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Chronic Epidural Morphine and Preservative-induced Injury

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Chronic self-administered epidural morphine is frequently used to control cancer pain.[1,2] Certain morphine products containing toxic preservatives should probably be avoided. The lack of awareness on the part of some physicians and pharmacists, not familiar with the technique, may result in patient injury from phenol and formaldehyde in the epidural space. Although potential problems have been described,[3] there have been no reports regarding preservatives found in American generic substitutes for morphine used in epidural analgesia. The following case report exemplifies the complications encountered following chronic phenol and formaldehyde epidural administration.

CASE REPORT

A 50-yr-old patient with pancreatic carcinoma was admitted for pain control to another hospital. He received a temporary, tunnelled lumbar epidural catheter, and received 8 mg of Duramorph™ every 12 h, with excellent pain control. Ten days after discharge, he received a non-specific prescription from his local physician, and the rural pharmacy gave him a generic morphine-substitute which would save him money. The morphine was to be diluted with 9 ml of saline drawn from a 1000-cc bag of normal saline, instead of using single-use 10-ml vials of preservative-free saline. During injection of the first dose, he noted a burning sensation, but continued the therapy as directed. Repeat doses resulted in similar discomfort, but did not give the same degree of pain relief as he had previously received. He was advised to increase the dose, as tolerance was thought to be occurring. After 10 days of home treatment and ever-increasing doses, he was referred to our hospital receiving 30 mg of epidural generic morphine every 4 h.

On admission, his confusion and disorientation were assumed to be secondary to the high dose of morphine. The epidural injections were discontinued and iv phenol and formaldehyde-free morphine sulfate was infused at 8 mg/h with excellent pain relief. An epidurogram showed the catheter in the epidural space, and some non-specific areas of flow restriction were noted when compared to preoperative epidurograms.

Examination of the generic morphine sulfate 1 ml vial produced by Elkins-Sinn, Inc., that he received revealed a content of 2.5 mg of phenol and 2.8 mg of formaldehyde in each ml containing 15 mg of morphine sulfate (table 1). This amount to a total dose of 5 mg of phenol and 5.6 mg of formaldehyde with each epidural injection of 30 mg of morphine sulfate, or 30 mg of phenol and 33.6 mg of formaldehyde per day. There were no clinical signs of sensory or motor loss detected on admission or after mental clearing.

After 3 days, the 23-day-old temporary epidural catheter was replaced with a permanent silicone-rubber lumbar epidural catheter (Davol-investigational permanent epidural catheter). Postoperative epidurograms showed epidural positioning, good flow, and the catheter tip at the T-6 vertebral level. Epidural morphine self-administration was restarted using 10 mg of Tubex morphine sulfate (Wyeth, Philadelphia, PA), diluted with 10 ml of preservative-free normal saline, every 8 h. Pain relief was reinstated and, after extensive instruction, he was discharged home and has been receiving this dose for the past 62 days.

DISCUSSION

The cost of medical care and medication can easily exceed the financial resources of the terminal cancer patient. Responding to these pressures, physicians and pharmacists use generic substitutes for higher-cost drugs. In this case report, the choice of a generic substitute of morphine containing both phenol and formaldehyde resulted in both central nervous system and local epidural tissue toxicity. There is little information on the central nervous system effects of chronic epidural formaldehyde, other than the neurobehavioral symptoms seen during chronic work exposure,[4] but phenol stimulates the central nervous system at low doses and, at high doses, has a depressant effect.[5] After admission, the 180 mg/day of preservative containing epidural morphine was replaced with 192 mg/day of preservative-free iv morphine with reinstatement of pain relief and clearing of disorientation and mental confusion. Therefore, the confusion and disorientation exhibited by this patient on admission were probably secondary to the chronic administration of these preservatives on the central nervous system.

Duramorph™ (Elkins-Sinn, Inc., Cherry Hill, NJ) is considered the industry standard for intraspinal administration, due to its preservative-free preparation. Duramorph was produced for postoperative use and, thus, has limited use for cancer pain because of its fixed concentration (1 mg per ml) and hospital cost of $7.41 for a 10-ml ampul; using this drug can cost as much as $1800

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TABLE 1. Commercially Available Morphine Products and Their Cost and Perservatives

