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Before Joint Meeting of the
Anesthetic and Life Support Drugs Advisory Committee
and the Drug Abuse Advisory Committee
August 24, 1993

I. Introduction

The Health Research Group became involved in the issue of fentanyl lollipops over four and one-half years ago thanks to a concerned call and correspondence from the patent-holder and major manufacturer of the drug, Janssen. Stating that the company had been approached by Dr.Ted Stanley and his colleagues to consider the licensing and marketing of fentanyl lollipops, Janssen wanted to know what I thought about the idea and subsequently sent information from the clinical trials which had been completed thus far.

In a December 7, 1988 Janssen letter to me, after discussing some of the possible advantages of the new dosage from, the company concluded that **"There is also the question of a controlled substance in a candy matrix. This is the issue that most concerns us at Janssen Pharmaceutica. The real question here is whether the potential advantages and benefits of the OTFC [oral transmucosal fentanyl citrate] for pediatric patients outweigh the possible negative connotation of an abusable substance in candy."**

On the safety side, the company added that there were also some areas of potential concern, including "the need to schedule sufficient time for this premedication (the time of peak effect for OTFC is approximately 15-30 minutes). There is also a potential for delayed post operative recovery as well as a possible increase in nausea and vomiting. There is need to monitor oxygen saturation and vital signs and a significant degree of facial pruritis."

After reviewing the published literature and the information the company had sent me as well as discussing the issue with the a DEA official who told me that the agency was more concerned about detecting the diversion of fentanyl in lollipop form than in the existing approved dosage forms, I advised Jannsen that I thought the idea of marketing fentanyl lollipops was a dangerous idea and hoped the company would turn down the offer. I subsequently learned that for the reasons stated above and for "business" reasons, they said no. Just this month, however, I learned that Abbott has said yes to Dr. Stanely's group and company, Anesta and thus, this meeting.

II.Drug Abuse Concerns

In re-examining this issue, I obtained a March 1, 1989 letter from Pediatric anesthesiologist Allen Hinkle, an Associate Professor of pediatrics and anesthesiology at Dartmouth Medical School written as a member of the American Society of Anesthesiology Committee on Pediatric Anesthesia. Dr. Hinkle stated that:

"Over the last decade drug abuse has become more rather than less prevalent in our society . In addition the age of the drug abuser has decreased and it is not unusual in major metropolitan cities to find adolescents and even younger children involved in drug taking habits. In view of this sociological background, it behooves us as physicians to not reinforce drug taking behavior in our children. Looking at the history of drug abuse in this country, it is hard to imagine that the inclusion of narcotics in lollipops won't find a route out of hospitals and into the streets."

"in addition to our societal obligation lets look for a moment into our own medical profession at the issue of narcotic control. I think it is true that physicians in general, and anesthesiologists perhaps moreso than other physicians, have been attracted to drug abuse. We can argue ad infinitum about the reasons for this occurrence but clearly even within the hospital environment we have been unable to guarantee the ability to totally control narcotic availability. I believe that until we can control our own narcotic abuse problems it makes little sense for us to develop easier drug delivery systems that will allow younger children to potentially enter into a drug abuse culture needing little or no sophistication on order to deliver narcotics into their bloodstream."When I spoke with him more recently, Dr. Hinkle said that if anything, his views against the fentanyl lollipop were even stronger than in 1989.

Bowman Gray Pediatric Anesthesiologist Gavin Elliot, M.D. was concerned that in lollipop form fentanyl would appear to be less risky and might invite, recruit teenagers who would not be as attracted to parenteral forms.

Harvard Medical School Pediatric Psychiatry Professor Leon Eisenberg, M.D. told me that even if there were no safety concerns, "The idea of putting a drug which has already demonstrated its abuse potential into a lollipop form makes no sense, and is a bad idea."

III. Safety Concerns

Pediatric Pharmacologist Jeffrey Blumer, M.D., Ph.D. of Case Western Reserve Medical School is mainly concerned about and opposed to the approval of the fentanyl lollipop for safety reasons, including the fact that it is difficult to adequately control administration, the related very low margin of safety and the frequent adverse effects such as vomiting, both in the pre- and postoperative phases. Dr. Elliot agreed that it was hard to titrate the dose and Dr. Hinkle said that "Since the lollipop has to be

administered 30-45 minutes preoperatively..most of these children [during consumption of the lollipops] need to be monitored for the occurrence of respiratory depression and arterial oxygen desaturation....requiring increased monitoring and nursing care."

There is also the problem of a guaranteed invitation to less supervised sedation than there would be if an anesthesiologist were present. The convenient packaging of the lollipop invites the use of an opioid in situations where thee is inadequate pediatric resuscitative equipment and expertise.

Studies, published since 1989, which may be of interest follow:

1. Freisen R. Oral transmucosal fentanyl citrate for preanesthetic medication of pediatric day surgery patients with and without droperidol as a prophylactic anti-emetic. Anesthesiology 76:46-51, 1992 (University of Colorado)

The author compares the safety and efficacy of OTFC (15-20 ug/kg) v. placebo with or without droperidol anti-emetic prophylaxis. The study group consisted of 100 children age 2-8 undergoing outpatient surgery. The author concluded that OTFC reliably induced preop sedation but was associated with significant decreases in respiratory rate and SpO_2 and a high incidence of postop nausea and vomiting, not prevented by preoperative droperidol.

Side Effects

Preop

• Facial Pruritus	70%
• Dizziness	12%
• SpO_2 < 90%	12%
• Decr. resp. rate	

Op

- Delayed extubation in OR

Postop

• Nausea/Vomiting	64% (v. 32% in placebo group)
• Delayed discharge home	207 min +- 65 (v. 152 +- 39 for placebo)

The author noted that lack of cooperation and displays of anxiety were rare in placebo and OTFC groups.

2. Goldstein-Dresner M. Double-blind comparison of OTFC with oral meperidine, diazepam, and atropine as preanesthetic medication in children with congenital heart disease. Anesthesiology 74:28-33, 1991 (University of Pittsburgh)

The author compared the safety and efficacy of OTFC (20-25 ug/kg)

v. a combination oral cocktail of meperidine, diazepam and atropine (MDA). The study population consisted of 40 pediatric patients, ages 2-12, scheduled to undergo repair of congenital heart defects.

Side effects

Preop

- Facial pruritus 65%
- Vomiting (6/20) 30%
- Decr. SPB, DPB, Resp rate - not clinically significant
- Decr. SpO_2 (2/20) 10% - did not increase when respiratory rate increased with command

The author concluded that the OTFC group experienced a more rapid onset of sedation. The child's emotional status was similar in both groups at the time of separation from the parents. The final recommendations were that high dose OTFC (20-25 ug/kg), not be used for preanesthetic in children with congenital heart disease, because of the high incidence of preinduction vomiting.

3. Ashburn M, Stanley T. Oral transmucosal fentanyl citrate for premedication in pediatric outpatients.
Can J Anest 37:8;857-66, 1990 (Utah)

The authors compared the effects of OTFC (10-15 ug/kg or 15-20 ug/kg) v. placebo with or without droperidol. The study population consisted of 105 healthy children ages 2-13, scheduled to undergo short (app. 1 hour) outpatient surgical procedures.

Side Effects

Preop

- Decr. resp. rate, decr. SpO_2
- Nausea 14%, Vomiting 11-14%
- Pruritus 58-76%

Postop

- Decreased ability to tolerate fluids, Delayed discharge home (45-50 min)