ters because most centers see only 15–20 such patients a year. Until data from such a study are available, postoperative monitoring for apnea is imperative in the high-risk group, regardless of the anesthetic technique used.

In summary, we have described an infant of 42 wk postconceptional age who had two episodes of life-threatening apnea in the postoperative period after an awake, caudal epidural anesthetic for a hernia repair.

The authors thank Dr. J. Ternberg for permission to report this case and acknowledge the care provided by the physicians and nurses at the St. Louis Children's Hospital. The authors also thank M. Bicknell for her assistance during the preparation of the manuscript.

References

1. Steward DJ: Preterm infants are more prone to complications following minor surgery than are term infants. ANESTHESIOLOGY 56:304–306, 1982
2. Liu LMP, Coté CJ, Goudsouzian NG, Ryan JF, Firestone S, Dedrick DF, Liu PL, Todres ID: Life threatening apnea in infants recovering from anesthesia. ANESTHESIOLOGY 59:506–510, 1983
3. Welborn LG, Ramirez N, Oh TH, Ruttimann UE, Fink R, Guzzetta P, Epstein BS: Postoperative apnea and periodic breathing in infants. ANESTHESIOLOGY 65:658–661, 1986
4. Kurth CD, Spitzer AR, Broennle AM, Downes JJ: Postoperative apnea in preterm infants. ANESTHESIOLOGY 66:483–488, 1987
5. Abaijian JC, Mellish RWP, Browne AF, Perkins FM, Lambert DH, Mazuzan JE: Spinal anesthesia for surgery in the high-risk infant. Anesth Analg 63:359–362, 1984
6. Harnik EV, Hoy GR, Potolicchio S, Stewart DR, Siegelman RE: Spinal anesthesia in premature infants recovering from respiratory distress syndrome. ANESTHESIOLOGY 64:95–99, 1986
7. Spear RM, Deshpande JK, Maxwell LG: Caudal anesthesia in the high-risk infant. ANESTHESIOLOGY 69:407–409, 1988
8. Eger EI II: Anesthetic Uptake and Action. Baltimore, Williams & Wilkins, 1974, pp 228–248
9. McIntosh TK, Bush HL, Palter M, Hay JR, Aun F, Yeston NS, Eqhdahl RH: Prolonged disruption of plasma beta endorphin dynamics following surgery. J Surg Res 38:210–215, 1985
10. Myer EC, Morris DL, Adams ML, Brase DA, Dewey WL: Increased cerebrospinal fluid beta endorphin immunoreactivity in infants with apnea and in siblings of victims of sudden infant death syndrome. J Pediatr 111:660–666, 1987
11. Thach BT: Sleep apnea in infancy and childhood. Med Clin North Am 69:1289–1315, 1985
12. Abu-Osba YK, Brouillette RT, Wilson SR, Thach BT: Breathing patterns and transcutaneous oxygen tension during motor activity in preterm infants. Am Rev Respir Dis 125:382–387, 1982
13. Yaster M, Maxwell LG: Pediatric regional anesthesia. ANESTHESIOLOGY 70:324–338, 1989
14. Ecoffey C, Desparmet J, Maury M, Berdeaux A, Guidicelli J, Saint-Maurice C: Bupivacaine in children: Pharmacokinetics following caudal anesthesia. ANESTHESIOLOGY 63:447–448, 1985
15. Dalens B, Hasnaoui A: Caudal anesthesia in pediatric surgery: Success rate and adverse effects in 750 consecutive patients. Anesth Analg 68:83–89, 1989
16. Takasaki M: Ventilation and ventilatory responses to carbon dioxide inhalation during caudal anesthesia with lidocaine or bupivacaine in sedated children. Acta Anaesthesiol Scand 32:218–221, 1988
17. Steinbrook RA, Concepcion M, Topulus GP: Ventilatory responses to hypercapnia during bupivacaine spinal anesthesia. Anesth Analg 67:247–252, 1988

Anesthesiology
71:615–617, 1989

Oral Transmucosal Fentanyl Citrate for the Treatment of Breakthrough Cancer Pain: A Case Report

MICHAEL A. ASHBURN, M.D.,* PERRY G. FINE, M.D.,† THEODORE H. STANLEY, M.D.‡

It is estimated that 29% of patients with cancer suffer from moderate to severe pain even when receiving analgesic therapy.[1] In addition, many patients who receive long-acting potent opioids for the management of severe cancer pain suffer from adverse effects such as over-sedation, constipation, nausea, and periods of inadequate pain relief. A noninvasive means of administering a rapidly absorbed potent analgesic with a relatively short duration would be desirable for the treatment of breakthrough pain experienced by these patients.

