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February 22, 1989

Frank Young, M.D., Ph.D.
Commissioner
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Commissioner Young,

We have obtained information from the drug industry and from other sources, documenting that in 1985, FDA approved human experimentation in which more than 300 children, from two to fifteen years old, have been given narcotic lollipops containing a powerful drug, fentanyl, 200 times more potent than morphine. A company, Anesta Corporation, in Salt Lake City, Utah, was established by several anesthesiologists, in conjunction with the University of Utah, to test and develop these narcotic lollipops for eventual marketing for premedication and/or for pain relief.

Given the loud rhetoric by the Reagan/Bush administration concerning the problem of drug abuse, we find it extraordinary that your agency, the Food and Drug Administration, would give approval to experimenting on children with these narcotic lollipops. Since these experiments are still ongoing, three and one-half years after clinical research was begun with FDA's blessing, it can only be assumed that the FDA believes that massive nationwide promotion and distribution of these narcotic lollipops--a certainty if they are ever approved--is possibly a good idea.

We urge you to use your authority to stop immediately these ongoing experiments. Under section 505 (i), 21 U.S.C. section 255 (i), and the regulations that have been issued pursuant to that section, the FDA has broad discretion to permit or halt the testing of drugs in human subjects. Since there are no circumstances under which such lollipops could be found safe, there is absolutely no legal or policy justification for permitting any further testing of these narcotic lollipops. Continued testing, with the goal of eventual market approval by the FDA, sets a disastrous precedent and significantly undermines the cautionary message being given to children today: "JUST SAY NO TO DRUGS!" Giving lollipops laced with a powerful narcotic

to children who, in the words of one research group, "visibly enjoyed the premedication experience", (as one might expect children sucking lollipops to do) is a major step in the wrong direction.

In addition to the symbolism of Medicine=Candy, there is the strong likelihood of an increased amount of drug abuse, as fentanyl, the active ingredient in the lollipops, is already a leading drug of abuse among health professionals and "street" users. This situation would only worsen if the more easily-used lollipop dosage form were approved for marketing.

We have also learned that Janssen Pharmaceutica, the company which originally developed the drug and leads in sales of fentanyl (an otherwise excellent drug in its approved intravenous or intramuscular dosage form) has recently turned down an offer to participate with Anesta in the further development or, if it were to be approved, marketing of fentanyl lollipops because it is concerned about the potential for abuse of the product.

Furthermore, a high-ranking official in the Drug Enforcement Administration (DEA) has told us that he is even more concerned about the problem of detecting diversion of fentanyl in lollipop form than in the existing approved dosage forms.

There are six aspects of the risks which far outweigh any potential benefits of fentanyl lollipops:

1. Symbolism
   A potent narcotic in a candy matrix clearly targeted at children, is inappropriate. It sends out the following dangerous message:

   MEDICINE=CANDY

2. High addiction potential
   The addiction potential of the fentanyls has been demonstrated in two important circumstances:

   a. Professionals (anesthesiologists[1] and oral & facial maxillofacial surgical residents[2]) who have exposure to the medical use of the drug are relatively high abusers of fentanyls.

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[1] Ward CF, et al: Drug abuse in anesthesia training programs. A survey: 1970 through 1980. JAMA 250:7 922-925 1983

[2] Rosenberg M: Drug abuse in oral and maxillofacial training programs. Journal of Oral and Maxillofacial Surgery, vol 44, 458-462, 1986

b. Systematic surveys of "street" users indicates that the fentanyls (fentanyl itself and a variety of analogs, sometimes referred to as "designer drugs") are an acceptable substitute for heroin. Street use has largely been limited to California where there have been over 100 overdose deaths[3,4,5,6]).

3. Narcotic for sedation

Some of the investigational drug protocols indicate that the use of narcotics will be promoted for situations where only a sedative effect is needed, e.g. premedication for anesthesia. In many situations, this can be achieved without resort to drugs--e.g. parents accompanying the child, hypnosis, use of play therapists. In those situations where a drug is clinically appropriate, shorter acting and less potent respiratory depressants can be utilized--e.g. rectal brevitol (a barbiturate) in 2-5 year olds; inhalation nitrous oxide in school-age children.

There are situations where both a sedative and an analgesic effect are desirable. Such situations include dressing changes and debridement of burns, and bone marrow aspiration (especially in children with cancer where it is likely to be a frequent procedure). There are many satisfactory alternatives to narcotic lollipops, and better methods may be available in the very near future.

4. Invitation to less supervised sedation

The convenient and seemingly innocuous packaging invites the use of an opioid in situations where there is inadequate pediatric resuscitative equipment and expertise, e.g. doctors' offices and emergency rooms for minor suturing, "premed" given by a nurse in the ward prior to operation (some hospitals premedicate in the wards, rather than in the anesthesia induction room).

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[3] Ayres WA, et al: The bogus drug, three methyl & alpha methyl fentanyl sold as "china white". Journal of Psychoactive Drugs, 13:1 91-93, 1981

[4] Siegel RK: New trends in drug use among youth in California. Bulletin on Narcotics, vol 27 nos 2&3, 7-17, 1985

[5] Henderson GL: Designer drugs: Past history and future prospects. Journal of Forensic Sciences 33:2 569-575, 1988

[6] LaBarbera M, Wolfe T: Characteristics, attitudes and implications of fentanyl use based on reports from self-identified fentanyl users. Journal of Psychoactive Drugs, 15:4 293-301, 1983

5. Prolonged duration of action
The medically used fentanyls (fentanyl, alfentanyl, sufentanyl) may have been misclassified as "short acting". Hess et al. warned of this in 1972[7]; further study by McQuay et al.[8] indicated there is a biphasic mode of distribution with a second peak of plasma concentration occurring about 45 minutes after the last dose given during surgery.

This is corroborated, to a limited extent, by interviews with street users who indicate the plateau ("nod") is of longer duration than heroin (10-12 hours versus 8 hours).[9] The street analogues of choice at the time were alpha methyl fentanyl and parafluro fentanyl.

6. Variable absorption rate
Clearly it is difficult to control the rate of sucking--and therefore of absorption--by children. Since fentanyl is quickly inactivated if it is swallowed, the major route into the body is by absorption through the mucous membrane of the mouth. This means that there is likely to be a wide and unpredictable variation in the tissue level of this potent and long lasting respiratory depressant. Clinical trials with adults have demonstrated this variability.[10]

We are aware that Dr. Theodore Stanley, a Professor of Anesthesiology from the University of Utah School of Medicine and originator of the fentanyl lollipop, believes that the benefits of this convenient dosage form, which does not involve the use of needles for injection, clearly outweigh the various risks outlined above. As far as is known, the research conducted by Dr. Stanley and other investigators has been done carefully. But

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[7] Hess R, et al.: Pharmacokinetics of fentanyl in man and the rabbit. European Journal of Clinical Pharmacology, vol 4 137-141, 1972

[8] McQuay HJ, et al.: Plasma fentanyl concentrations and clinical observations during and after operation. British Journal of Anaesthesiology, vol 51, 543-549, 1979

[9] LaBarbera M, Wolfe T: Characteristics, attitudes and implications of fentanyl use based on reports from self-identified fentanyl users. Journal of Psychoactive Drugs, 15:4 293-301, 1983

[10] Mock DL, et al.: Transmucosal narcotic delivery: An evaluation of fentanyl (lollipop) premedication in man. Anesthesia and Analgesia, 65:S1-S170, 1986

there are those who think that Dr. Stanley is extraordinarily naive about the implications of nationwide marketing of fentanyl lollipops as evidenced by the fact that the clinical trials of their use in children continue, with the obvious intention of eventual approval for marketing. Others, including ourselves, believe that his naivete and that of his company, Anesta, may be supported by the financial considerations of what would be gained if a lollipop form--of what is already the most widely used narcotic in the context of anesthesia--were approved for marketing.

