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Pharmaceutical update

The conversion challenge: From intrathecal to oral morphine

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Abstract

Numerous articles have described the methodologies used and outcomes achieved with the intrathecal (IT) administration of morphine for pain. However, only one case report has been published that describes converting a patient's IT morphine to an oral regimen. This case report describes the experience of converting a patient's IT morphine to oral morphine and discusses the scarcity of published data to validate suggested equianalgesic intraspinal morphine recommendations. The calculated

equianalgesic oral to IT ratio in this case was 12:1. This is substantially lower than the 300:1 ratio published by Krames and the 90:1 ratio employed by a commercially available software program for calculating equianalgesic opioid doses. We recommend caution when applying existing guidelines for conversion of morphine from an IT to an oral regimen.

Key words: intrathecal morphine, intraspinal morphine, equianalgesic doses, dosage conversion, equianalgesic conversion

Introduction

Administration of intrathecal (IT) morphine has become an accepted treatment option for selected patients with chronic pain. Numerous articles have described the methodologies and outcomes achieved in patients treated with IT morphine.¹⁻¹⁹ However, a MEDLINE search revealed only one citation that described the conversion

of a patient's IT morphine to an oral regimen. That report described a patient converted from IT morphine to oral methadone.²⁰ Our case report describes the experience of converting a patient's IT morphine to oral morphine and discusses the scarcity of published data to validate suggested equianalgesic intraspinal morphine recommendations.

Case report

A 60-year-old female nursing home resident with a 10-year history of multiple sclerosis was admitted to hospice after she decided to forgo replacing a battery in her implanted Synchronmed infusion system (Medtronic, Inc., Minneapolis, MN). She had the pump implanted five years ago for the treatment of chronic spinal pain unresponsive to oral morphine. Her pump was programmed to deliver morphine sulfate 12.5 mg, baclofen 125 mcg, clonidine 50 mcg, and

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300 mg oral morphine, equals
100 mg parenteral morphine, equals
10 mg epidural morphine, equals
1 mg intrathecal morphine

bupivacaine 4 mg intrathecally over 24 hours by continuous infusion. This regimen had been stable for the past nine months. In addition, she was also taking atenolol 25 mg qd, gabapentin 800 mg qid, tizanidine 4 mg q8h, sertraline 25 mg, furosemide 20 mg qd, tolterodine 2 mg bid, amitriptyline 75 mg qhs, dietary fiber 3 g tid, bisacodyl suppository prn, and morphine oral solution 5 mg q30min for breakthrough pain. Review of her medication administration record revealed that for the two weeks preceding the end of the intrathecal regimen, her daily dose of oral morphine was consistently 10 to 15 mg.

The IT morphine and baclofen were to be replaced orally. The pain clinic managing her treatment recommended an oral morphine equianalgesic dose of 1,080 mg/d. This estimate was substantially below equianalgesic opioid

conversion guidelines published by Krames¹⁰ (3,750 mg/d) as shown in Table 1 and within the range calculated by the Cynergy Group Opioid Calculator²¹ (1,125 mg/d).

The Cynergy Group Opioid Calculator provides conversion details for calculations performed by the program. Table 2 is a reproduction of the conversion detail provided for this patient's calculation.

We chose to take a cautious approach when converting our patient from IT to oral morphine for several reasons. First was the lack of literature and experience documenting the safety of using available equianalgesic dosage estimates to convert morphine from an intraspinal to a systemic route of administration. The equianalgesic ratios recommended by Krames and the Cynergy Group Opioid Calculator are for converting morphine from systemic

to intraspinal administration, not from intraspinal to systemic. The three-fold difference in the calculated equianalgesic oral doses (1,125 mg/d versus 3,750 mg/d) provided additional reason to question the reliability of these estimates. Furthermore, neither recommendation cites published data to support the recommendations (i.e., the number of patients studied; calculated mean or median equianalgesic doses with standard deviations). Also, the nurse noted increasing drowsiness several days preceding the termination of the pump.