It has recently been documented that fentanyl, a potent synthetic opioid, can be absorbed transmucosally through administration in lollipop form (Oral Transmucosal Fentanyl Citrate [OTFC]).[2,3]§ We report the use of OTFC for the treatment of breakthrough pain in a patient with metastatic carcinoma of the lung.

* Assistant Professor.
† Assistant Professor; stockholder, Anesta Corporation.
‡ Professor; stockholder, Chairman of Scientific Advisory Board, and Chairman of the Board of Directors of Anesta Corporation.

Received from the Pain Management Center, Department of Anesthesiology, University of Utah Health Sciences Center, 50 North Medical Drive, Salt Lake City, Utah 84132. Accepted for publication May 26, 1989.

Address reprint requests to Dr. Ashburn.

Key words: Analgesics: fentanyl. Delivery system: oral transmucosal. Pain: cancer.

§ Anesta Corp, Salt Lake City, Utah.

Case Report

A 62-year-old white male with widely metastatic adenocarcinoma of the lung, diagnosed a year previously, was referred to our pain clinic for management of severe left shoulder and arm pain. A course of external beam radiation to the tumor mass in the left upper lobe of the lung had failed to give protracted pain relief.

On initial pain clinic evaluation, he described this pain as constant and aching with frequent sharp, shooting sensations. Emotional stress and physical activity exacerbated these symptoms, and partial relief was obtained by rest and avoidance of stressful situations. These painful sensations were only slightly relieved with high doses of oral opioid and nonsteroidal anti-inflammatory analgesics, including Percocet® (10 tablets per day), MS Contin® (60 mg every 4 h), and ibuprofen (8 g per day). Though not providing adequate analgesia, these medications were causing sedation that was inhibiting his performance as the chief executive officer of a national corporation.

Examination of the chest and involved upper extremity revealed no neurological deficits and there was a full range of motion. There was no trigger-point tenderness or skin sensitivity, nor were there any palpable masses present.

Initial pain therapy involved the substitution of his then current analgesic medications with methadone, 20 mg every 6 h, diflunisal (Dolobid®), titrated up to 500 mg every 8 h, and a single 25-mg dose of amitriptyline prior to bedtime. Though he did well for a month on this regimen, recurrent upper extremity and shoulder pain began to interfere with his work, travel, and recreational activities (he was an avid golfer) and increasing the dose of methadone only led to aggravating sedation.

Various other pain management modalities were presented, including the use of spinal opioid analgesia *via* an indwelling epidural catheter; however, he preferred any noninvasive therapeutic options that might still be available. He agreed to try OTFC on a compassionate use basis to prevent incident pain and the predictable breakthrough pain associated with stressful work-related meetings.

After Institutional Review Board approval and informed consent, the patient completed a daily pain and activity diary for 1 week without changing his usual medication schedule. He then received two doses of OTFC, 700 μg, on consecutive days. The patient was instructed to place the OTFC in his buccal pouch and allow the OTFC to passively dissolve. Administration time for the complete OTFC was 15 min. He was observed for 6 h after each administration. Measurements of blood pressure, heart rate, respiratory rate, oxygen saturation (by pulse oximetry), and visual analog scale pain ratings (10-cm scale) were obtained before OTFC administration, every minute during drug administration, every 5 min for the first hour following administration, and then every 30 min thereafter for 6 h.

Pain ratings decreased from 5/10 to 1/10 2 min after the onset of OTFC administration and remained at that level throughout the observation period. There were no appreciable changes in vital signs or oxygen saturation.

The patient was then given a supply of OTFC, each with 700 μg of fentanyl, with instructions to suck on them as needed for breakthrough pain and to continue with his other medications. He was to self-administer the OTFC until he felt that the pain was controlled, and then save any remaining portion in the package provided. Meanwhile, he was to continue keeping a diary, recording OTFC use, pain ratings, activities, and side effects noticed with this drug.