The lacing of lollipops with fentanyl not only sends out a dangerous message about medicines; it is of dubious clinical need or safety and is a category of drug (synthetic opioid) that is of such addictive potential that its more widespread dissemination and publicity may pose a significant threat to drug enforcement. It is with these points in mind that we urge you to stop immediately the use of fentanyl lollipops in experiments on American children.

We look forward to your prompt response to this urgent issue.

Yours sincerely,

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January 24, 1994

Dr. David Kessler
Commissioner
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Kessler:

I have recently discovered that the fentanyl lollipop has received FDA approval to enter the healthcare market. I have been following this new product's development for several years hoping that it would never be approved by the FDA. I am writing to you today with regard to my concerns as both a pediatrician and pediatric anesthesiologist about the introduction of a candy that contains the potent narcotic fentanyl into pediatric medicine. My concerns and comments will be focused into five (5) categories.

- Patient Safety
- Medical Necessity/Patient Need
- Medical Efficacy
- Sociocultural Concerns
- Economic Implications

1. Patient Safety
   The fentanyl lollipop will deliver the potent narcotic fentanyl directly into the bloodstream of pediatric patients. My safety concern centers on the respiratory depression and respiratory arrest potential that will result. At least when under the direct supervision of an anesthesiologist in an appropriately equipped area one can hope that such respiratory events can be treated promptly. However, without a high level of vigilance I am concerned that the outcome could be tragic. The quality of patient monitoring as well as the airway management skills of medical personnel decreases significantly outside of the immediate operating room environment in our nation's hospitals. In addition, there is even greater variation in these two areas if we compare the 6500 hospitals in the U.S. to one another. Most children are cared for in our general hospitals that recently were criticized with regard to their inability to deal with pediatric emergencies (some simply because of a lack of appropriate sized equipment!)

The transdermal fentanyl tragedies will pale in comparison to the potential problems waiting to happen with the introduction of the fentanyl lollipop.

2. Medical Necessity/Patient Need
The issue of preoperative anxiety is of great interest to me as a pediatric anesthesiologist. My belief has always been that non-pharmacologic approaches are more appropriate in dealing with children on this issue. Utilizing preoperative teaching programs, hospital/OR visits, parent-child discussions of upcoming surgery, parents in the OR, pediatric nurses and other child-focused personnel can achieve anxiolysis better than any drug. All too often in America we reach for drugs to handle our stress when a much healthier alternative is available.

It is also more sensible to treat anxiety with a sedative class of medications rather than a pure, potent narcotic. Narcotics are superior analgesics but inferior anxiolytics when used alone. There is a vast difference between the anxiety of a 4 year old child coming for a herniorrhaphy and a 60 year old adult with coronary artery disease coming for a bypass operation. All too often the cardiac anesthesiologists conclude that their practice of administering highly potent narcotics is good for all patients. In the case of the fentanyl lollipop I think the developers of this product have missed answering two fundamental questions. What is the problem? How do we improve treating preoperative and pre-procedure anxiety without causing harm?

3. Medical Efficacy
Throughout the clinical trials with the fentanyl lollipop that where reported in the anesthesia literature over the past several years there has been reported a high incidence of nausea, vomiting and facial itching preoperatively. The induction of anesthesia in a child who is vomiting increases the risk of induction. It frequently results in the need for an intravenous line and the administration of succinylcholine so as to secure an airway before the patient aspirates gastric contents. Needless to say, the FDA has already advised the anesthetic community against using succinylcholine in children and yet the side effects of the fentanyl lollipop will lead to its increased use in these children. To treat anxiety by inducing vomiting in children seems counterproductive to me.

The small number of pediatric patients in need of having their preoperative anxiety treated pharmacologically is already handled effectively with oral midazolam or very rarely intramuscular agents. I do not believe the fentanyl lollipop has any benefits especially when we begin to look at the patient safety risk!

4. Sociocultural Concerns
Drug abuse continues to be a major societal problem in the U.S.. Younger and younger children are getting involved in this culture. What kind of message are we sending to our children when we mix potent narcotics, like fentanyl, into their candy? First, I think we are saying that all of their stressful

situations can be dealt with by reaching for drugs. Secondly, we are showing them that little sophistication is needed in order to deliver drugs into their bloodstream. And finally, by associating a child's popular item like the lollipop with the euphoria of narcotics, we are indeed sending a confusing message to our children.

5. Economic Implications
The cost of the fentanyl lollipop will be additive to the costs of current anesthetic practice and thereby increase the overall expense. Besides its direct cost there will be a profound increase in the cost associated with safely monitoring patients during this lollipop consumption period. Additional pulse oximeters and nursing personnel will be required in order to detect respiratory complications. There will also be control and access issues that revolve around this product. How will the residual lollipop be handled? Certainly increased costs will be involved. What if the child with teeth bites the whole lollipop off? What if a younger sibling starts licking the lollipop? Clearly constant observation by a well-trained pediatric nurse throughout the consumption period will be necessary which will lead to significantly more expense in safely caring for these children.

I hope the FDA will reconsider their decision with regard to approving the fentanyl lollipop. My primary concern is one of patient safety although I have elaborated about several other areas of concern I have about this product. I think the transdermal fentanyl experience should serve as a warning sign and that the fentanyl lollipop should be abandoned before it is too late for some American children.

Sincerely yours,

Allen J. Hinkle, M.D.
Certified, American Board of Pediatrics
Certified, American Board of Anesthesiology

cc: Sidney Wolfe, M.D.

The University of Texas Medical Branch at Galveston

School of Medicine
Graduate School of Biomedical Sciences
School of Allied Health Sciences
School of Nursing

Marine Biomedical Institute
Institute for the Medical Humanities
UTMB Hospitals

James F. Arens, M.D.
Vice President for Clinical Affairs

January 24, 1994

Dr. David Kessler
Commissioner
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Kessler:

I support the request to reverse the decision approving narcotic lollipops for use by children.

The danger of this product to children is predictable especially when it will certainly be used in conjunction with other sedatives, narcotics, and anesthetic drugs.

The potential for this product to be used by those physicians addicted to fentanyl is even more worrisome. Anesthesiologists readily become addicted to fentanyl because it is readily available and is very addicting. Many anesthesiologist addicts state that they have become addicted after the first use. Thus, you are really letting the diabetic addict in the narcotic candy store.

As president of the American Society of Anesthesiologists in 1988, I focused on the problem of fentanyl addiction in our specialty. Now in 1994, as a Professor of Anesthesiology, and as a very concerned physician, I ask that you reconsider the ill conceived approval of a product developed as a cute solution to a non-problem and disapprove the marketing of this truly dangerous product.

Sincerely yours,

James F. Arens, M.D.

James F. Arens, M.D.
Vice President for Clinical Affairs

JFA:dr

xc: Wilson C. Wilhite, Jr., M.D.
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Norig Ellison, M.D.
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The plasma protein binding of fentanyl is 80-85%. The main binding protein is alpha-1-acid glycoprotein, but both albumin and lipoproteins contribute to some extent. The free fraction of fentanyl increases with acidosis. Following an IV dose, fentanyl is rapidly redistributed from the blood to lung tissue and skeletal muscle and then more slowly to deeper fat compartments. It is then slowly released into the blood from the tissues during its metabolic elimination. Large single doses or many repeated doses can result in the accumulation of a large body burden of fentanyl that may take many hours to clear.

Fentanyl is primarily (more than 90%) eliminated by biotransformation to N-dealkylated and hydroxylated inactive metabolites. Less than 7% of the dose is excreted unchanged in the urine, and only about 1% is excreted unchanged in the feces. The metabolites are mainly excreted in the urine, while fecal excretion is less important.

Special Populations: The absorption, distribution, and metabolism of fentanyl have been shown to be relatively constant over the age range intended for FENTANYL ORALET, although the elderly patient has been shown to be approximately twice as sensitive to the same blood level of the drug as a younger patient.

