

Letter to the Editor

Continuous hydromorphone infusion for opioid intolerance

To the Editor:

Pseudoallergic reactions to opioids occur secondary to non-IgE mediated release of mediators from mast cells and basophils. The exact mechanism by which this occurs is unclear but may involve phospholipase C and phospholipase A2 dependent mechanisms.¹

Treatment of patients with pseudoallergic reactions to opioids has focused on 3 principles: (1) substitution of nonopioid medications for opioid medications, (2) identification of an opioid tolerated by individual patients, and (3) administration of antihistamines before and during administration of opioids.^{2,3} Although these methods are effective in the treatment of most patients, there are some patients for which these methods are inadequate. This may be a result of the presence of a clinical situation in which nonopioids are not a viable option, no well tolerated opioids are identifiable, or premedication with antihistamines is ineffective. Evaluation of these patients is further complicated by the fact that skin prick testing has no utility in the evaluation of opioid intolerance because skin test results are not significantly different in opioid-intolerant patients compared with opioid-tolerant patients.⁴ We present the case of a patient with opioid intolerance who was not able to be treated by standard methods yet required multiple major surgeries and opioids for postoperative pain control.

The patient was a 22-year-old woman with meningo-myelocele and hydrocephalus who had undergone 10 neurosurgical procedures since birth for repair of the meningo-myelocele and management of the hydrocephalus, including the placement of a ventriculoperitoneal shunt. The patient had a history of seasonal allergic rhinitis and developed a latex allergy in early childhood, manifesting as anaphylaxis. Beginning at 15 years of age, the patient began developing adverse reactions to opioids used for postoperative pain management. These reactions were similar regardless of the opioid administered and consistently manifested as pruritis and urticaria with the occasional occurrence of dyspnea. Reactions to opioids administered intravenously (fentanyl, hydromorphone, meperidine, and morphine) were all witnessed by the treating physicians while the patient was hospitalized for surgical procedures. These reactions occurred within minutes of the administration of the opioid and recurred each time a dose was administered. The reactions continued when other potential causative agents, such as antiemetics and postoperative antimicrobials given during the same time frame as the opioids, were withheld. The surgical team attempted to manage these adverse reactions by administering a different opioid after each surgery and by transitioning to oral formulations (oxycodone, codeine, propoxyphene) early in the postoperative period, yet the patient developed symptoms with all the opioids administered. Antihistamine therapy given concomitantly

TABLE I. Intravenous fentanyl challenge protocol

Dose #	Time (min)	Fentanyl intravenous (μg)
1	0	0.0002
2	15	0.0004
3	30	0.0008
4	45	0.0016
5	60	0.003
6	75	0.006
7	90	0.012
8	105	0.025
9	120	0.05
10	135	0.1
11	150	0.2
12	165	0.4
13	180	0.8
14	195	1.5
15	210	3
16	225	6
17	240	12
18	255	25

with the opioids was ineffective at preventing or lessening the severity of symptoms that occurred immediately after opioid administration, but antihistamine therapy was effective at decreasing the severity of the pruritis and urticaria in between scheduled doses of opioids.

The patient was admitted to the neurosurgical service with headache, dizziness, nausea, and emesis secondary to a malfunctioning ventriculoperitoneal shunt. A shunt revision was deemed necessary, but the surgical service would not proceed with this procedure because of the risk of a pseudoallergic reaction to the opioid medications that would be required postoperatively for pain management. A nonopioid medication was determined to be inadequate for pain control for the proposed procedure, and all opioid medications that could potentially be used in this situation were previously used and associated with a pseudoallergic reaction even when administered with antihistamines.

Allergy/immunology consultation was requested to manage the opioid intolerance. In a monitored environment, the patient was given escalating doses of fentanyl intravenously in an attempt to determine a highest tolerated dose (Table I). The patient developed fleeting urticarial lesions and generalized pruritis, which improved with the initiation of hydroxyzine 50 mg intravenously every 6 hours. She tolerated doses of 0.5 μg/kg with a cumulative administered dose of 50 μg without dyspnea or further progression of symptoms. Given that pseudoallergic reactions to opioids are frequently dose-dependent^{5,6} and that continuous intravenous administration of opioids can potentially reduce the total dose required for analgesia by nearly 50% in comparison with intermittent dosing,⁷ it was decided to place the patient on a continuous fentanyl infusion at 0.25 μg/kg/h in an attempt to avoid high-dose fentanyl boluses postoperatively for pain control. The patient was maintained at this dose for 8 hours and then

TABLE II. Oral hydromorphone challenge protocol

Dose #	Time (min)	Hydromorphone oral (μ g)
1	0	0.008
2	15	0.015
3	30	0.03
4	45	0.06
5	60	0.12
6	75	0.24
7	90	0.5
8	105	1
9	120	2
10	135	4
11	150	8
12	165	16
13	180	32
14	195	64
15	210	125
16	225	250
17	240	500
18	255	1000

taken to the operating room, where the drip was continued during the procedure.

