Beware the Siren's Song:
Why "Non-Lethal" Incapacitating Chemical Agents are Lethal

Lynn Klotz,[1] Martin Furmanski,[2] and Mark Wheelis[3]
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A number of events have brought "non-lethal" chemical incapacitating agents into the news recently. Most prominently, their use in the rescue of hostages held in the Moscow theater in October 2002 encouraged advocates of the military development of such weapons, since most of the hostages were rescued. Detractors were alarmed that over 15% of the hostages died of effects of the chemical agent (as well as all of the captors, who were executed by security forces while they were comatose).

In this paper we address only the causes of the high level of lethal effects among the captives in Moscow, and ask if that is typical, and whether truly non-lethal chemical weapons are feasible. We conclude that this level of mortality is to be expected, and that genuinely non-lethal chemical weapons are beyond the reach of current science.

The model

The following simplified analysis illustrates why seemingly non-lethal incapacitating agents may be quite lethal in actual use. The analysis assumes simple equilibrium theory for agents with a single molecular receptor causing incapacitation, and a different single receptor causing lethality. This two-receptor model may, for instance, include the anesthetic ketamine, the discontinued veterinary anesthetic phencyclidine ("angel dust"), and the classical chemical weapon agent BZ (3-quinuclidinyl benzilate), which exert their incapacitating effect via the muscarinic acetylcholine receptor in the central nervous system, but appear to cause death by independent cardiac effects.

In this simple model, we assume the fraction of receptor bound to the agent approximately parallels the statistical effect of the chemical agent. If 99% of receptors responsible for incapacitation are bound, there is a very high probability that the victim is incapacitated; and conversely if only 1% of the receptors are bound there is little probability that the victim is incapacitated. In this model, f_i is the fraction of receptors bound, and also the approximate fraction of people incapacitated:[4]

$$f_i = 1 / (1+ ED_{50}/A_0)$$

[1] Lynn Klotz, PhD, 5 Duley Street, Gloucester, MA 01930; 978-281-6015 (telephone); lynnklotz@cs.com (email)
[2] Martin Furmanski, MD, 333 East Bayfront, Newport Beach, CA 92662; 949-675-5155 (telephone); 949-675-5315 (fax); martinfurmanski@aol.com (email)
[3] Mark Wheelis, PhD, Section of Microbiology, University of California, 1 Shields Avenue, Davis, CA 95616. 530-752-0562 (telephone); 530-752-3633 (fax); mlwheelis@ucdavis.edu (email); http://microbiology.ucdavis.edu/faculty/mwheelis/ (internet)
[4] Derivation of all equations is given in the appendix

where ED_{50} is the dose that will incapacitate 50% of exposed individuals, and A_0 is the initial concentration or dose of agent.

We assume that the same simple analysis holds as well for fatalities :

$$f_L = 1 / (1+LD_{50}/A_0)$$

where f_L is the approximate fraction of people killed by the incapacitating agent, LD_{50} is the dose that will kill 50% of exposed victims, and A_0 is the initial concentration or dose of agent.

Example

Let us illustrate with an incapacitating agent that would be judged exceptionally safe by pharmacology standards. Let

ED_{50} = 1 concentration unit
LD_{50} = 1,000 concentration units

This is an agent with a therapeutic index (TI), or safety margin, of

$$TI = LD_{50} / ED_{50} = 1{,}000$$

However, incapacitating agents are intended by their military developers to be used in situations in which the goal will be to incapacitate almost everyone, not 50%, in a particular place (often an enclosed space), as in hostage rescue or urban military operations. Therefore, it is necessary to use agent concentrations considerably higher than the ED_{50} (Figure 1—left hand curve is a graph of f_i vs A_0 with ED_{50} = 1). To incapacitate nearly everyone, enough agent to incapacitate approximately 99% or more of the target individuals has to be used.