Although fentanyl kinetics are known to be altered in both hepatic and renal disease due to alterations in metabolic clearance and plasma proteins, individualized doses of fentanyl have been used successfully in anesthesia in both kinds of disorders. This is because the duration of effect for the initial dose of fentanyl is determined by redistribution of the drug, such that diminished metabolic clearance will only become significant with repeated dosing or with excessively large single doses. For these reasons, reduced doses titrated to clinical effect are recommended in the elderly, and in patients with severe hepatic and/or renal disease.

CLINICAL TRIALS

Premedication Before Anesthesia (in the Operating Room): The efficacy of FENTANYL ORALET was investigated in five randomized, placebo-controlled clinical trials as premedication for various pediatric surgical procedures (cardiovascular, orthopedic, urological and general surgery). Single FENTANYL ORALET doses of 5 to 20 mcg/kg (18 to 30 patients per treatment group) were compared to placebo in patients 2 to 18 years old. Patients receiving FENTANYL ORALET were significantly more sedated and experienced less apprehension than patients receiving placebo. Median time to peak sedative effect was 30 minutes. Generally, less intraoperative and postoperative analgesics were required in the FENTANYL ORALET group.

The efficacy of FENTANYL ORALET was also compared to an oral solution of meperidine 1.5 mcg/kg, diazepam 0.2 mg/kg and atropine 0.02 mg/kg (MDA solution) as premedication in pediatric patients undergoing cardiovascular surgery. In a study with 20 patients per treatment group, FENTANYL ORALET 20 to 25 mcg/kg was compared to MDA solution. In that study, a high incidence of nausea and vomiting suggested that 20 to 25 mcg/kg was an excessive FENTANYL ORALET dose. A second study in patients with a FENTANYL ORALET dose of 15 to 20 mcg/kg found that FENTANYL ORALET was similar in efficacy to MDA solution without the excessive vomiting seen in the first study.

The efficacy of FENTANYL ORALET with and without droperidol was also compared to placebo in 2 to 8 year old general surgery patients. FENTANYL ORALET was administered in doses of 15 to 20 mcg/kg with and without droperidol 50 mcg/kg versus placebo (also with and without droperidol). Use of FENTANYL ORALET was associated with improved induction and a reduced use of post operative opioids. Droperidol reduced the incidence of nausea and vomiting associated with FENTANYL ORALET, but the combination of droperidol and FENTANYL ORALET resulted in a significantly delayed awakening (the combination of droperidol and FENTANYL ORALET doubled the awakening time after surgery from that of FENTANYL ORALET alone).

Monitored Anesthesia Care Outside the Operating Room: FENTANYL ORALET has been evaluated for monitored anesthesia care outside the operating room environment. In two open trials, 8 adult and 34 pediatric patients have been administered FENTANYL ORALET 10 to 20 mcg/kg as a premedicant. Onset of analgesia occurred at approximately 6 to 8 minutes following FENTANYL ORALET. Patients who were administered 10 to 15 mcg/kg had efficacy similar to patients administered 15 to 20 mcg/kg. However, the lower dose range of 10 to 15 mcg/kg was associated with a lower risk of adverse effects.

In a double-blind, placebo-controlled trial, FENTANYL ORALET 15 to 20 mcg/kg was administered to 31 pediatric oncology patients with prior opioid experience. Based upon the patients' evaluation of their own pain, FENTANYL ORALET was better than placebo in reducing pain. More sedation, less apprehension and improved patient manageability were associated with FENTANYL ORALET. Median time to peak effect in these patients was 20 minutes.

Individualization of Dosage: Pediatric premedication, especially outside the operating room, is not free of risk to the child. Use of potent narcotics, such as fentanyl, is associated with a risk of hypoventilation ranging in severity from mild bradypnea to apnea. This risk cannot be totally eliminated even by proper choice of dose or skillful patient selection. Adverse consequences of hypoventilation, however, can be markedly reduced by appropriate clinical practices. Hypoventilation during monitored anesthetic care is an adverse event that should have no associated morbidity or mortality, provided it is immediately recognized and appropriately managed by stimulation, oxygen, and/or prompt ventilatory support according to severity.

In settings where the practitioner is unable to detect and manage hypoventilation, morbidity due to all forms of pediatric premedication is relatively frequent (10-50 cases per thousand). In anesthetic practice, morbidity due to hypoventilation is rare, occurring approximately once in every 5,000-10,000 cases. For this reason, the greatest risk associated with premedication occurs in single-operator settings where qualified personnel are not continually monitoring the patient. Such settings are dental offices without monitored anesthesia care, surgical settings without an anesthetist, single-operator endoscopy suites and radiological settings where access to the patient is restricted by the equipment. Given these risks, FENTANYL ORALET should be administered only in monitored settings and by persons specifically trained in the use of anesthetic drugs and the management of the respiratory effects of potent opioids, including maintenance of a patent airway and assisted ventilation.

Premedication: Use of a premedication is common in two clinical situations, preventing anxiety in a child undergoing a painful procedure and managing the fearful child.

1. Preventing Anxiety or Fearfulness. Premedication is commonly used for the prevention of anxiety in a child undergoing a painful procedure where narcotic analgesia is indicated. Despite the provision of gentle, non-pharmacologic reassurance to all patients, 42% of placebo patients remained anxious at induction. Doses of 5-10 mcg/kg of FENTANYL ORALET reduced the number of children fearful at 30 minutes from this 42% (in the placebo group) to about 7% (in the FENTANYL ORALET group). Larger doses provided no apparent gain in efficacy in preventing anxiety, but substantially increased the frequency of adverse events.

2. Managing the Fearful Child. The second major use of premedicants is to treat the child or adult who is unmanageable or excessively fearful and cannot be calmed by non-pharmacologic means. About 10-20% of the children (and some adults) who were studied preoperatively had symptoms of apprehension and anxiety that were so severe as to unequivocally need premedication. In those cases, FENTANYL ORALET, in doses of 5-15 mcg/kg, produced a dose-related reduction in apprehension that was sufficient to allow a calm, manageable, induction of anesthesia within 20-30 minutes. Doses above 5 mcg/kg (10 & 15 mcg/kg) were more effective in managing the already fearful child, but were associated with a dose-dependent increase in pruritus, vomiting and hypoventilation.

For these reasons the lowest effective dose of FENTANYL ORALET should be used, and it should be administered only in monitored settings and by persons specifically trained in the use of anesthetics and the management of the respiratory effects of potent opioids, including maintenance of a patent airway and assisted ventilation.

INDICATIONS AND USAGE

FENTANYL ORALET is indicated for anesthetic premedication in children and adults, and for use in anesthesia or monitored anesthesia care. FENTANYL ORALET has only been shown to be safe for use in a clinically monitored setting, and at doses chosen to minimize the risk of hypoventilation (see WARNINGS and DOSAGE AND ADMINISTRATION).

FENTANYL ORALET is not recommended for use in solo practice situations or in unmonitored settings where there is a risk of unrecognized hypoventilation (see Boxed WARNING).

The use of FENTANYL ORALET in treating acute or chronic pain is not recommended as the proper dose and dosing interval for the drug to avoid accumulation are not known and adequate information about the safety of FENTANYL ORALET in this setting is not available.

CONTRAINDICATIONS

FENTANYL ORALET is contraindicated in patients with known intolerance or hypersensitivity to any of its components or the drug fentanyl.

