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Self-administered nitrous oxide for the management of incident pain in terminally ill patients: a blinded case series

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The treatment of incident pain in terminally ill cancer patients receiving long-term opioid therapy remains a challenge. Self-administered inhaled nitrous oxide has been used for short-term analgesia in this setting, with mixed results. It is unclear whether nitrous oxide exhibits cross-tolerance with opioids, and there is the possibility of a strong placebo effect in previous unblinded reports. We report on a double-blind crossover case series, in which seven patients received either nitrous oxide/oxygen or a placebo air/oxygen mixture on each day of a two-day trial. Outcome indices were obtained before, during and after each use of the gas for anticipated incident pain. The patient population was very heterogeneous with respect to disease, pain scores and concurrent treatments. Nitrous oxide was beneficial during incidents in five of seven patients; the remaining two patients reported an overall preference for the nitrous oxide day. We conclude that a trial of self-administered inhaled nitrous oxide should be considered in patients with difficult incident pain. *Palliative Medicine* 2005; **19:** 3–8

Key words: analgesics; human; nitrous oxide; non-narcotic; pain; palliative care

Introduction

Incident pain represents a challenging problem in the management of terminally ill cancer patients with a background level of pain.[1] Incident pain is defined as pain which is 'caused by an action of the patient',[2] or that which is 'triggered by movement'.[3] While pain at rest can usually be controlled with long-acting opioids, incident pain is often acute, severe and of short duration, and is most often related to mobilization, and diagnostic or therapeutic procedures. The ideal analgesic modality to treat incident pain would be potent, with a rapid onset, titratable and short-acting, without significant impairment of consciousness or ability to mobilize, and with minimal adverse effects.

Self-administered inhaled nitrous oxide has been used for decades in the treatment of pain due to labour, trauma, surgical procedures and medical conditions as diverse as angina and kidney stones.[4,5] Nitrous oxide has potent analgesic properties, with rapid onset, minimal accumulation and a duration of action of several minutes following discontinuation.[6] In the absence of other central nervous system depressants, nitrous oxide preserves consciousness and airway protective reflexes at its usual analgesic concentration of 50% in oxygen. When used with a self-administered demand valve apparatus, the concentration of nitrous oxide is auto-titrated according to the patient's level of consciousness, and can also provide the patient with a sense of control, which can be of great benefit in terminally ill patients.

The use of nitrous oxide for the treatment of refractory pain in metastatic cancer patients has been reported in a number of case series, with mixed conclusions.[7–9] Possible factors influencing its effectiveness include multiple pain aetiologies, decreased compliance if consciousness is impaired and cross-tolerance with long-term, regularly administered opioids. In addition, lack of blinding of patients or assessors in previous reports may have prevented an accurate assessment of pharmacologic efficacy.[10] We therefore investigated a blinded case series of patients with incident pain related to malignant disease, randomized to receive nitrous oxide and a placebo gas on two different days, to assess the effectiveness of nitrous oxide in this setting.

Methods

Following approval by the Queen's University Research Ethics Board, a randomized double-blinded crossover study was carried out, in which eligible patients received a self-administered inhaled mixture of nitrous oxide/oxygen or air/oxygen on successive days. Patients were deemed eligible if they were over 18 years of age, admitted

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to hospital, diagnosed with end-stage malignant disease and receiving stable doses of opioids for cancer-related pain for at least seven days previous to enrollment. Exclusion criteria included planned surgical or diagnostic interventions or hospital discharge within the next 48 hours, impaired baseline mental status (baseline Folstein mental status exam score <24), and contra-indications to the use of nitrous oxide, including pneumothorax, bowel obstruction, and requirement for inspired oxygen fraction >0.50.

On Day 0, after patients were deemed eligible and signed informed consent, they received instruction and practice in using the study apparatus, which provides a self-administered inhaled gas mixture (Nitronox, Lifetronics Medical Inc, North York, Ontario). The portable Nitronox system provides a mixture of gases to a demand-valve mask, which is opened by negative pressure by the patient. Two identical blinded systems were employed, one containing 50% nitrous oxide in oxygen, and the other modified to provide air enriched to 50% oxygen. Patients were randomized using a random number table by a separate investigator to receive one of the study gases on Day 1 of the protocol, and the other study gas on Day 2.

On each study day, patients received their usual scheduled doses of analgesic medications. Breakthrough opioid doses (10% of total 24-hour dose, given hourly as requested) were available as rescue medication. On each of the two days they had immediate access to the Nitronox equipment between 08:00 and 18:00 hours. Patients were instructed to begin inhalation five minutes prior to any interventions which they anticipated may cause incident pain, such as turning in bed, using the commode, bathing, wound dressing changes or physiotherapy. Each use would be continued during the intervention, to a maximum of 20 minutes. It was anticipated from clinical observation that the patients would average five to ten such incidents per study day. These interventions were carried out as per usual routine by hospital staff, based on the patients' individual plan of care. A research nurse was dedicated to the study, and was available in person throughout each 10-hour period to assist the patient with proper use of the study gas apparatus, and to collect both quantitative and qualitative data during and between these interventions (Appendix 1).

