GUEST EDITORIAL

Fentanyl: Are we paying too high a price?

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INTRODUCTION

Fentanyl is an analgesic opioid that was introduced into medical practice in the 1960s. It has been commonly used for decades in anesthesia, sedation, and pain management. Along with nitrous oxide and thiopental, fentanyl is one of the anesthesiological drugs with the longest history of use. In fact, after about 50 years, it is still administered daily to millions of adult and pediatric patients. However, an increasing number of papers report that the use of fentanyl is correlated to unpleasant effects both in and out of clinical scenarios. Recently, *The Lancet* has focused on the drug's use and effects, not only in patients but also in healthcare professionals, offering evidence of its increasingly prevalent role as a drug of abuse and overdose. In fact, the drug has become so strongly associated with abuse in recent years that it has earned the new moniker of "killer fentanyl."[1,2]

Given the large number of patients receiving the drug, as well as of physicians administering it (anesthesiologists, intensive care specialists, pain professionals, etc.), queries about the validity of these accusations are both warranted and expected.

ABUSE AND OVERDOSE: A GLOBAL PROBLEM

The prevalence of overdose deaths attributed to opioids is increasing throughout the world. Heroin is still the predominant illicit opioid of interest for toxicology laboratories because of its widespread availability and its ability to elicit respiratory depression and coma,[3] but today, new, totally synthetic drugs are becoming an increasingly important subset of abused substances. Fentanyls, a family of very potent narcotic analgesics, are of particular concern. They first appeared on the streets in California in 1979 under the name "China White," sold as heroin substitutes or used to lace street drugs.

It is likely that as efforts to restrict the importation of natural opiates and prevent diversion of pharmaceuticals have become more effective, fentanyls have become increasingly important drugs of abuse.[4] The effects of fentanyl are indistinguishable from those produced by nasal inhalation of street heroin. In light of this, and because of its very low production costs, fentanyl is very attractive for the narcotics market.[2]

Health workers began to notice a spike in fentanyl overdoses and deaths late last year, thanks to new, sophisticated toxicology and autopsy tests.[1] At least 112 overdose deaths have been associated with the drug. No preexisting medical conditions were identified as possible risk factors in any of these recorded deaths. Although most of the fentanyl victims had a prior history of intravenous drug use, drugs such as morphine or codeine were not commonly found in their systems, which suggests that the victims had little or no opiate tolerance. It is probable that the general availability of the drug, rather than the potency of any particular analog, determined the incidence of overdose deaths.[5] More than 20 years ago, in California, increased fentanyl use was detected as a new trend in drug use in a sample population of young users.[6] In early 1992, the Office of the Chief Medical Examiner of the State of Maryland encountered 30 cases in which fentanyl was identified in postmortem examinations of victims.[7]

Increases in fentanyl abuse are therefore a growing public health problem, with the risk that within a few years, fentanyl abuse could evolve into a problem of global epidemic proportions.[2]

CLINICAL ASPECTS

As with other opioids, fentanyl use can induce opioid tolerance, physical dependence, and addiction. These consequences limit its applications for appropriate long-term use.

Cases of withdrawal syndrome related to fentanyl have been observed in both adult and pediatric patients in intensive care units (ICUs). There is an elevated incidence of abstinence syndrome in children in the pediatric ICU, owing to the interruption of fentanyl infusion and midazolam; this syndrome is related to fentanyl dose and time of use.[8] Symptoms include systemic convulsions

with loss of consciousness.[9] Acute withdrawal syndrome related to the administration of analgesic and sedative medications has also been observed in adult ICU patients, particularly in mechanically ventilated patients receiving extended ICU care (≥ seven days).[10]

Thanks to its highly lipophilic nature, fentanyl can be administered in the form of a transdermal patch to control pain. From 1997 to 2000, the Los Angeles County coroner's toxicology laboratory encountered 25 cases involving fentanyl patches. Causes of death included 15 accidental, five natural, three suicidal, and two undetermined.[11]

The number of fentanyl-related deaths increased between 2000 and 2002, and 19 out of 23 deaths attributed to fentanyl misuse or abuse were related to transdermal patches. Routes of administration included transdermal, transmucosal/oral, intravenous, and a combination of routes, suggesting that fentanyl is rapidly becoming a desirable opioid for street users, similar to oxycodone and methadone.[12]

