

Storm before the Calm

news

SCAN

CAN KNOCKOUT GASES REALLY BE NONLETHAL? BY DANIEL G. DUPONT

Last November 4 the Naval Studies Board of the National Research Council issued a report calling on the U.S. to increase its research into “calmatives,” drugs that could be used to control and sedate unruly or hostile groups of people. Whereas most of the board’s research had been finished a year earlier, the report was especially timely: nine days before, Russian troops had used a gas to subdue Chechen rebels in an attempt to rescue the 700 hostages they were holding in a Moscow theater. The gas—actually a nebulized aerosol said to contain fentanyl, an opiate used as an anesthetic—killed more than 100 hostages.

The U.S. looked into calmatives in the 1980s and 1990s, but the development of many types of chemical agents slowed or stopped in the wake of the Chemical Weapons Convention, ratified in 1997. The rise of terrorist activity throughout the world has led many military experts to believe that some kind of knockout gas would be helpful. Andrew Mazzara, a retired U.S. Marine colonel who heads the Institute for Emerging Defense Technologies at Pennsylvania State University’s Applied Research Laboratory, states that the Russian example highlights a need for “more research rather than less” into nonlethal means of incapacitating hostage takers.

Even before the Naval Studies Board, the Penn State lab had investigated nonlethal weapons and concluded that such calmatives could work safely. Researchers led by Joan Lakoski, now at the University of Pittsburgh, reviewed the medical literature on pharmaceutical agents that produce “a calm state.” Ideally, according to the investigators, an effective calmativ would be easy to administer and be adaptable for use in a variety of forms, fast-acting but short-lived, and reversible. After examining more than 7,800 articles and other references, the Penn State team declared in an October 2000 report that “the wide variety of drug classes and specific agents” that they studied “serve to underscore that the development and use of nonlethal calmativ techniques is achievable and desirable.”

The Penn State authors identified many compounds that have a “high potential for consideration” as nonlethal agents: sedative-

hypnotic agents, anesthetic agents, muscle relaxants, opioid analgesics, anxiolytics, anti-psychotics and antidepressants. But they singled out several major classes, two of which are convulsants and “selected drugs of abuse,” including certain “club drugs.” They also pointed to two drugs deserving immediate attention: diazepam (Valium) and dexmedetomidine.

Despite advances, drug delivery “remains a key issue in the development of calmativ agents as nonlethal techniques,” the Penn researchers pointed out. The problem is one of dosage: when an incapacitating gas is pumped into the ventilation system of a building, as was the case in the Moscow theater, some recipients will inevitably receive more than others. An opiate such as fentanyl is particularly crude when used in this way because it has a small dosage window in which it is considered safe. Benzodiazepines, used to anesthetize and to treat anxiety and amnesia (Valium is one), are considered more promising but do not act as fast.

For these reasons, a nonlethal and effective knockout gas is a myth, maintains Elisa Harris, a researcher at the University of Maryland and a former National Security Council staff member. “I just can’t see how [such a gas] is technologically feasible,” she says. “In decades and decades of research, it’s never materialized.” Harris and other opponents argue that knockout gases cannot be described as nonlethal—they will kill some of the people they are intended to save. James Cottrell, president of the American Society of Anesthesiologists, believes it would be “almost impossible” to develop an anesthetic gas that won’t kill.

One way to reduce casualties is to combine the use of a gas with postexposure treatment. Doctors in Moscow were reportedly not aware of what ailed the rescued hostages, which stymied their efforts to treat them. Russian authorities denied the charge,

PRESCRIPTION FOR PACIFICATION

According to the Naval Studies Board, the U.S. worked on calmatives in the 1980s and 1990s at the army’s Edgewood Chemical and Biological Command in Maryland. Moreover, it states that the use of calmatives has been discussed numerous times during meetings held by the Office of the Secretary of Defense and the Joint Staff. In May 2000 the Pentagon reportedly started at least one effort to research chemical immobilizing agents.