The dose of fentanyl in each OTFC was increased to 900 μg per lollipop after 6 days and increased to 1000 μg after an additional 11 days. OTFC dose was increased when the patient reported incomplete pain relief after consuming the entire OTFC. Pain relief was reported to begin 2–5 min after OTFC administration, with maximum effect occurring within 20 min of OTFC consumption. The patient remained active and relatively comfortable using two to three doses of OTFC each day. With progression of his disease, supplemental oxygen was required and he developed a partial vocal cord paralysis. Eight weeks after the OTFC trial began, there was a worsening of the left arm and shoulder pain, and a cervical epidural catheter was inserted through which preservative-free morphine (1.5 mg every 8–12 h) was delivered. He was able to decrease his methadone intake to 10 mg every 6 h, and continued the OTFC at a rate of two to three times each day, but required less time then previously to achieve good pain control.

Three weeks later, the epidural catheter had to be removed due to leakage that prevented adequate drug delivery. The patient decided not to have this replaced and his methadone dose was increased to 20 mg every 6 h and he continued using OTFC at the rate of up to five times each day. He would titrate his analgesia and save unused portions for later self-administration.

He died peacefully at home shortly after this time, under the care of his family members and primary physician. The family reported that he appeared quite comfortable up until the time of his death, which was determined to be the result of intestinal rupture and hemorrhage.

This patient received a total of 266 OTFC units over an 80-day period. He credited the addition of OTFC as significantly decreasing his pain and enhancing the quality of his life. In addition, the side effects of chronic opioid administration were not increased by the OTFC. The improvement in his pain management with the use of OTFC for the treatment of breakthrough pain is confirmed by comparison of his baseline visual analog pain assessment to his pain assessment while receiving OTFC (fig. 1).

Discussion

Worldwide, 5.9 million people are diagnosed with cancer¶ and 4.3 million people die of the disease every year.[4] Pain is a major symptom in about 70% of cancer patients.[5] Of those 3 million people requiring treatment for cancer pain, 92% required opioid analgesics, making this treatment modality the mainstay of cancer pain therapy.

The World Health Organization (WHO) Committee on the Comprehensive Management of Cancer Pain developed guidelines for the effective use of drugs to treat cancer pain in the hopes that cancer pain might be treated more effectively throughout the world than it has been in the past.** The program is based on a therapeutic strategy that uses an "analgesic ladder" for drug administration. This ladder recommends the use of a nonopioid, with an adjuvant (anxiolytic, antidepressant, anticonvulsant) if necessary, as the initial treatment of cancer pain. If pain persists, a weak opioid is added in addition to the nonopioid and the adjuvant. Finally, if pain persists, a strong opioid is begun in place of the weak opioid while the nonopioid and adjuvant is continued. Drugs are administered by the oral route if possible. Dosages are titrated against the patient's pain report and administered on a time contingent basis, according to the drug's phar-

¶ World Health Organization. Cancer as a global problem. Weekly Epidemiological Record. Geneva: Office of Publications, World Health Organization, 1984; 59:125–126.