WARNINGS

FENTANYL ORALET DELIVERS FULL DOSES OF THE POTENT OPIOID NARCOTIC FENTANYL AND CARRIES A RISK OF HYPOVENTILATION WITH ITS USE. IT IS INTENDED FOR USE WHERE A NARCOTIC ANALGESIC EFFECT BEYOND SEDATION IS INDICATED IN PREMEDICATION, ANESTHESIA AND/OR IN MONITORED ANESTHESIA CARE. IT SHOULD BE ADMINISTERED ONLY IN MONITORED SETTINGS AND BY PERSONS SPECIFICALLY TRAINED IN THE USE OF ANESTHETIC DRUGS AND THE MANAGEMENT OF THE RESPIRATORY EFFECTS OF POTENT OPIOIDS, INCLUDING MAINTENANCE OF A PATENT AIRWAY AND ASSISTED VENTILATION.

FACILITIES FOR THE ADMINISTRATION OF INTRAVENOUS FLUIDS, OPIOID ANTAGONISTS, OXYGEN, AND RESUSCITATIVE EQUIPMENT INCLUDING FACILITIES FOR ENDOTRACHEAL INTUBATION SHOULD BE READILY AVAILABLE.

Patients receiving FENTANYL ORALET should be monitored by direct visual observation and by some means of measuring respiratory function such as pulse oximetry until they are recovered (See also discussion of narcotic antagonists in PRECAUTIONS and OVERDOSAGE).

If fentanyl is administered with a sedative, the user should become familiar with the special properties of combinations of opioids and other CNS depressants, particularly the extended duration of action. Hypotension has also been reported with the concomitant use of fentanyl and droperidol. If it occurs, the possibility of hypovolemia should also be considered and managed with appropriate parenteral fluid therapy.

Fentanyl may cause muscle rigidity, particularly involving the muscles of respiration. Muscle rigidity after IV use is related to the dose and speed of injection. Although muscle rigidity interfering with respiration has not been seen following the use of FENTANYL ORALET, the possibility of it happening should be kept in mind. If it occurs, it should be managed by the use of assisted or controlled respiration, by an opioid antagonist, and as a final alternative, by a neuromuscular blocking agent.

As with other potent narcotics, the respiratory depressant effect of fentanyl may persist longer than the analgesic effect. The total dose of all narcotic analgesics administered, *including FENTANYL ORALET*, should be considered before ordering narcotic analgesics during recovery from anesthesia. For patients who have received FENTANYL ORALET within 6-12 hours, it is recommended that if other narcotics are required, they should be used at starting doses 1/4 to 1/3 those usually recommended.

FENTANYL ORALET is not recommended for use in patients who have received MAO inhibitors within 14 days, because severe and unpredictable potentiation by MAO inhibitors has been reported with narcotic analgesics.

Head Injuries and Increased Intracranial Pressure: FENTANYL ORALET, as with other opioids, should be used with caution in patients who may be particularly susceptible to respiratory depression, such as patients who may have a head injury or brain tumor. As with all opioids,

FENTANYL ORALET may obscure the clinical course of a patient with a head injury and should be used only if clinically indicated.

PRECAUTIONS

General: The initial dose of FENTANYL ORALET should be appropriately individualized by assessing the clinical status of the patient in regard to the desired clinical effect(s). The effect(s) of the initial dose should be considered in subsequent administration of any additional CNS depressive agents.

Use in Ambulatory Surgery: Orthostatic hypotension has been observed following the use of fentanyl in the ambulatory setting. Therefore, if FENTANYL ORALET is used, care should be exercised in moving and positioning patients preoperatively, intraoperatively and postoperatively, and fluid status should be evaluated prior to discharge.

VITAL SIGNS SHOULD BE MONITORED ROUTINELY. SOME MEANS OF MEASURING RESPIRATORY FUNCTION, SUCH AS A PULSE OXIMETER, IS RECOMMENDED IN BOTH ADULTS AND CHILDREN.

Use of Narcotic Antagonists: Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists. Because the duration of respiratory depression may be longer than the duration of the narcotic antagonist action, appropriate surveillance should be maintained. (Consult relevant prescribing information before employing narcotic antagonists). Opioid analgesia is often accompanied by respiratory depression and diminished sensitivity to CO_2 stimulation that may persist into or recur in the postoperative period. Intraoperative hyperventilation may further alter postoperative response to CO_2. Appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained in the absence of stimulation prior to discharging the patient from the recovery area.

Use in Respiratory Disease: FENTANYL ORALET should be used with caution in patients with chronic obstructive pulmonary disease, patients with decreased respiratory reserve, and others with potentially compromised respiration. In such patients, narcotics may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration. As with many opioid drugs, fentanyl can cause histamine release in some patients, which may be of clinical significance in patients with asthma or other reactive airway disorders.

Use in Hepatic or Renal Disease: FENTANYL ORALET should be administered with caution to patients with liver and kidney dysfunction because of the importance of these organs in the metabolism and excretion of drugs (see PHARMACOKINETICS).

Cardiovascular Effects: Fentanyl may produce bradycardia, which may be treated with atropine. FENTANYL ORALET should be used with caution in patients with bradycardias. As with other μ opioids, orthostatic hypotension is possible (see USE IN AMBULATORY SURGERY).

Laboratory Tests: FENTANYL ORALET is without known effects on common laboratory tests, but may produce hypoxia, respiratory acidosis, and hypercarbia if given in doses that depress respiration.

Drug Interactions: Other CNS depressant drugs (e.g., barbiturates, tranquilizers, narcotics and general anesthetics) have additive or potentiating effects with fentanyl. When patients have received such drugs, the dose of fentanyl required may be less than usual. Likewise, following the administration of fentanyl, the dose of other CNS depressant drugs should be reduced.

The particular enzyme(s) responsible for fentanyl biotransformation has (have) not been identified even though the major metabolites are well known. Because swallowed fentanyl is known to undergo extensive hepatic first-pass metabolism, FENTANYL ORALET has the potential to have an increased bioavailability in the presence of an inhibitor of drug metabolism, e.g., a food component or another drug. Caution should therefore be exercised in such cases.

Use in Anesthesia: Certain forms of conduction anesthesia, such as spinal anesthesia and some peridural anesthetics can alter respiration by blocking intercostal nerves. Through other mechanisms (see CLINICAL PHARMACOLOGY) fentanyl can also alter respiration. Therefore, when FENTANYL ORALET is used before these forms of anesthesia, the anesthesia provider should be familiar with the physiological alterations involved, and be prepared to manage them in the patients selected for these forms of anesthesia.

Nitrous oxide has been reported to produce cardiovascular depression when given with higher doses of IV fentanyl.

Elevated blood pressure in patients with and without pre-existing hypertension has been reported following administration of fentanyl citrate combined with droperidol. This might be due to unexplained alterations in sympathetic activity following large doses; however, it is also frequently attributed to anesthetic and surgical stimulation during light anesthesia.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No carcinogenicity or mutagenicity studies have been conducted with fentanyl citrate. Reproduction studies in rats revealed a significant decrease in the pregnancy rate of all experimental groups. This decrease was most pronounced in the high dose group (1.25 mg/kg) in which one of twenty animals became pregnant. This high dose is approximately 180X the maximum recommended human dose of 400 mcg for a 60-kg patient.

Pregnancy – Category C: Fentanyl citrate has been shown to impair fertility and to have an embryocidal effect in rats when given for a period of 12-21 days in doses of 30 mcg/kg iv or 160 mcg/kg sc, equivalent to 4 and 23 times, respectively, the maximum recommended human dose. No evidence of teratogenic effects have been observed after administration of fentanyl citrate to rats. There are no adequate and well-controlled studies in pregnant women. Fentanyl should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: Use of FENTANYL ORALET in labor and delivery is not recommended as there are insufficient data to support such usage.

Nursing Mothers: Caution should be exercised when FENTANYL ORALET is administered to a nursing woman, since it is not known if fentanyl (like many other drugs) is excreted in human milk.

Use in Children Below Two Years of Age: The use of FENTANYL ORALET in such patients is not recommended because of the physical characteristics of the dosage form.