The dose necessary to incapacitate a given fraction of the target population is:

$$A_0 = ED_{50} / (1/f_i - 1)$$

If we set f_i = 0.99, and ED_{50} = 1, then $A_0 = 1/(1/0.99 - 1) = 99$ concentration units; that is, a concentration 99-times greater than the ED_{50}. This is indicated by the dotted line in Figure 1.

How many people will this high concentration kill? This is easily calculated using LD_{50} = 1,000 and A_0 = 99

$$f_L = 1/(1+1{,}000/99) = 0.09$$

That is, 9% of the victims are expected be killed even with this exceptionally high therapeutic index. This is illustrated graphically in Figure 1 by the intersection of the vertical dotted line with the right hand curve (a graph of f_L vs A_0 with LD_{50} = 1,000).

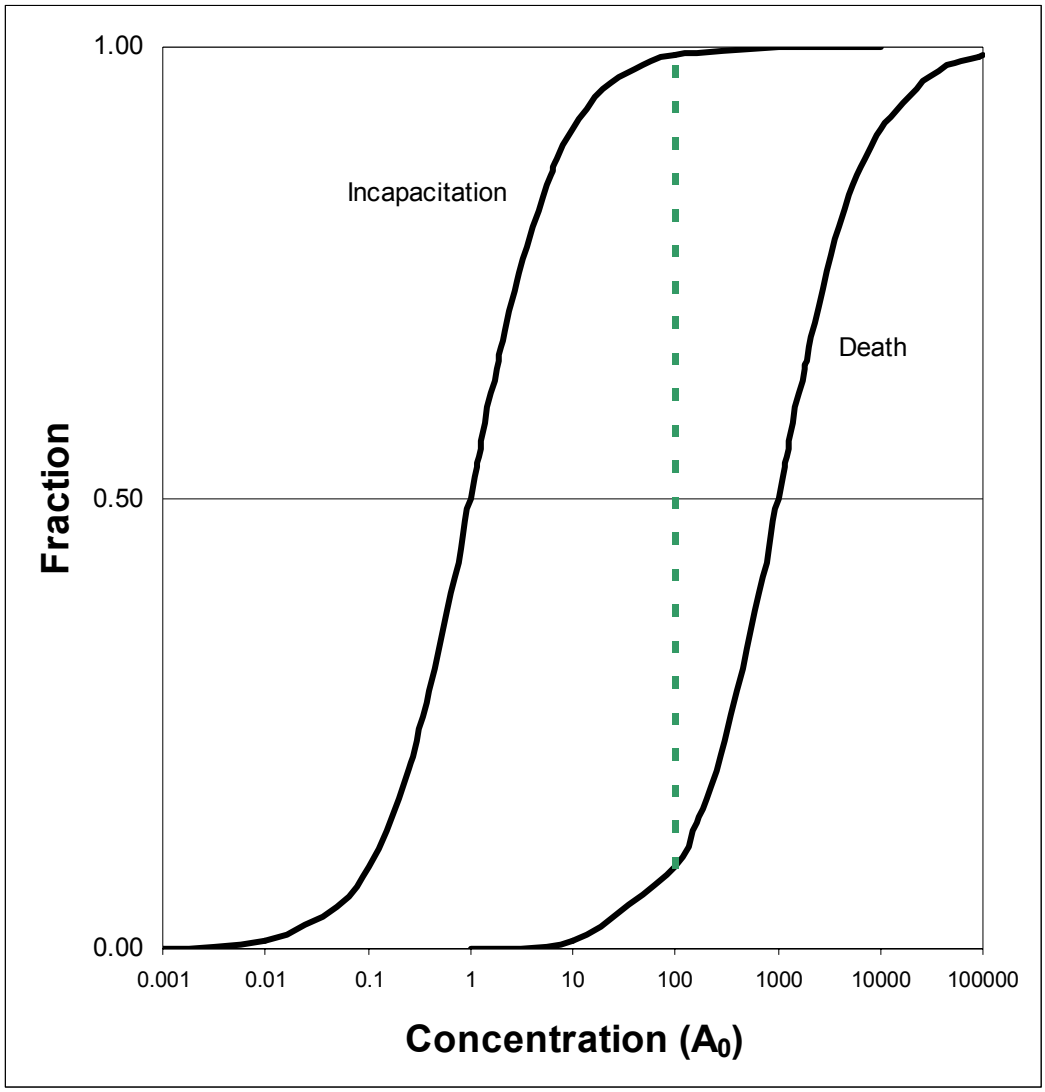

Figure 1. Relationship among dose, incapacitation, and lethality in a two-receptor model at equilibrium

Thus significant levels of lethality are expected when chemical calmatives are used as incapacitating weapons. This is exactly what happened in the Moscow hostage rescue; 127 of the 750 hostages died, or about 17%.

Adequacy of the model

Although the model is a simple one involving a single receptor for each effect (incapacitation and death), assuming a more complex anesthetic physiology involving more than one receptor for each would not change the analysis much. If binding to *any* of the receptors will cause the effect, the receptor with strongest binding to the agent will determine the position and shape of the dose curve. Similarly, where binding to *all* receptors is needed to cause the effect, the receptor with weakest binding to the agent will determine the position and shape of the dose curve. If the affinities are similar, the midpoint position will change somewhat, but shape will not be significantly changed (analysis available from LK). Our arguments below depend only on the shape of the dose curves, not the midpoint position, which is determined experimentally.

Of course, our model does not accommodate a case in which the incapacitating and lethal effects are the result of interaction with the same receptor, with the effect dependent on the fraction of receptors bound. In this case, incapacitation and death represent different regions of the same curve. Such agents have very low TIs, and thus would not be non-lethal weapons candidates. These include barbiturates and diazepams, which typically have TIs around 10 or less when used to induce stupor or anesthesia. This is acceptable in medical usage because such incapacitation is done in a clinical setting where the dose can be precisely controlled, and potentially fatal consequences can be managed—conditions that clearly would not obtain for military or police use. Thus the more conservative two-receptor model we use will more accurately fit the types of agents that might be considered as non-lethal weapons.

