HYPERALGESIC RESPONSE IN A PATIENT RECEIVING HIGH CONCENTRATIONS OF SPINAL MORPHINE

To the Editor.—A recent article by Yaksh et al. demonstrated that the intrathecal administration of high concentrations of morphine in experimental animals resulted in a profound agitation response that was associated with hyperesthesia. We report here a hyperalgesic response in a patient with terminal cancer who required high doses of intrathecal morphine for the management of pain.

REPORT OF A CASE

A 63-year-old woman suffering from recurrent pelvic squamous cell carcinoma presented with intractable pain in the distribution of the right sciatic nerve. The pain was refractory to high doses of systemic analgesics. She subsequently underwent the placement of an intrathecal catheter and an Infusaid* pump. During the patient’s remaining 9 months of life, intrathecal morphine was continuously infused for pain relief. The pain had been shooting in character and was initially controlled by intrathecal morphine 1 mg/day. However, recurrence of pain necessitated a gradual increase of morphine dosage over a 9-month period to a maximum of 68.4 mg/day delivered in a concentration of 38 mg/ml at a pump flow rate of 1.8 ml/day. Five months after the initiation of intrathecal morphine treatment (at a dose of 32 mg/day delivered in a concentration of 16 mg/ml at a pump flow rate of 2 ml/day), the patient started to complain of a new type of burning pain in the same lower extremity. Hyperesthesia was manifested in the whole extremity; there was no similar sensation in the other extremity. Burning pain was intermittent and refractory to increasing doses of intrathecal morphine; it was partially relieved by the addition of systemic methadone, amitriptyline, and ibuprofen. There was no evidence of thrombophlebitis in the extremity.

DISCUSSION

We did not observe similar hyperalgesic responses in three other patients who received comparable high concentrations of intrathecal morphine over 2-, 4-, and 10-month periods. We cannot determine whether the hyperesthesia noted in this patient is analogous to that reported by Yaksh et al. or alternatively represents progression of the disease, inflammation, or other neurologic dysfunction.

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PHARMACOKINETIC DIFFERENCES COULD EXPLAIN THE LACK OF REVERSAL OF NITROUS OXIDE ANALGESIA BY LOW-DOSE NALOXONE

To the Editor.—The recent report by Willer et al. is of interest; however, the conclusion that nitrous oxide does not produce its analgesic effects on the blink reflex through an interaction with the endogenous opioid system is open to question. The main problem is related to the effectiveness of naloxone as an opioid antagonist in the dose used and the manner of administration. We have shown that the effect of naloxone on nitrous oxide analgesia at doses below 2 mg, even when given as a bolus, decays rapidly and disappears within 10 min. This is not surprising because the concentration of naloxone in the brain rises and falls rapidly after intravenous administration. For this reason a low dose of naloxone given slowly over 2–4 min may not have been sufficient to antagonize the effects of nitrous oxide, which was given continuously and would be expected to have a constant high concentration at the opioid receptor. Apart from this, not all opioid receptors are equally susceptible to
antagonism by naloxone. For instance, the delta opioid receptor (with which nitrous oxide interacts) is much more resistant to naloxone antagonism than the mu receptor with which the gas has also been shown to interact. For this reason it is important to appreciate that naloxone up to a dose of 0.3 mg/kg has been shown to act as a specific opioid antagonist using pharmacologic criteria. Although it is not clear from their description whether naloxone was given as a bolus, much larger doses (4–8 mg) of naloxone were used by Yang et al. for successful reversal of nitrous oxide analgesia than were used by Willer and his co-workers.

Another point worth noting is that the R2 reflex involves a multisynaptic pain pathway that was reported to be more depressed by the nitrous oxide than the oligosynaptic pathway mediating the R1 reflex. This could, in itself, indicate that analgesic nitrous oxide was acting on opioid pathways, because such multisynaptic pathways (particularly those in the mesencephalic reticular formation) are rich in opioid peptides and receptors, whereas this is not the case with oligosynaptic pathways.

Finally, the statement that the data presented are consistent with those of Smith et al. is also debatable because the loss of righting reflex measured by Smith et al. would more correctly be associated with anesthesia rather than analgesia. This distinction is of considerable importance because anesthesia and analgesia (the subject of the work under discussion) are quite different states. For this reason the underlying mechanisms involved in producing these clearly distinguishable phenomena may be quite different.

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Lower Lip Numbness Following General Anesthesia

To the Editor:—We have recently observed transient numbness of the lower lip in two patients following general anesthesia. To our knowledge, this has not previously been reported. The following are the case reports.

REPORT OF TWO CASES

Case 1. A 44-yr-old woman with menometrorrhagia was scheduled for dilatation and curettage under general anesthesia. She had no prior history of medical problems. The preoperative findings were as follows: blood pressure 130/70 mmHg, heart rate 86 beats/min, serum sodium 141 mEq/l, and serum potassium 4.2 mEq/l. The patient was premedicated with droperidol 1.25 mg and fentanyl 0.1 mg iv a few min before induction of anesthesia. Anesthesia was induced with sodium thiopental 350 mg iv and maintained with nitrous oxide-oxygen and isoflurane administered by mask. A plastic oropharyngeal airway was used. The procedure lasted 30 min, and recovery from anesthesia was uneventful.

On the day following surgery the patient noticed numbness of the lower lip; she could sense neither temperature nor touch with the lip. When she drank, the fluids would spill from both corners of her mouth.