Candidate compounds:

- Benzodiazepines
- Alpha₂-adrenoreceptor agonists
- Dopamine D3 receptor agonists
- Selective serotonin reuptake inhibitors
- Serotonin 5-HT_{1A} receptor agonists
- Opioid receptors and mu agonists
- Neurolept anesthetics
- Corticotropin-releasing-factor receptor antagonists
- Cholecystokinin B receptor antagonists



GASSED VICTIM is carried by a Russian officer after a raid to free hostages in a Moscow theater on October 26, 2002.

saying that antidotes were prepared and used.

In the end, determining whether a calmativ gas can be made safe and effective depends on how those criteria are defined. Whereas the gas used in Moscow killed more than 100 of the hostages, it contributed to the rescue of six times that many. Alan Zelicoff, a senior scientist at Sandia National Laboratories, remarks that "it might be nice to have something other than high-speed lead, chemical explosives and other lethal means to quell

riots or even deny terrorists their targets."

Hostage negotiations should be tried first, although in the case of the Moscow incident, a peaceful end seemed unlikely. As Penn State's Mazzara notes, without the use of calmatives, such no-win situations might "very possibly lead to more tragic results."

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CANCER

T Cell Triumph

IMMUNOTHERAPY MAY HAVE FINALLY TURNED A CORNER BY DIANE MARTINDALE

Immunotherapy for cancer is a targeted treatment that uses a patient's own immune cells to attack and destroy tumors. Highly touted when it was conceived in the early 1980s, the approach has met with little success. Now researchers think they may have gotten over the hump: they have successfully treated several cases of a deadly skin cancer with immune cells taken from the patients, grown in large numbers in the laboratory and then given back to them. "We can now repopulate the body's immune system with cells that fight the cancer," says Steven A. Rosenberg of the National Cancer Institute, who pioneered immunotherapy.

The idea is to exploit a subset of T cells, the so-called tumor-infiltrating lymphocytes (TILs), found deep inside cancerous tissue. These killer T cells attack the rapidly dividing cells and provide a natural protection against cancer.

But the body seldom makes enough to keep the disease in check.

Rosenberg first isolated and grew TILs and gave them to patients in the 1980s, in a process called adoptive T cell therapy. Although the T cells retained their antitumor properties, they did not proliferate or survive long enough in patients to kill their tumor cells. The recent success came when Rosenberg's team altered

its method in two crucial ways. First, the scientists improved the way antitumor T cells are generated. TILs were isolated from multiple samples of each patient's tumor and grown in the lab. The group then tested up to 50 different samples against each patient's cancer cells and chose the most reactive T cells to expand and reinfuse into the patients. Previously, cells were simply extracted from the tumors without any type of selection.

Second, the researchers changed the way patients are prepared before the treatment. This time subjects underwent robust chemotherapy to wipe out their immune systems temporarily and thereby make room for the incoming tumor-killing T cells. The procedure may have removed suppressor cells (made by the immune system or the tumor), which prevent T cells from proliferating, Rosenberg says. After the reinfusion,

patients received repeated doses of interleukin 2, a potent immune system hormone that stimulates the growth of T cells.

The study relied on 13 individuals with advanced metastatic melanoma, a skin cancer that eventually spreads to other organs. The patients, who had exhausted all other treatments, including surgery, received on average 80 billion of their own TILs—enough to give



T CELL (yellow) attacks a cancer cell.

A TREATMENT IN WAITING

Despite the recent success, immune cell therapy is still highly experimental. Side effects were serious in some cases: they included vitiligo (white patches of skin where normal pigment cells were attacked by the tumor-infiltrating lymphocytes) and opportunistic infections. This is not like a drug you can just pull off the shelf. "Every cell we give is basically a different drug because it's unique to that patient. And every patient has a different kind of tumor," says Steven A. Rosenberg of the National Cancer Institute, who is still trying to understand why the therapy works in some and not in others. Rosenberg thinks it will be at least two years before the therapy is ready for other types of cancer patients.