** World Health Organization. Cancer pain relief. Geneva: Office of Publications, World Health Organization, 1986.

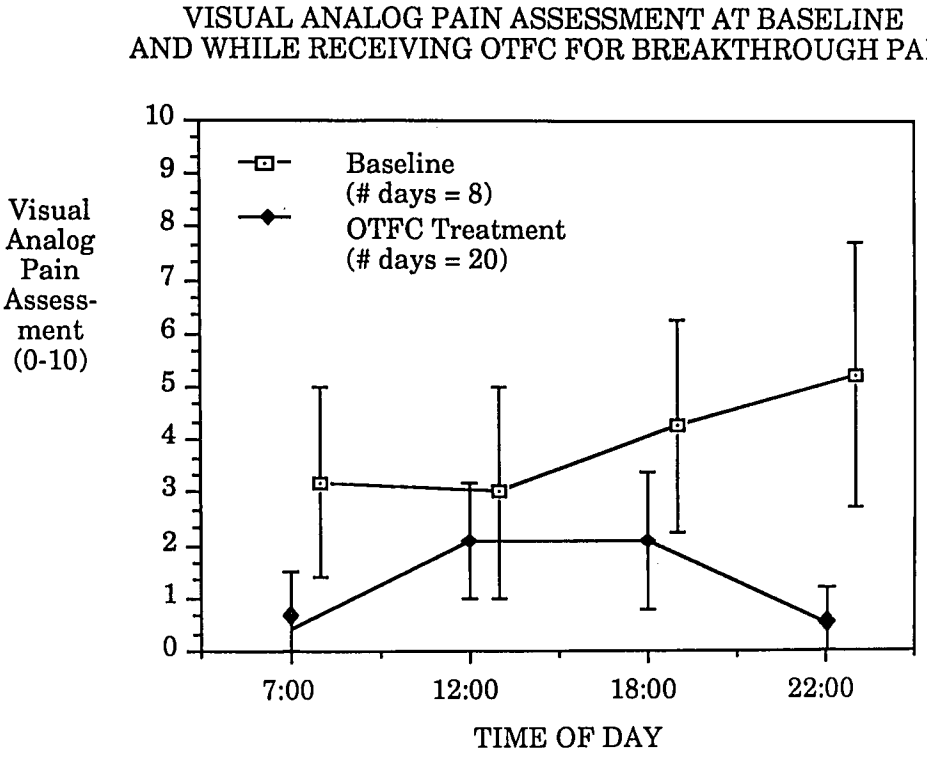

FIG. 1. Mean and standard deviation of visual analog pain assessment at baseline and while receiving OTFC for the treatment of breakthrough pain. The patient made an assessment of his pain at four regular daily intervals using a visual analog pain scale. Because of the small amount of data presented, statistical analysis is not warranted.

macokinetics. This general approach toward managing cancer pain has also been advocated by other organizations.††

Fortunately, when appropriate analgesic therapy is used, 71% of cancer patients receive adequate pain relief; however, 29% do not. Also, the use of long-acting potent opioids for the management of severe cancer pain may be accompanied by undesirable effects such as sedation, constipation, nausea, and vomiting, and there may be periods of inadequate pain relief.[1]

The treatment of significant cancer pain can often be difficult and frustrating. In order to control the episodes of severe pain that some patients experience, it may be necessary to administer high doses of potent opioids. While this treatment modality may control these episodes, the patient then experiences over-sedation during other times of the day with an increased incidence of the dose-related side effects listed above and tolerance may develop more rapidly. For these reasons, a drug with a rapid onset time that could be administered nonparenterally would be advantageous for this patient group.

In this case report, we demonstrated the efficacy of OTFC in the treatment of breakthrough cancer pain in a terminally ill but cooperative patient functioning at a relatively high level. Fentanyl has a relatively short duration of effect, allowing the treatment of breakthrough pain while avoiding over-sedation and the other side effects of using high-dose, long-acting oral opioids for the same purpose. The lollipop form allowed for easy self-administration and titration. We realize that this successful experience with the OTFC in this setting does not prove its usefulness. We do believe, however, this case report identifies an exciting new method of drug delivery that could improve the treatment of breakthrough cancer pain. Careful, controlled studies evaluating the use of the OTFC in the treatment of breakthrough cancer pain are warranted.

†† American Pain Society. Principles of analgesic use in the treatment of acute pain and chronic cancer pain. Washington, D. C., American Pain Society, 1987.

REFERENCES

1. Ventafridda V, Tamburine M, Caraceni A, De Conno F, Naldi F: A validation study of the WHO method for cancer pain relief. Cancer, 59:850–856, 1987
2. Mock DL, Streisand JB, Hague BS, Dzelzkalns R, Bailey PL, Pace NL, Stanley TH: Transmucosal opioid delivery: An evaluation of fentanyl lollipop premedication in man (abstract). Anes Analg 565:S102, 1986
3. Nelson PS, Streisand JB, Mulder SM, Pace NL, Stanley TH: Comparison of oral transmucosal fentanyl citrate and an oral solution of meperidine, diazepam, and atropine for premedication in children. ANESTHESIOLOGY 70:616–621, 1989
4. Parkin M, Stjensward J, Muir C: Estimates of the worldwide frequency of twelve major cancers. Bull WHO 62:163–182, 1984
5. Bonica JJ: Treatment of cancer pain: Current status and future needs, Advances in Pain Research and Therapy, vol 9. Edited by Fields HL, Dubner F, Cervero F. New York, Raven Press, 1985, pp 589–616