Use in Elderly Patients: If FENTANYL ORALET is to be used in patients over age 65, the dose should be reduced to 2.5-5 mcg/kg. Although studies of FENTANYL ORALET in the elderly have not been conducted, elderly patients have been shown to be twice as sensitive as the younger population to the effects of other forms of fentanyl. Caution is indicated since (like all potent opioid analgesics), FENTANYL ORALET has the ability to depress respiration and reduce ventilatory drive to a clinically significant extent.

ADVERSE REACTIONS

The safety of FENTANYL ORALET has been formally evaluated across a broad range of doses in a total of 825 patients. The primary adverse event of concern is opioid-induced hypoventilation, the severity of which is related to the patient's age, physical condition, the dose employed, and the clinical setting.

Ventilatory response to FENTANYL ORALET was examined over doses ranging from 5 to 25 mcg/kg in both clinical and pharmacokinetic studies. Hypoventilation, usually defined as either desaturation (85-90%) or by clinical observation, was the most common potentially serious adverse event and occurred during the first 30 minutes following administration in 6% of patients (14% of adults and 5% of children) participating in clinical trials investigating premedication.

Desaturation and/or hypoventilation was generally dose-related, occurring in 0-7% of children across the dose range from 5-20 mcg/kg and 25-42% of adults across the dose range of 5-15 mcg/kg.

The hypoventilation observed in clinical studies was usually mild, owing in part to prompt response by the monitoring physician, usually responding to gentle stimulation or administration of oxygen. Cases of serious hypoventilation (delayed onset of respirations, and apnea) were observed but were uncommon (8 of 825 cases). All cases of apnea involved doses greater than 15 mcg/kg, and readily responded to a single dose of naloxone.

Doses above 15 mcg/kg are not recommended regardless of age, and doses above 5 mcg/kg (400 mcg maximum regardless of weight) are not recommended in adults, because of this excessive frequency of significant hypoventilation at higher doses.

Besides hypoventilation, other dose-related adverse events occurring in the first 30 minutes following administration in premedication studies included flushing in adults and pruritus in children. Pruritus occurred in over half of the cases studied, and was manifest by the child's touching their face and/or complaining of mild itching. Urticaria or generalized pruritus was uncommon.

Common Adverse Events (> 1%, probably causally related): The following adverse events were reported at a frequency of 1% or more in 189 patients who received FENTANYL ORALET as premedication in anesthesia or in monitored anesthetic care settings at the recommended doses. No adjustment has been made for the rate at which events were observed in placebo treated patients, for causality, or for severity. It should be noted that the reported adverse events include the intraoperative and postoperative period for patients undergoing surgery.

Body as a Whole: headache
Cardiovascular: bradycardia, flushing*, hypotension, pallor, ventricular extrasystole
Digestive: nausea (17%), vomiting (34%)
Nervous: apathy, dizziness (15%), euphoria, paresthesia
Respiratory: hypoventilation (11%)
Skin: pruritus (56%), rash
Special Senses: vision abnormality

(%) adverse reaction above 10%
(*) adverse reactions 3-9%
all others 1-3%

Uncommon Adverse Events Related to FENTANYL ORALET (< 1%, probably causally related): The following adverse events occurred in less than 1% of patients who received FENTANYL ORALET in the recommended doses, or were only observed in patients who were studied outside the recommended dosage range and indication (N=636).

Body as a Whole: asthenia, hypertonia, spasm
Digestive: anorexia, dyspepsia, dysphagia, gastrointestinal disorder
Musculoskeletal: myasthenia
Nervous: agitation, anxiety, confusion, dry mouth, emotional lability, miosis, somnolence, speech disorder, stupor, urinary retention, vertigo
Respiratory: airway obstruction, apnea, exacerbation of asthma
Skin: urticaria
Special Senses: accommodation abnormality

Uncommon Adverse Events (< 1%, Relationship Unknown): The following adverse events were uncommon, usually occurred during or after surgery, and their relationship to FENTANYL ORALET administration is unknown. They are provided as alerting information for the physician.

Body as a Whole: abdominal pain, anaphylactoid reaction, back pain, chest pain, chills, fever
Cardiovascular: bigeminy, tachycardia, ventricular fibrillation
Metabolism and Nutrition: dehydration, hypoglycemia
Musculoskeletal: myalgia
Nervous: abnormal dreams, dystonia, hostility, hypertension, hysteria, nystagmus, twitch
Respiratory: dyspnea, hiccup, increased cough, laryngismus, pharyngitis, rhinitis, voice alteration
Special Senses: ear disorder, lacrimation disorder, photophobia, perverse taste

DRUG ABUSE AND DEPENDENCE

Fentanyl (the active ingredient in FENTANYL ORALET) is a controlled substance listed in Schedule II by the Drug Enforcement Administration. Fentanyl can produce drug dependence of the morphine type and therefore, has the potential for being abused. The handling of FENTANYL ORALET should be managed to minimize the risk of

diversion, including restriction of access and accounting procedures as appropriate to the clinical setting.

OVERDOSAGE

Manifestations: The manifestations of FENTANYL ORALET overdosage are expected to be similar to IV fentanyl and are an extension of its pharmacologic actions (see CLINICAL PHARMACOLOGY & INDIVIDUALIZATION OF DOSAGE).

Treatment: Management of severe FENTANYL ORALET overdose includes: securing a patent airway, assisting or controlling ventilation, establishing intravenous access, use of naloxone or other opioid antagonists and GI decontamination with lavage and/or activated charcoal once the patient's airway is secure. In the presence of hypoventilation or apnea, oxygen should be administered and respiration should be assisted or controlled as indicated. Fentanyl may cause muscle rigidity, particularly involving the muscles of respiration. Although muscle rigidity interfering with respiration has not been seen following the use of FENTANYL ORALET, this is always possible with fentanyl and other opioids. If it occurs, it should be managed by the use of assisted or controlled respiration, by an opioid antagonist, and as a final alternative, by a neuromuscular blocking agent.

The patient should be carefully observed and appropriately managed until his or her clinical condition is well controlled. The duration of respiratory depression following overdosage of fentanyl may be longer than the duration of narcotic antagonist action. Consult the package insert of the individual narcotic antagonists for details about such use.

Dialysis is not likely to be effective because of the large volume of distribution and high lipid solubility of fentanyl.

DOSAGE AND ADMINISTRATION

DOSES SHOULD BE INDIVIDUALIZED BASED UPON THE STATUS OF EACH PATIENT, THE CLINICAL ENVIRONMENT, AND THE DESIRED THERAPEUTIC EFFECT. DOSAGE SHOULD BE REDUCED IN ELDERLY, DEBILITATED, OR OTHER VULNERABLE PATIENTS. (SEE PRECAUTIONS)

Some of the factors to be considered in determining an individualized dose are age, body weight, physical status, general condition and medical status, underlying pathological condition, use of other drugs, type of anesthesia to be used and the type and length of the procedure.

Premedication: FENTANYL ORALET is not recommended for use in premedication unless such usage is part of monitored anesthetic care (see BOX WARNING), due to the risk of hypoventilation. In monitored usage, FENTANYL ORALET doses of 5 mcg/kg provide effects similar to the usual doses of fentanyl given IM for premedication (0.75-1.25 mcg/kg). Larger doses have not been shown to increase efficacy in preventing anxiety or apprehension. As with all opioids, the dosage should be reduced in vulnerable patients (see *PRECAUTIONS*).

Use in Anesthesia (and in Monitored Anesthesia Care): FENTANYL ORALET is recommended for use as an adjunct to the induction of general, regional or conduction anesthesia. The magnitude of the expected effect will vary from mild with doses of 5 mcg/kg to marked with doses of 15 mcg/kg. FENTANYL ORALET should be administered only in monitored settings and by persons specifically trained in the use of anesthetics and the management of the respiratory effects of potent opioids, including maintenance of a patent airway and assisted ventilation.