The choice of an equilibrium model for our analysis makes physiological sense for the use of a gaseous or aerosolized agent acting on the brain, since transfer of material from the alveoli into the bloodstream is very rapid (perhaps seconds), and transfer across the blood/brain barrier to the molecular receptor while often slower (perhaps a few minutes) is rapid enough for use as an anesthetic in a hospital.

But for weapons, which will need to act quickly before targets can react with defensive or offensive action, there likely are serious pharmacokinetic issues. The requirement for speed will require higher doses to overcome kinetic bottlenecks. For instance, consider the likely case in which achieving equilibrium across the blood/brain interface requires several minutes. To achieve incapacitating levels in the brain in less than a minute (a long time in a military operation requiring surprise), higher doses than those required at equilibrium would have to be delivered rapidly. Several minutes later, when blood/brain equilibrium is reached, the concentration would be far above the level intended, and thus further into the lethality zone.

A further problem bedevils use of aerosol agents (droplets or tiny particles) in enclosed spaces, where initial air concentrations might be maintained for some time. This is precisely the type of use envisaged for these weapons—in hostage rescue operations, like the Moscow incident, and in urban warfare. But such use means that the total dose continues to increase until casualties are evacuated, because even after incapacitation, agent continues to be inhaled and the dosage increases. This overdosage can easily lead to concentrations 10 times the planned dose, or more.[5]

Furthermore, actual hostile use of such weapons would usually require large safety margins (for the user) to compensate for uneven distribution of agent, and because for the user the potential costs of using too much (increased lethality in the target population) are much less than those of using too little (inadequate effect, endangering one's own forces). Thus in actual use, higher than necessary concentrations are expected to be used deliberately.