During the study days, for each incident, use of the study gas was documented, as well as the type and duration of each activity or intervention. Incident pain was grouped into three categories to account for the varying potential for different types of interventions to cause pain:

Category 1. Care in bed: turning, bathing, changing bedding;
Category 2. Mobilization: to commode, up in chair, to bathroom;
Category 3. Procedures: wound dressing changes, physiotherapy.

As this was a relatively small case series, data are presented in descriptive form (Table 1). A comparison of pain scores for all incidents grouped together by study drug was carried out using paired *t*-tests.

Results

Ten patients were enrolled into the study. Two patients had Folstein scores of <24 at the start of the first day of the protocol and were therefore withdrawn; one patient was withdrawn by his attending physician after the first study day due to a rapid deterioration of the patient's medical condition. Seven patients thus completed the two-day protocol. The group of patients were heterogeneous with respect to site of disease, duration of opioid use, coanalgesic use and time since radiotherapy treatments (Table 1). All patients had an Edmonton Staging System score of 3, and the median Present Pain Index from the Short Form McGill Pain Questionnaire was 3. Four patients were randomized to receive nitrous oxide on the first study day, the other three received air on the first day.

Baseline pain scores were comparable between the air and nitrous days (mean 4.6 versus 4.7, median 4.3 versus 5.0). Table 1 lists the mean incident baseline and peak pain scores for each study day. Five of seven patients showed less of an increase in mean pain scores due to incidents on the nitrous oxide day (Figure 1). The remaining two patients did not show a benefit due to nitrous oxide (Figure 1); however, these two patients still felt that, overall, they were more comfortable during the nitrous oxide day than the air day (Table 1). When all pain scores were grouped together and compared by study day, there was no difference detected. Breakthrough opioid requirements were not different between days.

Blood pressure, heart rate and respiratory rate were unaffected by nitrous oxide administration. Drowsiness scores did not change during or following administration, and Folstein mental status scores did not change over each study day. There was no difference in response to nitrous oxide related to type of pain or category of incident.

Table 1 Characteristics of seven patients prior to enrollment and during study days

	Patient T	Patient D	Patient W	Patient R	Patient S	Patient G	Patient H
Prestudy data							
Age	54	71	45	65	68	45	80
Sex	M	M	F	F	M	M	M
Type of cancer	Prostate	Bladder	Endometrium	Uterus	Haemangio-endothelioma	Plasmacytoma spine	Lung
Months since diagnosis	48	48	18	24	4	2	12
Months of chronic opioid use	24	5	3	14	1	1	2
Daily regular opioid dose (mg)*	105	450	945	25	210	90	180
Daily breakthrough dose (mg)**	476	5	0	280	7	1	32
Coanalgesics	ster, NSAID, baclofen, benzo	ster, acetamin ophen, baclofen	ster, NSAID	gabapentin, benzo	Acetaminophen	ster, NSAID	ster, amitriptyline
Radiotherapy (days prior to study)	15	7	5	150	None	1	2
Randomization order	Air–nitrous	Nitrous–air	Nitrous–air	Nitrous–air	Nitrous–air	Air–nitrous	Air–nitrous
Preferred day	Nitrous	Nitrous	Air	Air	Air	Nitrous	Nitrous

	Nitrous/O_2	Air/O_2	Nitrous/O_2	Air/O_2	Nitrous/O_2	Air/O_2	Nitrous/O_2	Air/O_2	Nitrous/O_2	Air/O_2	Nitrous/O_2	Air/O_2	Nitrous/O_2	Air/O_2
Study data														
No. of incidents per day	4	8	6	5	4	4	8	9	10	10	5	6	4	8
Mean (median) baseline pain score	4.3 (4.5)	3.3 (3.0)	0.8 (1.0)	0.9 (1.0)	6.8 (6.0)	4.0 (4.5)	6.3 (6.0)	6.7 (6.0)	6.1 (6.0)	6.8 (8.0)	2.0 (1.0)	2.5 (2.0)	6.0 (6.0)	4.9 (4.3)
Mean (median) peak pain score	3.5 (3.0)	3.5 (3.0)	2.7 (3.0)	2.4 (2.0)	8.3 (9.0)	6.6 (6.8)	4.5 (5.0)	6.3 (6.0)	5.3 (5.5)	6.8 (7.5)	2.0 (1.0)	4.3 (4.0)	5.3 (5.0)	4.1 (4.0)
Regular daily opioid (mg)*	30	30	375	475	930	900	25	28	250	179	90	90	240	180
No. of breakthrough doses	2	2	1	1	0	0	4	5	1	3	1	1	2	1
Total breakthrough opioids (mg)**	168	168	5	5	0	0	224	280	21	63	2	2	20	10
Mean baseline systolic BP (heart rate)	120 (83)	122 (89)	149 (87)	145 (86)	160 (102)	161 (93)	134 (88)	128 (83)	87 (73)	83 (75)	135 (94)	137 (98)	131 (78)	149 (84)
Mean peak systolic BP (heart rate)	105 (88)	122 (87)	150 (85)	169 (85)	170 (113)	168 (93)	128 (83)	126 (86)	78 (66)	77 (71)	128 (93)	139 (99)	129 (75)	136 (82)