Adults should not receive doses larger than 5 mcg/kg (400 mcg), and most children not fearful at onset may be managed with the same 5 mcg/kg dose. Children fearful at onset, and some younger children may need doses of 5-15 mcg/kg, with an attendant increased risk of hypoventilation.

Because of the risk of hypoventilation and apnea, patients receiving above 5 mcg/kg should be under the direct observation of a health care professional able to recognize and manage hypoventilation during the administration period and until the patient is fully recovered.

I. Normal children: Selection of dosage strength based on patient weight with a dose range of 5-15 mcg/kg is recommended. Premedication of children below 40 kg may require doses of 10-15 mcg/kg.

Patient Weight Kilograms (kilos)	5-10 mcg/kg	10-15 mcg/kg
<15 kilograms	not recommended	not recommended
15 kilos	not available	200 mcg
20 kilos	200 mcg	200 or 300 mcg
25 kilos	200 mcg	300 mcg
30 kilos	300 mcg	300 or 400 mcg
35 kilos	300 mcg	400 mcg
40 kilos and over	400 mcg	Use 400 mcg (see II)
Adults	400 mcg	Use 400 mcg (see II)

II. Normal adults: To avoid hypoventilation, a dose of 400 mcg is recommended for all adults 50 kilograms and over regardless of actual weight.

III. Vulnerable patients: Selection of a lower dose should be considered for vulnerable patients, for example: patients with head injury, cardiovascular or pulmonary disease, hepatic disease, liver dysfunction, or other vulnerable patients. If signs of excessive opioid effects appear before the unit is consumed, the dosage unit should be removed from the patient's mouth immediately.

IV. Elderly Patients: If FENTANYL ORALET is to be used in patients over age 65, the dose should be reduced to 2.5-5 mcg/kg. Although studies of FENTANYL ORALET in the elderly have not been conducted, elderly patients have been shown to be twice as sensitive to the effects of other forms of fentanyl as the younger population. Like all potent opioid analgesics, FENTANYL ORALET has the ability to depress respiration and reduce ventilatory drive to a clinically significant extent.

Administration of FENTANYL ORALET: The foil overwrap should be removed just prior to administration. After the plastic overcap is removed, the patient should be instructed to place the FENTANYL ORALET unit in his/her mouth and to suck (not chew) it. Chewed or swallowed fentanyl contributes little to the peak concentration, but is responsible for a prolonged "tail" on the blood level profile as it is slowly absorbed.

The FENTANYL ORALET unit should be removed, using the handle, after it is consumed or if the patient has achieved an adequate sedative and anxiolytic level and/or shows signs of respiratory depression. Place any remaining portion of the FENTANYL ORALET unit in the plastic overcap and dispose of the unit appropriately.

Administration of the FENTANYL ORALET unit should begin 20 - 40 minutes prior to the anticipated start of surgery, diagnostic or therapeutic procedure. Patients typically take 10 - 20 minutes for complete consumption. Peak effect occurs approximately 20 - 30 minutes after the start of FENTANYL ORALET administration. In the uncommon event that hypoventilation or some other adverse event occurs before the dosage unit is consumed, the unit should be removed from the patient's mouth immediately.

The patient should be attended at all times by a health care professional skilled in airway management and resuscitative measures. FENTANYL ORALET should be administered only in monitored settings and by persons specifically trained in the use of anesthetics and the management of the respiratory effects of potent opioids, including maintenance of a patent airway and assisted ventilation. Some means for measuring respiratory function is recommended, such as pulse oximetry.

SAFETY AND HANDLING

FENTANYL ORALET is supplied in individually sealed dosage forms that pose no known risk to health-care providers having incidental contact. Accidental dermal exposure to FENTANYL ORALET should be treated by rinsing the affected area with cool water.

FENTANYL ORALET should be protected from freezing and moisture. Do not store above 30°C (86°F). Store in the protective foil pouch until dispensing. Do not use if the foil pouch has been opened.

Cases of self-administration of fentanyl by health care professionals, including fatalities, have been reported with all fentanyl products. The handling of FENTANYL ORALET should be managed to minimize the risk of diversion, including restriction of access and accounting procedures as appropriate to the clinical setting.

DISPOSAL OF FENTANYL ORALET: The disposal of Schedule II controlled substances must be consistent with State and Federal Regulations. In general, the following procedure is recommended.

Remove the drug matrix from the handle by grasping it with tissue paper and separate the drug matrix from the handle using a twisting motion. Then flush the drug matrix down the toilet. If any drug matrix remains on the handle, it may be removed by placing the handle under warm running tap water until the remaining portion of the drug matrix is dissolved. The drug-free handle should be disposed according to institutional protocol. During the disposal process, avoid contact of the drug matrix with the skin, eyes, or mucous membranes. Wash hands thoroughly when complete.

HOW SUPPLIED

FENTANYL ORALET (Oral Transmucosal Fentanyl Citrate) is supplied in three dosage strengths. Each unit is individually wrapped in protective foil. There are 5 units per package and 25 units per carton. Each dosage unit has a characteristic red raspberry colored lozenge, but the different doses can be distinguished via color highlighted labels as follows:

200 mcg Fentanyl base (Yellow) cartons of 25 (NDC 0074-2444-25)

300 mcg Fentanyl base (Green) cartons of 25 (NDC 0074-2445-25)

400 mcg Fentanyl base (Blue) cartons of 25 (NDC 0074-2446-25)

Note: Colors are a secondary aid in product identification, please be sure to confirm the printed dosage before dispensing.

Store in protective foil pouch at controlled room temperature 15-30°C (59-86°F) until dispensing.

Caution: Federal (USA) law prohibits dispensing without prescription.

Manufactured and Distributed by:

ABBOTT LABORATORIES, NORTH CHICAGO, IL 60064, USA

Under license from ANESTA Corp.,
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U.S. Patent No. 4,671,953

Printed in USA

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ABBOTT ANESTHESIA

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Some Doctors Urging FDA to Withdraw Approval of Abbott's Anesthetic Lollipop

WSJ 1/26/94

By Thomas M. Burton
Staff Reporter of The Wall Street Journal

Several doctors are urging the Food and Drug Administration to withdraw approval of a narcotic lollipop, given to children entering surgery, that may cause nausea and severe breathing difficulties.

In letters this week to FDA commissioner David Kessler, some anesthesiologists and other physicians expressed concerns the lollipop could lead to deaths if properly trained hospital personnel aren't present when it's administered. The lollipop contains fentanyl, an opiumlike sedative and painkiller that is far more potent than morphine.

Abbott Laboratories, of North Chicago, Ill., has the marketing rights for the lollipop under license from **Anesta** Corp. of Salt Lake City. An Abbott spokeswoman said the criticisms of the product were raised at the time the FDA approved the lollipop in October, and that it will be sold to hospitals or physicians with strict limitations on its use.

Warning Label

Because the drug can slow or even stop a patient's breathing, a product warning label says the lollipop "should be administered only in monitored settings and by persons specifically trained in the use of anesthetic drugs." The candy is designed for children who can't otherwise be calmed down before being given an anesthetic by injection.

"Without a high level of vigilance I am concerned that the outcome could be tragic," Allen J. Hinkle, a Dartmouth Medical School anesthesiology professor, wrote FDA commissioner David Kessler. "I do not believe the fentanyl lollipop has any benefits especially when we begin to look at the patient safety risk."

James F. Arens, vice president for clinical affairs at the University of Texas Medical Branch at Galveston, termed the lollipop a "cute solution to a nonproblem" and a "truly dangerous product." By contrast, Myron Yaster, director of the pediatric pain service at the Johns Hopkins Hospital, said in an interview that the lollipop "fills a niche that needed to be filled. It's a way to help stop pain without inflicting pain."