Even more seriously, there is considerable variation within a population in sensitivity to the effects of any pharmaceutical agent. Thus populations are quite heterogeneous, causing the curves in figure 1 to flatten significantly, while keeping nearly the same midpoints. This leads to significantly more overlap of the incapacitating and lethal curves at any given TI. Furthermore, significant numbers of very young, old, sickly, or malnourished in the exposed population extends the lower end of the lethality curve (right hand curve in Figure 1) even farther down into the overlap zone with incapacitation. This would be expected when civilians are among those targeted, as is specifically envisaged for these weapons. In such a case, combatants are likely to be young, healthy, alert, and motivated, requiring high doses for incapacitation. Civilian bystanders or hostages are likely to represent a random sample of the population, and thus to include some that are unusually sensitive to lethal effects.

All of the above considerations suggest that in actual usage the dose curves would be more gradual (lower slope) than theory predicts. Partially offsetting this might be the presence of threshold effects. For instance, if 75% of receptors had to be bound before effects began to appear, the dose curve would be quite a bit steeper, with the midpoint displaced slightly to the right. Threshold effects in the lethality systems could thus reduce somewhat the overlap of incapacitating and lethal doses.

Taking all of these effects into consideration, we suggest that this simple two-receptor equilibrium model will, if anything, underestimate the fatalities that are likely to result from the use of a "non-lethal" chemical incapacitant.

[5] Furmanski, M. Efficacy and lethality of chemical incapacitants: applied population pharmacology. In preparation.

Are non-lethal chemical incapacitants possible?

The US Joint Non-Lethal Weapons Directorate defines a non-lethal chemical weapon as one that incapacitates 98% of the target population while causing fewer than 0.5% fatalities.[6] What kind of TI would be required?

$$TI = [f_i(1-f_L)] / [f_L(1-f_i)] = [0.98(1-0.005)] / [0.005(1-0.98)] = 9751$$

Thus under ideal conditions of use, a non-lethal calmative agent would have to have a TI of about 10,000 to meet the stated goals. And of course, given all of the uncertainties of actual use, realistic non-lethal weapons would have to have TIs considerably higher. This is far above the TIs of known sedative, anaesthetic, or hypnotic agents, which are typically in the range of 5-10, rarely above 20 (when used to induce stupor or unconsciousness).

Psychedelic and delirium-inducing compounds also have TIs well below those needed for true non-lethal incapacitating agents, or they have side effects too severe or unpredictable to be considered as military incapacitating agents.[7] LSD (lysergic acid diethylamide), a potent hallucinogen and recreational drug, has a TI greater than 1000, but was rejected by the military after considerable study, due to the unpredictability of its effects. The deliriant 3-quinuclidinyl benzilate (BZ), an anticolinergic glycollate closely related to the belladonna alkaloids atropine and scopolamine, was produced and stockpiled during the 1960s as the standard US incapacitating chemical agent, but was ultimately abandoned, and stockpiles destroyed, because its effects were also too unpredictable. Its TI is reported to be about 40. Atropine is similar, and scopolamine is a bit higher (about 100). Phencyclidine, formerly used as a veterinary anesthetic but no longer approved because of rampant abuse (the street drug PCP, or "angel dust"), and the related human anesthetic ketamine ("special K" on the street), appear to have high TIs, but they are highly unpredictable in their effects and have been ruled out as militarily useful compounds.

The special case of opiates deserves some additional comment, as the agent employed in the Moscow hostage rescue was a member of this class. Opiates have three principal types of receptor, each of which has several subtypes. Mechanisms of anesthesia, and of respiratory depression (the proximal cause of death in opiate overdoses in humans), remain unclear. It appears that both incapacitation and death are mediated largely by the μ receptor, but they may involve different subclasses.[8]

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[6] Kenny, J. M. 2001. The human effects of non-lethal weapons. Human Effects Advisory Panel presentation to to the Committee for an Assessment of of Non-Lethal Weapons Science and Technology, April 30, 2001. Viewgraphs. ONR-NLW.239. National Academy of Sciences

[7] Ketchum, J. S., and F. R. Sidell, 1997. Incapacitating agents. pp 287-305 in Sidell, S. R., Takafuji, E. T., and Franz, D. R. (Eds), *Textbook of Military Medicine Part I: Warfare, Weaponry, and the Casualty. Vol 4 Medical Aspects of Chemical and Biological Warfare*. Falls Church, Virginia: TMM Publications, Office of the Surgeon General.