The operation was successfully completed, but in spite of increasing the rate of the fentanyl infusion, bolus doses were required for pain control postoperatively, which led to worsening pruritis, urticaria, and mild dyspnea without wheezing. The addition of regularly scheduled diphenhydramine improved the patient's pruritis and urticaria. Furthermore, the addition of acetaminophen achieved adequate pain control so that bolus doses of fentanyl were no longer needed. The patient was eventually discharged home with transdermal fentanyl, oral fentanyl for breakthrough pain, acetaminophen, and hydroxyzine. The patient was already in possession of self-injectable epinephrine because of her latex allergy, and she was familiar with its use in the event that she developed dyspnea secondary to the fentanyl after discharge. The patient reported only pruritis and intermittent, mild urticaria with the use of the transdermal fentanyl patch in association with scheduled hydroxyzine. In addition, she did not require the use of the oral fentanyl because her pain was adequately controlled with the transdermal formulation.

Three months after discharge, the patient was readmitted to the hospital for another shunt revision. Because doses of fentanyl necessary for pain control were not previously well tolerated, it was decided to attempt the administration of hydromorphone based on the patient's report that this medication provided excellent pain control in the past. The patient was premedicated with diphenhydramine and hydroxyzine, and escalating doses of hydromorphone were administered (Table II). The patient tolerated as much as 1 mg with the development of generalized pruritis but no urticaria or dyspnea. She was started on a continuous hydromorphone infusion at 0.2 mg/h and was maintained at this dose and taken to the operating room 8 hours later. The operation was once again

successfully completed, but the patient was inadvertently administered a bolus dose of 1 mg hydromorphone in the postanesthesia care unit in addition to the continuous infusion. This led to severe dyspnea requiring the administration of epinephrine intramuscularly. No further bolus doses were administered after this event, and the patient's pain was well controlled by increasing the infusion rate by 0.05 mg/h as needed, to a maximum of 0.35 mg/h, plus the addition of acetaminophen. After achieving adequate pain control, the drip rate was decreased by 0.05 mg/h every 8 hours to a minimum dose of 0.05 mg/h. Attempting to wean at a faster rate or discontinuing the drip at a higher dose of hydromorphone led to loss of pain control.

The patient has since been readmitted for repeat neurosurgical procedures, and after premedication with diphenhydramine and hydroxyzine, she has been placed immediately on a continuous infusion of hydromorphone at 0.2 mg/h with rate increases and decreases as noted above. She is able to maintain good pain control with this regimen and does not develop significant adverse events.

To our knowledge, this is the first report of the use of continuous opioid infusions to provide analgesia in an opioid-intolerant patient. This report demonstrates that patients who fail to respond to traditional measures for the prevention of pseudoallergic reactions secondary to opioid medications and who have an absolute need for this class of medication may tolerate continuous opioid infusions with slow dose escalations. Continuous infusions may be superior to bolus doses of opioids, such as in patient-controlled analgesia, because histamine release from mast cells secondary to opioids is dose-dependent, and the total dose of opioid administered and peak serum concentrations attained are less with continuous infusions than with bolus doses.^{5,6} In the case of hydromorphone, serum hydromorphone concentrations of at least 4 ng/mL are required for adequate analgesia.⁸ To achieve this goal, dosing guidelines recommend hydromorphone infusion rates of up to 0.2 mg/h with the addition of bolus doses as needed.⁹ Because bolus doses of opioids may lead to pseudoallergic reactions in opioid-intolerant patients, higher infusion rates than those routinely recommended may be required to achieve adequate pain control.

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REFERENCES

1. Veien M, Szlam F, Holden J, Yamaguchi K, Denson DD, Levy JH. Mechanisms of nonimmunological histamine and tryptase release from human cutaneous mast cells. *Anesthesiology* 2000;92:1074-81.
2. Joint Council of Allergy Asthma and Immunology. Practice parameters for drug hypersensitivity. *Ann Allergy Asthma Immunol* 1999;83:S665-700.
3. Grammer LC, Greenberger PA. Individual drugs or problems: summary of useful techniques. *Allergy Asthma Proc* 2005;26:66-72.
4. Nasser SMS, Ewan PW. Opiate-sensitivity: clinical characteristics and the role of skin prick testing. *Clin Exp Allergy* 2001;31:1014-20.
5. Ebertz JM, Hermens JM, McMillan JC, Uno H, Hirshman C, Hanifin JM. Functional differences between human cutaneous mast cells and basophils:

- a comparison of morphine-induced histamine release. *Agents Actions* 1986; 18:455-62.
6. Hermens JM, Ebertz JM, Hanifin JM, Hirshman CA. Comparison of histamine release in human skin mast cells induced by morphine, fentanyl, and oxymorphone. *Anesthesiology* 1985;62:124-9.
 7. White PF. Use of continuous infusion versus intermittent bolus administration of fentanyl or ketamine during outpatient anesthesia. *Anesthesiology* 1983;59:294-300.
 8. Reidenberg MM, Goodman H, Erle H, Gray G, Lorenzo B, Leipzig RM, et al. Hydromorphone levels and pain control in patients with severe chronic pain. *Clin Pharmacol Ther* 1988;44:376-82.
 9. Thompson Micromedex Healthcare Series DRUGDEX Evaluation [database on internet]. Greenwood Village (CO): Thomson Healthcare, Inc; 1974-2006. Available at: <http://www.thomsonhc.com/home/dispatch>. Accessed February 20, 2006.

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