FDA to Take Another Look

Fentanyl, when used in patches for chronic cancer and other pain, has been associated with more than 50 deaths reported to the FDA. An FDA spokesman said the deaths were caused by abuse of the patch, excessive dosing, or the cancer itself. Nevertheless, the spokesman said the agency will consider whether the approval of the lollipop should be reversed. The lollipop hasn't yet been marketed, and the FDA currently is discussing with Abbott how the delivery and use of the product will be controlled.

Citing the deaths associated with fentanyl in patch form, Sidney Wolfe, director of the consumer-oriented Public Citizen Health Research Group, called the FDA's approval of the lollipop "dangerous and ill-conceived" and called on Dr. Kessler to reverse the marketing approval. Dr. Wolfe said that in one use of the fentanyl patch, a 17-year-old Florida boy went to an oral surgeon, had a tooth extracted and died after being given the product for postoperative pain.

Doctors have raised other concerns about the lollipop, such as the nausea sometimes associated with fentanyl, and the possibility that the lollipops could be obtained by drug abusers through illegal means. Dr. Hinkle noted in his letter to Dr. Kessler that "anesthesia in a child who is vomiting increases the risk" of the entire procedure. Treating "anxiety by inducing vomiting in children seems counterproductive to me," Dr. Hinkle wrote.

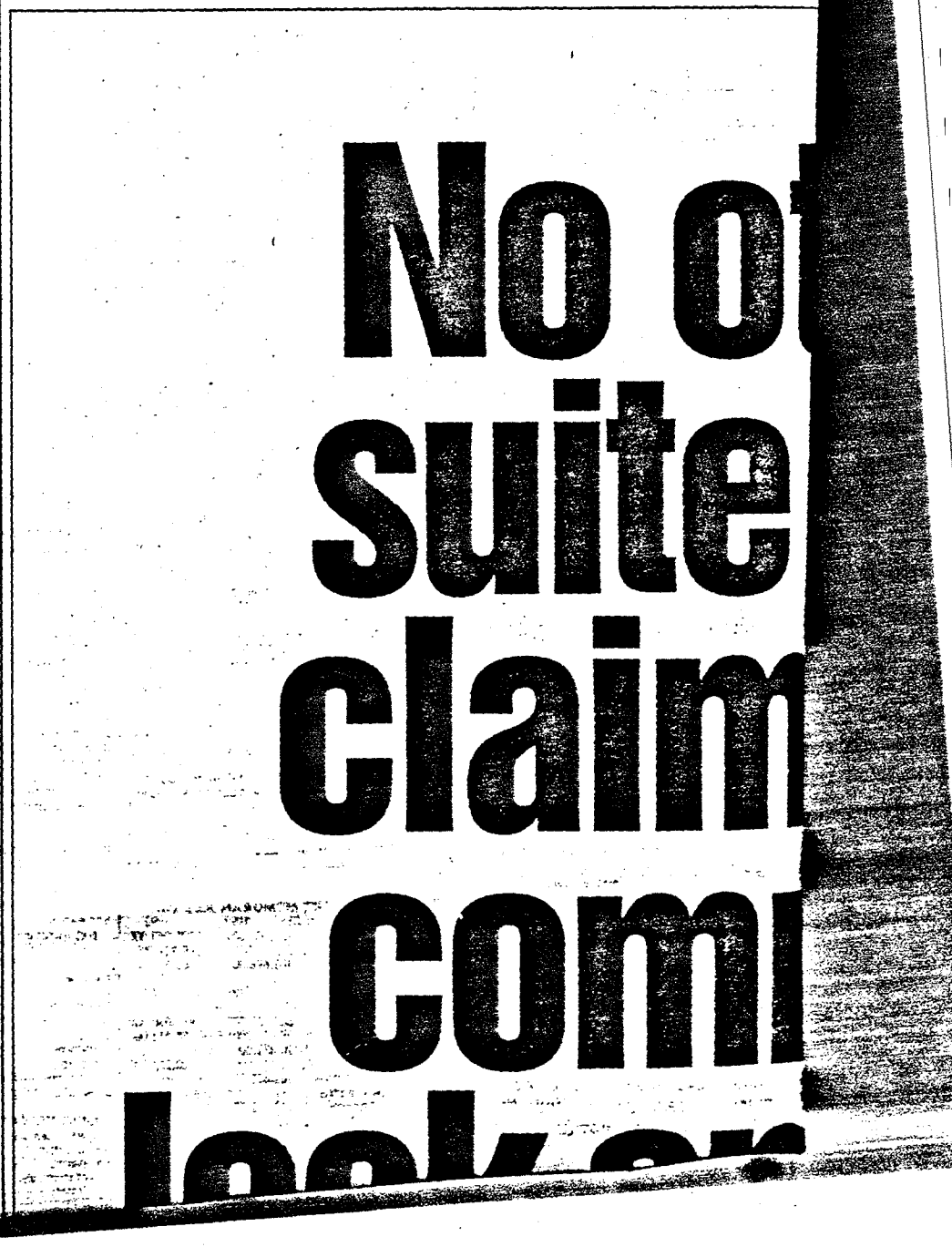
New Gene Therapy May Work as a Switch To Tell Cells to Fight

Continued From Page B1

"fail safe" switch that will cause the genetically engineered cells to self-destruct if they malfunction, cause unwanted side effects or have simply finished their job.

The invention hinges on the workings of cell receptors — specialized proteins on or near the cell's surface. These receptors are designed to grab hold and react to chemical signals drifting by in the bloodstream. Each protein receptor reacts to one particular chemical signal and no other.

When a receptor is tripped by a passing chemical, it launches a train of signals that reach into the nucleus of the cell where the genes reside. The signals tell the cell to start reading the "message" written in a particular gene: instructions to begin mak-



Electronic Data Buys A Stake in Europe's

Wash. Post 4/31

The Good and Bad Sides Of a Narcotic Lollipop

Critics Cite Risks of Fruit-Flavored Sedative Developed to Ease Pediatric Patients' Fears

By David Brown and John Schwartz
Washington Post Staff Writers

This is what Philip Scott remembers of the first of his daughter's five bone marrow taps:

"She had local anesthesia and was wide awake. The pain was so excruciating that her body was convulsing, like an epileptic fit. The noise a child can make—it is not the typical one that you hear when they fall down and you put a Band-Aid on what hurts."

He pauses. When he starts up again, his voice has the same flat cadence of a stunned trauma victim.

"It's a shrieking noise that makes your blood curdle. One of the things she screamed was: 'Daddy, please make them stop.' "

Samantha Rose Scott was 2 years old then. Now she is 6 and four adults hold her down when she has a bone marrow aspiration.

In a few weeks, the Anaheim, Calif., girl will undergo bone marrow transplantation in attempt to cure her of aplastic anemia. Before that procedure, she must have her teeth cleaned and two cavities filled. She is now so afraid of doctors, hospitals and needles, however, that it may take general anesthesia to get the work done.

"It's a permanent fear of pain," says her father, a 38-year-old unemployed contractor. "She has a total mental breakdown with anything even minor. She's even scared of X-rays."

Scott's story is the sort that underlies the search for better ways to control the suffering of children who must undergo painful medical treatment. It is a search that has led to one of the more controversial new drugs in recent years: a raspberry-flavored lollipop, called Oralet, that is loaded with an opiate called fentanyl.

Approved by the Food and Drug Administration in October, Oralet is officially intended only for use as a sedative for children about to receive general anesthesia. Its potential "off-label" market, however, is much larger. It includes use in bone marrow aspiration, in which a large needle is inserted into the pelvic bone and marrow is removed. The procedure is unpleasant under the best circumstances, and no amount of local anesthesia can make it entirely painless.

There is little dispute that undertreatment of pain in children has been one of medicine's biggest blind spots. Historically, an overweaning fear of complications, a psychological denial of children's unpleasant experiences and a huge void of scientific knowledge have combined to allow doctors to treat children in ways they would never treat adults.