[8] Bailey, P. L., Egan, T. D., and Stanley, T. H. 2000. Intravenous opiod anesthetics. pp 273-376 in Miller, R. D. (Ed.) *Anesthesia* Vol 1.Philadelphia: Churchill Livingstone.

There are a number of different chemical classes of opiates, but the most attractive ones for weapons use would be the high potency fentanyls—compounds related structurally to the anesthetic fentanyl. The agent used in Moscow was said to be an unspecified fentanyl derivative. Because opiates are important as analgesics for severe pain and as anesthetics, a large number of experimental fentanyls have been synthesized. Some are reported to have exceptionally high TIs. For instance, for analgesia in rats, fentanyl has a TI of 277, carfentanil 10,000, and sufentanil 25,000. Since TIs for anesthesia are commonly about one tenth or one twentieth of that for analgesia, this would suggest that some fentanyls might have TIs for incapacitation of around one thousand.

However, this promise is illusory. There is large variation among species in the response to opiates, and primates are especially susceptible to opiate-induced respiratory depression. Sufentanil is used for analgesia and anesthesia in humans. Plasma concentration for full anesthesia is around 5 ng/kg, whereas concentrations above 0.4 ng/kg (at the top end of the range for analgesia, and the bottom of the anesthetic range) threaten spontaneous respiration. Thus despite its astronomical TI for analgesia in rats, for incapacitation in humans sufentanil appears to have a TI that barely exceeds 1.

Carfentanil appears similar. It is approved as a veterinary incapacitant (it is a common agent for "darting" wild animals), but experience of wildlife biologists in the field is of low safety margins, despite the rat data, and substantial species variability. In chimpanzees and gorillas, severe respiratory depression and even death are encountered at incapacitating doses,[9] suggesting that the human TI for incapacitation is likely very low. Thus it appears that there are no opiates currently known that could be developed into non-lethal weapons, and that the over 15% mortality encountered in the Moscow hostage rescue was, if anything, mercifully low.

The low TIs that characterize chemical incapacitating agents is not surprising, given the great complexity of receptor biology and signal transduction in the central nervous system. Thus the default assumption for any new (or existing) agent must be that it is too lethal to be developed as a non-lethal weapon, absent convincing evidence that it has a TI for incapacitation, in humans, of at least 10,000, and preferably higher.

Conclusion

We have shown, at least within the approximations of our simple (but generous) two-receptor equilibrium model, that even with a therapeutic index of 1,000 (above any known anaesthetic or sedative agent), a chemical agent used as an incapacitating weapon can be expected to cause about 10% fatalities. Even with an astronomical TI of 10,000, under actual conditions of use in the field, fatalities could easily reach the same level. This is comparable to the effects of traditional "lethal" technologies. For instance, in military combat, firearms typically cause about 35% deaths among total casualties, shells about 20%, and grenades about 10%.[10] "Lethal" chemical weapons are comparable; in

[9] Kearns, K. S., Swenson, B., and Ransay, E. C. 1999. Dosage trials with transmucosal carfentanil citrate in non-human primates. *Zoo Biology* 18, 397-402.
[10] Bellamy, R. F. 1992. Medical effects of conventional weapons. *World Journal of Surgery* 16, 888-892.

World War I the lethality of gas was about 7%.[11] All currently available chemical incapacitating agents would certainly fall into this range in normal use, and thus must be considered lethal technologies, in the same category as traditional chemical weapons. Chemical incapacitants are clearly not comparable to riot control agents, which act by non-specific sensory irritation and have TIs in the range of several hundred (CN) to over 10,000 for the most commonly used agent (CS),[12] and they are clearly not suitable for law enforcement uses. Any attempt to develop chemical incapacitants for military purposes is prohibited by the CWC.