Pharmacogenomics—the study of genetic contributions to drug action—may aid in certifying fentanyl toxicity. As suggested in 92 percent of fentanyl-related deaths, toxicity may be partially due to cytochrome P450 (CYP) 3A4*1B and 3A5*3 variant alleles, resulting in variable fentanyl metabolism. In fact, postmortem/in vivo data have provided scientific evidence that CYP3A5 is involved in fentanyl metabolism, and that homozygous CYP3A5*3 causes impaired metabolism of fentanyl.[13]

Large-dose fentanyl anesthesia induces prolonged suppression of natural killer (NK) cell cytotoxicity in patients undergoing abdominal surgery, and this increases the risk of tumor metastasis. In fact, suppression of NK cells at the time of surgery may induce tumor dissemination and the spread of metastases.[14]

There are numerous problems for patients and healthcare providers regarding use, abuse, or overdose of fentanyl in anesthesia, intensive care, and pain therapy; these are summarized below. The quantity of related international research published in the last few decades is quite impressive.

Problems for patients include the following:

- dependence and withdrawal syndromes after long-term infusion in adults and children;[15,16]
- muscle rigidity (increased large-trunk-muscle tone with decreased thoracic compliance);[17,18]
- respiratory depression (inhibition of brain stem respiratory center);[19-21]
- glottic closure (effects on vagal motor neurons with tonic vocal-fold closure and pharyngeal obstruction of airflow);[22-25]
- nausea and vomiting (stimulation of brain stem chemoreceptor trigger zone);[26,27]
- misperceptions of sexual abuse by critically ill patients;[28]
- analgesic abuse;[29,30] and
- improper intravenous injection of fentanyl derived from transdermal systems.[31,32]

Problems in healthcare providers include the following:

- high risk of addiction for medical staff working with these drugs;[33]
- dependence in anesthesia providers;[34]
- substance abuse by anesthesiologists;[35] and
- increased mortality resulting from overdose and abuse by healthcare professionals.[36]

FENTANYL ADDICTION

Risk of addiction through occupational exposure to drugs of abuse is an important but relatively neglected public health problem. It is well known that secondhand inhalation of vapors from crack cocaine can be quite dangerous, but rarely has the alarm been raised about exposing anesthesiologists to secondhand fentanyl.[37] To explain the high incidence of this problem, it has been hypothesized that aerosolization of anesthetics administered intravenously to patients in the operating room may be an unintended source of exposure for physicians.[38]

Fentanyl has been detected in the air of cardiovascular operating rooms, and the highest concentrations were close to the patient's mouth, where anesthesiologists sometimes work for hours.[39] As with tobacco, secondhand exposure to opioids can inadvertently sensitize, increasing the risk of developing addiction, and brain changes may occur, leading to abuse, dependence, and behavioral disorders; these problems are more likely among anesthesiologists and surgeons.[39] Moreover, there are many risk factors, such as psychiatric stress and a family history of substance use disorders, that are implicated in fentanyl addiction in healthcare professionals and anesthesiologists.[40] Additionally, chemical impairment may be more common than usually thought in anesthesiologists, perhaps in part because of drug availability.[41] This may contribute to the overrepresentation of certain specialties among physicians with addiction.[38] The ends to which an individual motivated by an addicted

brain will go to obtain drugs to quench his or her chemical addiction has been described in fascinating detail.[42]

CONCLUSION

The introduction of a new drug into clinical practice is welcomed when it helps our efforts at improving a patient's clinical course or the medical practice as a whole. Fentanyl's entrance into the anesthesiological setting, about 50 years ago, contributed greatly to the evolution of our science.

Half a century has passed since then, and clinical practice has undergone substantial evolution. Anesthesiology has witnessed rapid, continuous changes in anesthetic drugs, as well as inhalational and neuromuscular blocking drugs. But its very low price has made fentanyl an "evergreen," and in today's climate of cost consciousness, hospital administrations still push its use and avoid promoting newer and more specific opioids.[2] Military units' interest in the toxic effects of fentanyl is also increasing, as suggested by the Dubrovka theater incident of 2002. The Russian military pumped a fentanyl-related compound into the theater two and a half days after it was seized by armed Chechen militants, who were holding 850 occupants hostage. Because of respiratory depression induced by the compound, all of the militants were killed—along with over 100 hostages.[43]

Fentanyl is implicated in complications, toxicity, addiction, abuse, overdose, and death in patients and healthcare professionals. The "gentlemanly" face of fentanyl has changed, and it is now becoming viewed as a potential killer. In light of its potentially fatal side effects and growing popularity as a street drug, maybe the widespread use of fentanyl should be reconsidered. Since legally related problems should also be taken into consideration, recommendations by various institutions for the limitation of fentanyl use could be devised.

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