2. Loizeau E. Can antibiotic-associated diarrhoea be prevented? Ann Gastroenterol Hepatol 1993;29(1): 15–18.

3. Evans-Jones G, McDowell HP. Sugar intolerance complicating acute gastroenteritis. Arch Dis Child 1986;61(7):716–717.

4. Shaw AD, Davies GJ. Lactose intolerance: problems in diagnosis and treatment. J Clin Gastroenterol 1999;28(3):208–216.

5. Gardinier AJ, Tarlow MJ, Sutherland IT, Sammons HG. Lactose malabsorption during gastroenteritis, assessed by the hydrogen breath test. Arch Dis Child 1981;56(5):364–367.

6. Tamm A. Management of lactose intolerance. Scand J Gastroent 1994;202 (Suppl):55–63.

Pilot Dose Finding Study of Intranasal Sufentanil for Breakthrough and Incident Cancer-Associated Pain

To the Editor:

We concur with the promising experience reported by Dr. Gardner-Nix[1] in using transmucosal (sublingual) sufentanil for incident pain. We wish to report preliminary data from a pilot study of nasal transmucosal administration of this drug for breakthrough pain in an acute hospital-based palliative care unit.

Up to 60% of patients with cancer-associated pain suffer from episodes of breakthrough or incident pain.[2] The standard management of this is bolus oral or subcutaneous administration of an immediate-release opioid, usually morphine. However, this does not meet the ideal characteristics of a breakthrough drug, which are rapid onset, early peak effect and duration of action of 1–2 hrs. Postoperatively, the problem is often overcome using an intravenous patient-controlled analgesia (PCA) device, but this has not found favor in the palliative care setting.

The sublingual (SL) and intranasal (IN) routes are both being re-explored as they avoid first-pass effect metabolism, allow for rapid absorption by an area with a rich blood supply, and are not painful to administer. The initial applications of these routes were for pre-medication prior to surgery, particularly in children. Subsequently, this has been extended into the palliative care field,[3] initially for breakthrough dosing in patients requiring the use of fentanyl or sufentanil for background control due to demonstrated adverse effects to other opioids or in patients with significant renal impairment.

Fentanyl and sufentanil are synthetic opioids with higher lipid solubilities and shorter durations of action than morphine when given intermittently. The physico-chemical properties of sufentanil and the concentration of the commercially available formulation suggest that it may be the most suitable of the available opioids for use by transmucosal routes of administration.[4]

As in Canada, oral transmucosal fentanyl citrate (OTFC) is not yet available in Australia. In this unit, sublingual sufentanil drops have been used for several years, but results have not been evaluated. It was decided to explore the intranasal route for a number of reasons: 1) the better bioavailability intranasally (up to 70%),[5] as compared to sublingually (50%);[6] 2) the availability of a cheap and simple device for intranasal administration; and 3) the difficulty with sublingual administration (particularly with volumes of 0.5 ml or greater) of knowing how much is absorbed, and how much is being swallowed reflexively and hence subject to first pass metabolism.

A commercially available patient-controlled intranasal analgesia (PCINA) spray device is manufactured by GO Medical™ and delivers a 0.18-ml dose as a fine spray to the nasal mucosa. This device was developed as an inexpensive low-tech device to mimic the efficacy of intravenous PCA.[7] It is manufactured with variable lock out times, commonly 0, 3, or 4 minutes. We are using this PCINA device in an open label pilot study of intranasal sufentanil for breakthrough analgesia, to demonstrate efficacy, safety, and both patient and staff acceptability.

All inpatients who are receiving opioid therapy and require breakthrough analgesia have been considered for the study. Exclusion criteria include cognitive impairment or English language skills insufficient to allow for reliable pain reporting, the terminal phase of illness, respiratory failure, and nasal deformity such as to contraindicate nasal drug ad-

Table 1
Administration of Intranasal Sufentanil to Four Patients with Cancer-Related Pain

Patient No.	Diagnosis	Pain Mechanism	IN Sufentanil Administration (s)	24 hr Opioid Dose	Usual Breakthrough	IN sufentanil dose μg	VRS 0 min	VRS 15 min	VRS 30 min
A	Recurrent adenocarcinoma parotid	N	1	SRM 70 mg	oral morphine 10 mg	4.5 + 4.5	7	3	0
			2	SRM 70 mg	oral morphine 10 mg	4.5 + 4.5	7	3	0
B	Adenocarcinoma lung	N	1	SRM 80 mg	oral morphine 5 mg	4.5 + 4.5 + 4.5	5	1	0
	vertebral metastases	I							
	spinal cord compression								
C	Carcinoma prostate	S	1	SRM 60 mg	oral morphine 5 mg	4.5 + 4.5	8	4	2
	bone metastases	I	2	SRM 70 mg	SC morphine 5 mg	9	8	1	1
	fracture/dislocation hip, awaiting THR								
D	Carcinoma colon	N	1	hydromorphone 60 mg CSCI	oral hydromorphone 16 mg	4.5 + 4.5 + 4.5	6	4	4
	vertebral metastases	I							
			2	hydromorphone 60 mg CSCI	oral hydromorphone 16 mg	9 + 9 + 9	6	4	4

N = Neuropathic; S = Somatic; I = Incident; CSCI = continuous subcutaneous infusion; SC = subcutaneous; SRM = sustained-release morphine; THR = total hip replacement.

ministration. Written informed consent is obtained.

As a zero lockout device has been used for the trial, the application is nurse- rather than patient-controlled. All other medications are unchanged, except that once a day, the patient may be given intranasal sufentanil instead of their usual breakthrough opioid medication.