[11] Robinson, J. P. 1971. *The Problem of Chemical and Biological Warfare I. The Rise of CB Weapons.* Humanities Press, New York. p. 129.

[12] Sidell, F. R. 1997. Riot control agents. pp 307-324 in Sidell, S. R., Takafuji, E. T., and Franz, D. R. (Eds), *Textbook of Military Medicine Part I: Warfare, Weaponry, and the Casualty. Vol 4 Medical Aspects of Chemical and Biological Warfare*. Falls Church, Virginia: TMM Publications, Office of the Surgeon General.

Appendix: derivation of equations

For binding of agent (A) to a single receptor (R) the chemical equation is

$$A + R \leftrightarrow AR$$

A = agent
R = unbound receptor
AR = agent-receptor complex

The standard dissociation constant is

$$K_d = [A][R]/[AR] \qquad (1)$$

For almost all drug-receptor interactions, drug is in great excess over receptor. This would be the case for incapacitating agents as well. Therefore, $[A] = A_0$ throughout the interaction, where A_0 is the initial (and final) agent concentration.

Substituting for constant agent concentration into equation (1) yields

$$K_d = A_0 [R]/[AR] \qquad (2)$$

Calculating the fraction incapacitated or killed

By definition, fraction of receptor bound is

$$f = [AR]/R_0$$

where R_0 is the initial (unbound) receptor concentration.

Since $[AR] = R_0 - [R]$ and $[R] = R_0(1-f)$, substituting into equation (2) and solving for f gives

$$f = 1 / (1+ K_d/A_0) \qquad (3)$$

We set $f = f_i$ and $K_d = K_{di}$ to explicitly denote incapacitation with the subscript "i." With this new notation, equation (3) becomes

$$f_i = 1 / (1+ K_{di}/A_0) \qquad (4)$$

We assume that the same simple analysis holds as well for fatalities where the subscript "L" denotes lethality:

$$f_L = 1 / (1+K_{dL}/A_0) \qquad (5)$$

For both incapacitation and lethality, we assume that the fraction of receptors bound is equal to the fraction of victims incapacitated or killed.

Thus when $A_0 = K_{di}$, $f_i = 0.5$; that is, in this model the concentration K_{di} is also the concentration that will incapacitate 50% of victims. This concentration is called the IC_{50} (50% inhibitory concentration) or ED_{50} (50% effective dose) in the usual nomenclature. Similarly, a concentration (or dose) equal to K_{dL} will kill 50% of victims, so it is equal to the LD_{50} (50% lethal dose).

Substituting $ED_{50} = K_{di}$ and $LD_{50} = K_{dL}$ into equations (4) and (5) gives

$$f_i = 1 / (1+ ED_{50}/A_0) \quad (6)$$

and

$$f_L = 1 / (1+LD_{50}/A_0) \quad (7)$$

Calculating dose necessary for specified levels of incapacitation

Solving equation (6) for A_0 yields:

$$A_0 = ED_{50} / (1/f_i - 1) \quad (8)$$

Calculating TI necessary for given incapacitation and lethality levels

By definition

$$TI = LD_{50} / ED_{50} = K_{dL}/ K_{di} \quad (9)$$

Substituting equation (9) into (5) yields

$$f_L = 1 / [1 + TI(K_{di}/A_0)] \quad (10)$$

Solving equation (4) for K_{di}/A_0

$$K_{di} /A_0 = 1/f_i – 1 = (1- f_i) / f_i \quad (11)$$

and substituting into equation (10) gives

$$f_L = 1 / (1 + TI (1- f_i) / f_i) \quad (12)$$

which may be solved for TI and rearranged:

$$TI = [f_i(1-f_L)] / [f_L(1-f_i)] \quad (13)$$