Drug	Company	Cost per MG*	Preservatives
Duramorph™ PF	Elkins-Sinn, Inc. (10 mg/10 ml ampule)	$0.74	None
Morphine sulfate	Eli Lilly, and Co. (15 mg/ml, 20 ml vial)	$0.025	Chlorobutanol 0.5%, sodium bisulfite 0.1%
Morphine sulfate	Wyeth (15 mg/ml, 1 ml Tubex™)	$0.034	Chlorobutanol 0.5% edetate disodium 1%
Morphine sulfate	Winthrop (15 mg/ml, 1 ml syringe)	$0.042	Sodium biphosphate 8 mg, sodium metabisulfite 1 mg, sodium formaldehyde 1 mg, phenol 5 mg
Morphine sulfate	Elkins-Sinn, Inc (15 mg/ml, 1 ml vial)	$0.030	Phenol 2.5 mg, formaldehyde 2.8 mg
Morphine sulfate	I.M.S. (Select-A-Jet™ 100 mg/4 ml)	$0.025	Sodium bisulfite 0.1%

* Cost calculated from AMFAC Healthcare Co., February, 1987, Master Product Pricing List. Prices converted from unit price to $/mg for comparison. AMFAC—Health Care Co., 81 Blue River Road, Folsom, California 95630.

a month if doses reach 15 mg every 6 h (table 1). Due to these restrictions, substitute morphine preparations, such as Tubex™ morphine (Wyeth) have been used to obtain higher concentrations and cost savings.[2] The preservative chlorobutanol (a derivative of chloroform) in Tubex™ morphine (Wyeth) has not been shown to have neurotoxic properties. We have found that the simplicity of the Tubex™ delivery system has aided patient teaching, especially in the elderly non-medically oriented patients. Our experience with chronic Tubex™ morphine administration has resulted in no complications during 15,023 catheter-days of use and 57,087 injections with serial epidurograms to appraise epidural space continuity.[2]

Other companies, including Eli Lilly, Winthrop, Elkins-Sinn, and International Medication Systems (IMS, South El Monte, CA), also market other morphine sulfate products (table 1). IMS stands alone in marketing a high-concentration morphine sulfate syringe system designed to assist pharmacists in preparing intravenous infusion solutions. This system, using a 25-mg/ml morphine concentration, may be easily adapted for epidural use in patients requiring morphine doses over 25 mg. The concentration of sodium bisulfite used by both Lilly and IMS in their products is below the 2 mg/ml concentration incriminated in the early Nesacaine products as causing both spinal cord and nerve root injury.[6] Astra currently markets Nesacaine with 0.7 mg/ml sodium bisulfite, which is felt to be a non-toxic concentration. Lilly and IMS include sodium bisulfite in concentrations not to exceed 1 mg/ml. Table 1 outlines the confusing choices encountered by both physicians and pharmacists when attempting to find a drug to prescribe for epidural administration. The ideal product would have the advantages of the Tubex™ system for teaching, the lack of preservatives in Duramorph™, and the price of the generic substitutes.

The economic pressure, along with requirements for high narcotic concentrations not available from Duramorph™, have forced physicians and pharmacists to use generic morphine substitutes for epidural analgesia. We currently use Tubex™ morphine (Wyeth) as our drug of choice, due to its ease of use; Lilly morphine is used by patients more familiar with drug preparation procedures for cost savings. When faced with morphine doses above 25 mg, or when mixing epidural morphine infusion solutions, we use the IMS morphine system.

This clinical report will give physicians and pharmacists involved in the care of the terminally ill a better understanding of the choices and risks when prescribing epidural morphine generic substitutes. A patient education program with written instructions will allow patients to protect themselves from the risk of neurotoxicity from preservatives in some generic narcotic products, and give the primary physician a guide to follow in prescribing future drugs.

REFERENCES

1. Cousins MJ: Intrathecal and epidural administration of opioids. ANESTHESIOLOGY 61:276–310, 1984
2. Du Pen SL, Peterson DG, Bogosian AC, Ramsey DH, Larson C, Omoto M: A new permanent exteriorized epidural catheter for narcotic self-administration to control cancer pain. Cancer 59:986–993, 1987
3. Mathews E: Epidural Morphine. Lancet 1:673, 1979
4. Kilburn KH, Warshaw R, Boylen CT, Johnson S, Seidman B, SinClair R, Takaro T: Pulmonary and neurobehavioral effects of formaldehyde exposure. Archives of Environmental Health 40:254–260, 1985
5. Klaassen CD: Nonmetallic environmental toxicants: Air pollutants, solvents and vapors, and pesticides, The Pharmacological Basis of Therapeutics, 7th edition. Edited by Goodman LS, Gilman AG. New York, Macmillan Publishing Company, 1985 pp 1628–1638
6. Wang BC, Hillman DE, Spielholz NI, Turndorf H: Chronic neurological deficits and nesacaine-CE—An effect of the anesthetic, 2-chloroprocaine, or the antioxidant, sodium bisulfite? Anesth Analg 63:445–447, 1984