Two days before the IT morphine infusion was terminated, the patient was started on morphine 15 mg sustained-release tablet every eight hours and 5 mg morphine solution every 30 minutes for breakthrough pain. Oral baclofen 20 mg qid was also started. Dose titration was based on the patient's comfort level utilizing a 0 to 5 point visual analog scale (VAS). The patient's stated goal for acceptable pain management is 1 to 2.

The patient received a total of 70 mg of oral morphine on the day that IT morphine infusion stopped. The patient's dose was titrated upwards based on the daily amount of morphine taken for breakthrough pain. Within two weeks, her daily dose

The equivalencies used for converting to morphine PO are given below	
Conversion from morphine IT	Source
Morphine 3.3 mg EP = morphine 0.33 mg IT	Consensus/anecdotal
Morphine 10 mg IV/SQ/IM = morphine 3.3 mg EP	<i>Principles of Analgesic Use in the Treatment of Acute and Cancer Pain, 4th edition.</i> Skokie, Illinois: American Pain Society, 1999.
Morphine 30 mg PO = morphine 10 mg IV/SQ/IM	Management of Cancer Pain; Clinical Practice Guideline Number 9. Agency for Health Care Policy and Research; Publication No. 94-0592. Rockville, MD: US Dept. of Health and Human Services, March 1994.

plateaued at 150 mg of extended-release morphine with infrequent need for breakthrough doses. At no time did the patient report any intolerable pain or symptoms of opioid withdrawal. The highest VAS pain score recorded for the patient during this time was 3 (Table 3).

Discussion

The IT administration of morphine to treat patients with chronic malignant pain was first reported by Wang in 1977.¹ In 1981, Onofrio et al.² published the first case of administration of IT morphine by continuous infusion using an implantable pump. Subsequently, numerous researchers and clinicians documented the effectiveness of IT morphine for treating refractory chronic pain of malignant and nonmalignant origin.³⁻¹⁹

However, when faced with the challenge of converting a patient's morphine from an IT to an oral regimen, a MEDLINE search did not identify any primary literature that addressed this issue. The preservative-free morphine sulfate (Duramorph[®]) package insert does not include any information regarding the conversion of IT morphine to parenteral or oral morphine. It does contain the following statement, **Note: Intrathecal dosage is usually 1/10 of the epidural dosage.**²⁴ We called the manufacturer and asked for the primary literature supporting that ratio. The manufacturer's representatives said that the ratio was based on anecdotal reports and they did not have any clinical data to provide us in support of it. Krames¹⁰ does not cite or provide any clinical data documenting the ratios published in his practice guidelines, but states those ratios represent "the intraspinal conversion that we use in our clinic for morphine."

Our review of the literature did not discover any persuasive data to corroborate the ratios published by

Krames. Gourlay et al.⁷ reported that a five- to 10-fold reduction in a patient's morphine dose usually occurred when the route of administration was changed from an epidural to IT route. One of their patients achieved a 25-fold reduction in morphine dosage after conversion to IT administration. Samuelsson et al.²² summarize nine years of experience with epidural morphine administration. They reduced a patient's morphine requirement "three-fold when changing treatment from oral or parenteral to epidural."

Kalso et al.²³ conducted a randomized, double-blind and crossover study comparing the effectiveness of epidural and subcutaneous morphine in 10 patients suffering from severe cancer-related pain. They reported that the median subcutaneous to epidural ratio was 3:1, with individual ratios ranging from 1:1 to 10:1. Du Pen and Williams⁸ noted that experts had proposed systemic to epidural conversion ratios "diverse as 10:1, 10:2, and 10:5 but have neither established validity nor elicited consensus." They proposed a model for converting systemic to epidural morphine that factors in the variables of pain severity, age, previous systemic dosage, and presence of neuropathic pain. They concluded that their individualized epidural morphine conversion tool (IEMCT) required further study to firmly establish its validity and reliability.