*Oral morphine equivalents.
**sc morphine equivalents.
ster = corticosteroids, benzo = benzodiazepine, NSAID = nonsteroidal anti-inflammatory drugs.

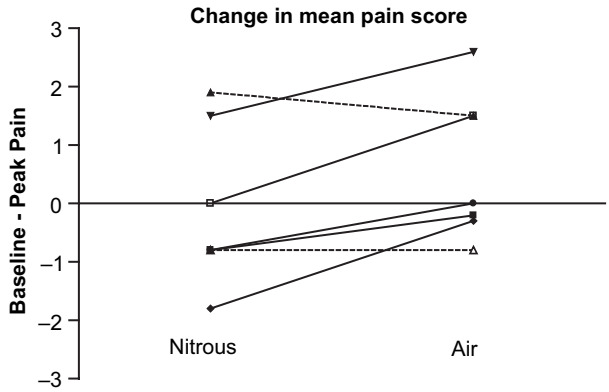

Figure 1 Comparison of the mean change in pain score from baseline to peak during incidents between the day of 50% nitrous oxide self-administration and the day of placebo (oxygen–air) self-administration. Each pair of points represents the mean pain score difference for each patient on each study day.

Discussion

This is the first series reported on the blinded use of nitrous oxide or placebo gas for incident pain in patients with terminal cancer. As compared with the placebo day, the changes in pain scores during incidents were improved on the nitrous oxide day in five of seven patients.

According to the World Health Organization (WHO), approximately five million people die each year of malignant disease.[11] It is estimated that 70–90% of those with advanced cancer have significant pain, with studies showing that undertreatment of the pain of malignant disease is common.[12] The mainstay of treatment of pain due to malignant disease is the use of opioid drugs, supplemented, where necessary, by a number of pharmacologic and nonpharmacologic coanalgesic therapies.

Commonly, an analgesic regimen may be effective at producing comfort at rest, while ineffective at preventing the pain of movement and activity. This 'incident pain' has been found to be a major limiting factor to activity.[1,2,13] It is often worse toward the end of the dosing interval, and is generally not easily managed with breakthrough doses of opioids, which tend to be slow in onset. Additional opioids can also lead to excessive sedation, confusion and nausea when the incident pain subsides, due to a state of relative opioid overdose. Sources of incident pain can be unpredictable, such as bouts of coughing or bowel movements, or predictable, relating to planned movement or diagnostic and therapeutic procedures. Thus, the ideal agent to treat short-term incident pain would be a safe and easily deliverable agent which has a rapid onset of action and a rapid return to baseline status when no longer required. Newer strategies to manage incident pain have included rapid-onset, short-acting potent opioids such as sufentanil, delivered sublingually, and potent intravenous sedatives.[14–16]

Nitrous oxide is an inhaled agent with potent analgesic properties and a low incidence of side effects. It is a commonly used adjunct to general anaesthesia which reduces the required concentration of the primary anaesthetic agent. Nitrous oxide has a number of advantages which would also make it a potentially useful analgesic in the setting of incident pain.[6] First, its very low solubility provides for a quick onset time and short duration of action. Secondly, there is little effect on respiration, cardiovascular system or airway reflexes. Thirdly, the depth of nitrous oxide analgesia is determined by its concentration rather than the duration of administration, as it equilibrates rapidly in the brain. Thus at the commonly administered analgesic concentration of 50%, level of consciousness is maintained, regardless of the duration of inhalation. Nitrous oxide has been used as a self-administered patient-controlled analgesic for managing acute pain, including that caused by dental procedures, reduction of fractures, dressing changes and other procedures of short duration.[17] Its effectiveness and safety has popularized its use in the setting of obstetrics, paediatrics, trauma, prehospital care and even acute myocardial infarction.[4,5]

Nitrous oxide has been employed in the cancer setting for refractory pain, including that experienced by children.[7,18] The use of nitrous oxide for the treatment of incident pain has been reported in two small case series, with mixed results. Keating found self-administered nitrous oxide to be effective as a supplement to long-acting opioids in six patients with poorly controlled cancer pain.[8] Side effects were found to be insignificant, and environmental exposure to the gas minimal. Enting *et al.* found the anticipatory use of nitrous oxide for incident pain to be ineffective in five patients, while its use to treat breakthrough pain in a second subset of five patients was more effective.[9] Neither of these series were controlled, nor was a placebo drug used. In the current study, five of seven patients showed an overall effectiveness of nitrous oxide as compared with placebo, when used preemptively.

