain receptors, induce unconsciousness, and subsequently redistribute harmlessly to other body compartments. The result is transient sleep and an opportune moment for law enforcement.

Because the anesthetic concentration will be very low and applied for only for a very short period of time, toxic side effects should be minimal. Ideally, low concentrations of the anesthetic will function effectively and quickly, rendering the individual incapacitated, but not subject to respiratory depression. This scenario contrasts surgical anesthesia, in which an individual is "put under" for a considerable period of time. During surgery, redistribution of the anesthetic ultimately lowers the concentration of and anesthetic in the brain. The anesthesiologist must consequently maintain drug concentration by continually dosing the drug. The goal is to sustain brain-level concentrations well into Stage 3 anesthesia. The

potential for side effects and residual cardio-pulmonary depression is significant following surgery because of the quantity of anesthetic utilized during the procedure. In contrast, a pharmaceutical-based, less-than-lethal technology is intended to elicit a low-level, short-duration anesthetic concentration, thereby furthering the safety margin.

From our evaluation, it does not appear that respiratory depression will be a significant side effect under these low-level anesthetic administrations. Our approach to also implement a timed-release antidote (naloxone or naltrexone) should afford an additional level of safety. This consideration will be important for narcotic-sensitive individuals, or for targets who have recently ingested or injected other narcotic agents.

In Vitro Studies

It appears that *in vitro* studies with animal and human cadaver skin can be utilized to develop this new less-than-lethal technology. Techniques are well developed in the pharmaceutical and cosmetics industries for skin-penetration testing. The *in vitro* testing of projectiles soaked with penetrating solvents and anesthetic drugs is an essential and logical next step in the development of a reliable, pharmaceutical-based, short-duration anesthetic approach for law enforcement.

Animal and In Vivo Testing

We have demonstrated two similar approaches for the delivery of anesthetic-based, less-than-lethal drugs to targets. They both utilize solvent soaked projectiles, launched with either an air gun or a 38-caliber pistol. It is proposed that this approach be utilized for experiments that would deliver non-lethal, anesthetic/DMSO-soaked felt pads for animal studies.

Experiments should be conducted under well-controlled laboratory and field conditions in order to gather reliable physiological and dose-response data for the five fentanyl-related anesthetics dissolved in DMSO. These experiments should investigate relationships between projectile speed, distance to target, drug delivery capabilities upon impact, drug concentration, and time to maximum anesthetic response of the animal. Additional studies and observations of the penetration of the solvent/drug system through different types and layers of clothing would contribute field operational data for future deployment of the new

technology. Detailed delivery studies and pharmacokinetic data in animals such as hairless mice or pigs could generate essential data that would be necessary prior to human testing.

Animal studies should also explore the effects of pre-treatment with narcotics and their result on targeting with variable concentrations of the anesthetic agents. These studies would generate informative data and an understanding of the pharmacokinetic parameters and anesthetic rendering capabilities associated with mixed drug impairment (morphine, amphetamines, cocaine, etc.) that could be encountered during street-crimes or in a prison environment. In these experiments, variable concentrations of the timed-release antidotes could be also be tested in order to insure maximum efficacy and safety. A favorable aspect of the antidote treatment in animal investigations is that these compounds generate few side effects.

Human Volunteer Testing

After extensive in vitro and in vivo testing, human trials should be conducted with the new less-than-lethal technology. At face value, this recommendation may appear extreme. However, human volunteers have somewhat routinely been subjected to sticky foam, mechanically restrained and crushed in the rear seat of police cars, shot with pancake bullets, netted with exploding grenade launchers, and rendered unconscious with stun-guns and high-voltage Tasers. Thus, human trials with anesthetic-based, less-than-lethal technology is not an outlandish extension of this new technology.

To test an anesthetic projectile delivery system, a university medical center and associated hospital environment would provide an ideal facility to determine the merit of this less-than-lethal technology. Many university research hospitals in the US and worldwide conduct investigational drug studies every year with both animals and human volunteers. Many of these studies are conducted with paid subjects exposed to a variety of new pharmaceutical agents. Such experiments are typically performed on healthy adult males. All necessary emergency medical support would thus be available for any contingency. Such experiments with human subjects should be coordinated through a staff composed of both research anesthesiologists and attending emergency physicians. These would be the initial studies of very controlled environments to obtain baseline data on human responses. These results would guide further human studies and determine the feasibility of this new technology.

Future Design Concepts for Anesthetic-Based, Less-Than-Lethal Technologies

From this detailed summary of anesthesia pharmacology, the potency of fentanyl-related anesthetics, non-injected, solvent/drug projectile delivery systems, timed-release antidotes, and data obtained from potential animal and human studies, a projected, less-than-lethal field design package can be envisioned. This could be an emergency briefcase containing a weapons delivery component, color-coded projectile cartridges, and additional auto-injector naloxone antidote syringes. The weapon system could be configured for the environment in which deployed (e.g., prison riot, street crime, hostage rescue, etc.), where law enforcement may be either at a distance or near the subject. The sealed, less-than-lethal cartridge arrangement could also contain a dye to mark where a projectile had hit the target. Such a stain would also indicate the likely location of the anesthetic agent during prisoner clean-up and surveillance following apprehension. The shelf-life of the anesthetic cartridge projectile would reasonably be on the order of one or two years.

Conclusions

In many situations an anesthetic-based, less-than-lethal technology would be most desirable for law enforcement. However, this technology must be simple to use and safe for the law enforcement officer. The pharmacologic, physiologic, and pharmacokinetic parameters associated with the new delivery system must be well established through extensive in vitro and in vivo testing. An experimental outline to measure these essential data was presented in this report. Focused experimental work can begin through studies using human cadaver skin and live animal models. Such studies can be performed in a safe and humane manner to assess the viability of this future technology. Human trial experiments could then be performed in a research hospital environment. With positive results, we estimate that a final anesthetic-based, less-than-lethal delivery weapon could be possible in 2-5 years, depending upon the available funding, number of research institutions involved, and extent of validation testing. The success of such a promising program would be a great benefit to law enforcement and other agencies often confronted by situations that would be humanely resolved by less-than-lethal solutions.

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