A Horrifying History

It now horrifies most people to realize that, 30 years ago, newborns undergoing major surgery—surgery that required wide abdominal incisions, for example—were treated with drugs that temporarily paralyzed them so they would not move but did not block their perception of pain.

Research has since shown that newborns not only experience pain, but are more at risk for complications if their pain is not relieved.

Many experts believe, however, that in less dramatic circumstances than major surgery, inadequate pain relief is still a large and avoidable problem in pediatrics. Most circumcisions of newborns, for example, are performed without anesthesia, even though studies have shown that baby boys feel their penises being cut and are jumpier even two days later than those who undergo the procedure with local anesthesia.

"The biggest problem is not that we don't have the knowledge, but that we don't routinely apply the knowledge in clinical practice," said Patricia A. McGrath, a researcher at the University of Western Ontario and head of the committee on pain in children in the International Association for the Study of Pain.

"Some of these cancer patients are just pitiful, these little kids," said Joanne Shay, an anesthesiologist on the "pain service" at Children's National Medical Center in Washington. "They see a doctor coming and they just moan."

Before Oralet, no pediatric sedative for premedication had ever been approved by the FDA. Doctors prescribed medicines that were used in adults but which in most cases had not been extensively tested in children.

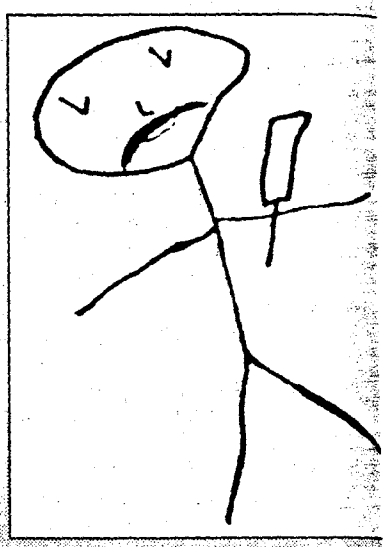
Fentanyl, a synthetic opiate 20 to 30 times more powerful than morphine, has been in use for two decades. Its delivery in lollipop form "fills an important need for children," said Bill Moeller, head of Anesta Corp., the Utah-based company that developed Oralet. It is an opinion not universally shared.

Critics say a "narcotic lollipop" is a terrible idea that could endanger children, increase the number of drug-addicted doctors and perpetuate wrong-headed attitudes about drugs. Sidney M. Wolfe, executive director of Public Citizen's Health Research Group, wrote an angry petition to FDA Commissioner David A. Kessler last week urging that the agency "reverse this dangerous and ill-conceived decision" to approve the drug "before the first child is killed by this potentially deadly drug/candy."

Wolfe said that because fentanyl—like virtually all opiates—depresses the brain's respiratory

TAK

The new-found recognition that n
the search for ways to give them
devices—Fentanyl Oralet from Abb
potent than morphine in a fruit-fla

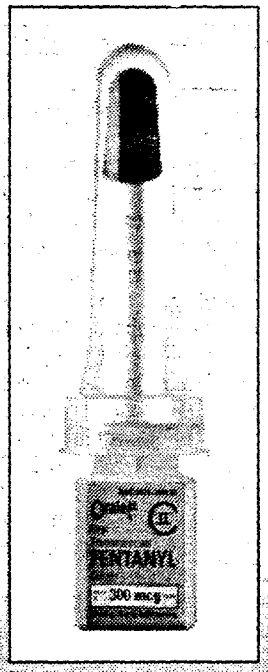


KING THE PAIN OUT OF PAINKILLERS FOR CHILDREN

many children suffer unnecessary pain as part of medical treatment has spurred m analgesic drugs in ways that are not themselves painful. One of the newest bbott Laboratories—is a lollipop that contains an opiate 20 to 30 times more lavored lozenge.

◀ Needles often become both the actual and symbolic focus of a child's fear of the pain of medical procedures. Children often depict hypodermic syringes as large—sometimes larger than themselves—and deeply penetrating, as in this drawing made by a 6-year-old. "I am concerned about painful experiences that occur to children even before they have words to describe the experiences," says David Fassler, a psychiatrist in Burlington, Vt., who collected the drawing as part of his research on children's fear of needles. Although there are few hard data on the long-term psychological effects of childhood pain, Fassler says he's seen many people whose unpleasant medical experiences as children seem "to be tied to fears in later life."

Several studies have shown that children often will put up with pain rather than accept painkillers delivered by injection. In recent years, researchers have experimented with: skin-numbing creams that allow shots to be given painlessly; sedatives given by nasal spray that make emergency room suturing less traumatic; and the Oralet lollipop (right) designed to calm children before they are given general anesthesia by face mask—an experience that, though not painful, is often very upsetting. In most cases, however, these new "routes" deliver drugs less precisely than by injection, causing some physicians and regulators to worry about their safety. ▶



BY JOHN ANDERSON—THE WASHINGTON POST

"drive," children run the risk of breathing problems, and possibly death, if they use the lollipop without supervision by people who can attach them to mechanical ventilation machinery in case of an emergency. Wolfe cited a recent FDA report that about 50 people have died while taking fentanyl through a skin patch—a "delivery system" intended for use in cancer patients with intractable pain.

"There's probably close to a 100 percent certainty that within a month of this coming on the market a child will die," Wolfe said.

A Popular Drug of Abuse

He is also concerned because fentanyl is one of the more popular prescription drugs of abuse among doctors, especially anesthesiologists, who have access to it in operating and recovery rooms.

James Arens, vice president for clinical affairs at the University of Texas Medical Branch in Galveston, agrees. He wrote a letter to the FDA warning that greater physician addiction could result if fentanyl becomes available in the new, palatable form. Arens said 12 of the 144 anesthesiology residents he has trained in the last dozen years became addicted to the drug.

Wolfe said using narcotics to calm children before surgery is often unnecessary, and pointed to programs at hospitals such as Children's National Medical Center, where doctors use behavioral methods.

But Shay, the anesthesiologist who works there, said there are limits to the approach. "Try reasoning with a 2-year-old," she said. When it comes to severe pain, "no matter how much you reason with them they still won't understand."

Doctors who advocate the lollipop say its benefits far outweigh potential risks.

"Should we not license cars because somebody could drive up into a mall and kill someone?" asked Michael Roizen, chairman of the department of anesthesia at the University of Chicago Medical Center. "No—we try to regulate it so that unintended uses don't happen." He said he believes the new drug "could be safer" than the unapproved drugs currently used.

There is little doubt that Oralet has a strong symbolic punch. Many people are offended by the idea that something as appealing as candy should be laced with a powerful narcotic. FDA Commissioner Kessler, a pediatrician by training, said that speaking "as a pediatrician or as a parent, you don't want a child to grow up thinking that medicine is candy." The FDA has called a panel of experts to meet in March to discuss the broad issue of pain treatment in children.

Kessler said there could be some increased risk for addiction for doctors and some risk to children associated with medical misuse. But ultimately "that's not a reason to deny kids access to a useful drug," he said. To get a fentanyl high from the lollipops comparable to injection, an abuser would have to stuff at least 11 into his mouth.

FDA officials also dispute Wolfe's contention that the deaths reported with the fentanyl patch were caused by the drug. Many of the patients were in the terminal stage of cancer.

In any case, the FDA is taking unprecedented measures to try to ensure that the drug's distribution is tightly controlled and that the medical professionals who use it get extensive training.

Kessler acknowledges that if the drug is used without close medical monitoring by an anesthesiologist or a nurse anesthetist, someday a child will die. "That's the one I lose sleep on," he said.

The FDA, consequently, has conditioned Oralet's release on its manufacturer coming up with a plan to assure that doctors will be instructed to administer it only in controlled settings and to distribute it in a way that will minimize chances for abuse.

"We really want to make sure that this drug is used right," Kessler said.