The daily dose could be escalated, if required, to a maximum of 3 doses of 36 μg daily. The initial dose, 4.5 μg, may be repeated at 10 minutes and 20 minutes, if required and the drowsiness scale is less than 2. If this was ineffective at 30 minutes, the usual opioid breakthrough medication was given. If this occurred, the dose on the next day started with 9 μg, which could be increased as described above. If three doses of 9 μg were ineffective, the dose on the next day was increased to an 18 μg dose. If the latter dose was ineffective, the next increment was to 36 μg.

Pain was rated using a verbal rating scale (VRS) pain (0–10 scale; 0 = no pain, 10 = worst possible pain). Drowsiness scores were designated on a scale that ranged from 0–4 (0 = alert, 4 = patient unrousable). Respiratory rate and oxygen saturation (SpO_2) are collected for 2 hrs after each episode. Each episode of IN sufentanil was analyzed individually for response, time to response, adverse effects if any, and patient preference, as compared to the usual breakthrough medications.

The study is still accruing. The first seven applications in four patients are summarized in Table 1. Very good pain relief occurred in 5 of 7 episodes and lasted for around 2 hours. No patient developed drowsiness, nausea, vomiting or respiratory depression after the IN sufentanil. All patients who achieved good pain relief rated IN sufentanil as much better than their usual opioid breakthrough, both in speed of onset and efficacy.

Comment

These pilot study data suggest that IN sufentanil administration in this dose range is safe and effective. A multicenter study protocol is now being designed to continue the evaluation of this way of managing breakthrough and incident pain.

Kate Jackson, MB BS, DTM&H, FRCA, FAChPM
Michael Ashby, MD, MRCP, FRCR, FRACP, FAChPM, MRACMA

Jane Keech, MB BS, BA, FAMAS
Palliative Care Unit, McCulloch House, Monash Medical Center and Southern Clinical School, Faculty of Medicine, Nursing and Allied Sciences, Monash University, Clayton, Victoria, Australia

PII S0885-3924(02)00406-2

References

1. Gardner-Nix J. Oral transmucosal fentanyl and sufentanil for incident pain. J Pain Symptom Manage 2001;22:627–630.

2. Portenoy RK, Hagen NA. Breakthrough pain: definition, prevalence and characteristics. Pain 1990; 41:273–282.

3. See Harlos M, St Boniface Palliative Care Unit, Winnipeg, Manitoba, Canada. Incident pain protocol, using fentanyl and sufentanil by the sublingual route. Available at http://pallitive.info/IncidentPain.htm.

4. Stanley TH. The history and development of the fentanyl series. J Pain Symptom Manage 1992;7(3 Suppl):S3–8.

5. Helmers JH, Mooduin H, Van Peer A, et al. Comparison of intravenous and intranasal sufentanil absorption and sedation. Canadian J Anaesthesia 1989; 36(5);494–497.

6. Streisand JB, Varvel JR, Stanski DR, et al. Absorption and bioavailability of oral transmucosal fentanyl citrate. Anesthesiology 1991;75:223–229.

7. O'Neil G, Peach M, Wood F. Preliminary clinical use of a patient-controlled intranasal analgesia (PCINA) device. Anaesth Intens Care 1997;25:408–412.

Re: Uncertainty and Opposition of Medical Students Toward Assisted Death Practices

To the Editor:

Warner et al.'s survey tool to assess University of New Mexico medical students' attitudes toward "assisted death" apparently made it through testing by the "Therapeutic Care Committee of the Group for the Advancement of Psychiatry," as well as perusal by multiple co-authors and peer review by this journal.[1] But patient vignettes 5–6 have me flummoxed.

> *Patient Vignette 5: A 27-year-old woman with AIDS has severe pneumonia, is unresponsive to antibiotic treatment, and has been in a coma for 2 months. She receives intravenous morphine and is on a respirator. Her loving family cannot bear her state, knowing her EEG deems her "brain dead," and hope that her death will occur soon.*
>
> Would you turn off the respirator and let her die?
>
> Would you allow someone else to turn off her respirator and let her die?
>
> Would it be acceptable for other physicians to turn off the respirator for similar patients to die?
>
> Would it be acceptable for her family to turn off the respirator?

Patient Vignette 6 concerns the same patient, withdrawn from the ventilator, and alive three weeks later. The four questions that follow ask about the acceptability of active euthanasia by means of morphine.

I cringe to think of the 166 medical students reading these vignettes and imagining this patient as she is described. Brain death, according to the so-called "Harvard Criteria" for the determination of death and current practice parameters, consists of irreversible cessation of clinical function in the whole brain, including both the neocortex and brain stem.[2,3] An EEG cannot—in and of itself—be the means of determining brain death in this patient or any other patient. An EEG suggestive of brain death should prompt efforts at a definitive determination of brain death—namely, by formal findings of coma, absence of brainstem reflexes, and positive apnea test results, all in a context where complicating/confounding medical conditions have been excluded. Determination of brain death serves, in turn, as justification for confirmatory testing, which may include cerebral angiography, cerebral blood flow studies, and so forth. A repeat neurological exam after a set period (usually six hours) is also standard.

Once brain death has been properly determined and confirmed, the patient is understood to be dead.[4] In the United States (with only New Jersey allowing for objections to the determination of death by brain criteria), brain dead is dead, and no one need then hope "that death will occur soon" or make decisions about "let[ting] die."

Careless use of the term "brain death" exacerbates confusion and uncertainty. In the clini-