A number of factors may play a role in the inconsistent effectiveness of nitrous oxide in this setting. Terminally ill cancer patients comprise a very heterogeneous population, with variable stages and origins of disease.[19] These patients also exhibit different pain syndromes, which are variably responsive to opioids and other coanalgesics. In addition, most patients in our series had been admitted for nonpharmacologic treatments, primarily local radiotherapy, which may also have an important effect in reducing incident pain symptoms. Thus a very large population would be necessary to gain statistically relevant data, with control for the multiplicity of factors involved in their pain experience. For this reason,

statistical analysis was deemed not to be appropriate for most of the endpoints in the current case series, and the results are presented descriptively.

Despite the many years of use, the exact mechanism of action of nitrous oxide induced analgesia is still unclear. A number of investigators have examined the possible sites of action. As the opiate receptor antagonist naloxone has been shown to antagonize the analgesic effect of nitrous oxide, nitrous oxide has been assumed to act on opiate receptors, or via the release of endogenous opioids such as endorphins.[20] However, other studies have questioned the ability of naloxone to reverse the anaesthetic effects of nitrous oxide.[21,22] As with opioids, tolerance also appears to develop to the analgesic effects of nitrous oxide after chronic administration.[23] In addition, animals chronically exposed to nitrous oxide exhibit withdrawal symptoms upon its discontinuation, although this syndrome shares features with alcohol rather than opiate withdrawal.[24]

Bearing in mind the postulated effect of nitrous oxide on the opiate system, it is unclear whether cross-tolerance occurs between nitrous oxide and opioid drugs.[23] If cross-tolerance occurs, it may be assumed that the analgesic effect of acutely administered nitrous oxide in patients chronically receiving opioids may be reduced. In this way, opioid-tolerant patients may require unacceptably high concentrations of nitrous oxide to achieve sufficient analgesia. Although cross-tolerance has not been proven in a controlled environment in human subjects, clearly some subjects on chronic opioid therapy derive some benefit from using nitrous oxide at a concentration of 50%.

In conclusion, self-administered nitrous oxide can be an effective analgesic modality for terminally ill cancer patients experiencing incident pain. Side effects are minimal, and no persistent sedation occurs. Although effectiveness has been shown to be inconsistent, likely due to the heterogeneity of this patient population, a trial of self-administered nitrous oxide should be considered in patients with incident pain.

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Appendix A – Assessments and endpoints

Baseline assessments at the time of enrolment

1) Folstein Mental Status Exam (score <24 excludes patient)
2) Short-form McGill Pain Questionnaire[25]
3) Baseline pain scores (as below)
4) Baseline drowsiness score
5) Edmonton Staging System for cancer pain.[26]

Study endpoints

1) Pain assessment. 11-point numeric score with verbal anchors (0 = no pain to 10 = worst imaginable pain)
   a) at baseline, immediately prior to each use of the study gas and
   b) the maximum pain experienced during the incident, determined 10 min after discontinuation of the gas.
2) Drowsiness assessment.
   a) Patient: 10 min after discontinuation of study gas (10 cm visual analog scale; 0 = 'wide awake' and 10 = 'almost asleep')
   b) Research nurse: during the use of study gas (maximal score on 5 point Observer Scale of Sedation (1 = wide awake; 2 = slightly drowsy; 3 = dozing intermittently, easy to rouse; 4 = asleep, difficult to rouse; 5 = unresponsive).
3) Physiologic parameters. Respiratory rate and heart rate and blood pressure prior to, immediately following and 10 min after discontinuation of each use of study gas.
4) Folstein Mental Status Exam
   a) Prior to enrolment
   b) At 08:00 h on each study day
   c) Thirty minutes after the first use of each study drug
   d) At the end of each study day – at least 30 min after last use of study drug.
5) Satisfaction interview (at completion of the two-day protocol)
   a) Overall, on which study day was the patient found most comfortable
   b) Side effects or difficulties using study drugs.
6) Breakthrough opioids. The drug, and the number, total dose, and timing of requests for breakthrough doses.