Sarvela et al.²⁵ compared the effectiveness of single injections of morphine administered as 100 µg IT, 200 µg IT, or 3 mg epidural in 150 patients undergoing elective cesarean delivery. The study was double-blinded and randomized. They reported that pain relief was reported as good by > 90 percent of patients in all groups. The clinical guidelines for intraspinal infusion published by an interdisciplinary panel with extensive clinical experience with intraspinal infusion therapy noted "large practice variation in virtually all

aspects of intraspinal dosing." Perhaps that explains why the guidelines did not address equianalgesic intraspinal morphine doses.¹⁹

After finding no reliable published clinical data to support existing intraspinal conversion ratios, we opted to convert our patient to a low, scheduled dose of sustained release morphine with liberal allowance for morphine sulfate solution for breakthrough pain. Our rationale was to avoid the potential dangers of central nervous system depression. In the weeks following the termination of the patient's IT morphine, her oral dose of morphine was titrated upwards and plateaued at a total 24-hour dose of 150 mg. The calculated equianalgesic oral to IT dose ended up being 12:1. This is substantially lower than the 300:1 ratio published by Krames¹⁰ and the 90:1 ratio employed by the Cynergy Group Opioid Calculator.²¹

Whether the patient would have experienced significant respiratory depression if administered the estimated equianalgesic oral morphine doses calculated using the Cynergy (1,125 mg/d) or Krames (3,375 mg/d) equianalgesic ratios is not known. However, the large discrepancy between these estimated doses and the dose the patient determined was effective gives cause for concern that central nervous system effects including respiratory depression may have resulted.

Several possible explanations may account for this discrepancy. First, pharmacokinetic and pharmacodynamic responses are known to be extremely variable. Perhaps this patient would represent an "outlier" when compared to a larger database. Second, the patient may have developed hyperalgesia while receiving IT morphine which dissipated after conversion to low dose oral morphine and resultant lower morphine cerebral spinal fluid (CSF) levels. Third, it has

Table 3. Intrathecal morphine to oral morphine conversion

Date	Daily extended release dose (mg)	Daily PRN break-through dose (mg)	Total daily dose (mg)	Pain rating (scale of 0 to 5)
6/6/02	15	0	15	3
6/7/02	45	5	50	
6/8/02	45	15	60	
6/9/02*	45	25	70	
6/10/02	60	30	90	2
6/11/02	75	30	105	
6/12/02	75	20	95	
6/13/02	75	30	105	
6/14/02	75	20	95	
6/15/02	75	30	105	
6/16/02	75	20	95	
6/17/02	105	40	145	
6/18/02	120	10	130	
6/19/02	120	10	130	
6/20/02	120	20	140	
6/21/02	135	10	145	3
6/22/02	150	0	150	
6/23/02	150	0	150	
6/24/02	150	0	150	
6/25/02	150	0	150	1 to 2
6/26/02	150	40	190	
6/27/02	150	0	150	
6/28/02	150	0	150	

* pump to run out.

been established that morphine has activity in peripheral tissue.²⁶ If the patient's pain had a significant peripheral locus, higher systemic levels of morphine and its active metabolite morphine-6-glucuronide (M-6-P) would be beneficial. Most likely, when the patient's morphine was converted from IT to oral administration, an

increase in the systemic levels of morphine and M-6-P resulted.²⁷ Finally, when using the Cynergy or Krames equianalgesic ratios for converting doses, one might assume that equianalgesia is the same when converting from the systemic to IT route as from the IT to the systemic route. Perhaps this assumption is incorrect, and the

equianalgesic ratio for converting morphine from systemic to IT administration is substantially different from the equianalgesic ratio for converting from IT to systemic administration. Whether such directional differences in equianalgesia ratios exist remains to be evaluated.

Several weeks after converting our

patient's morphine to an oral regimen a second MEDLINE search identified a recently published case report similar to ours. Gebhardt and Kinney²⁰ reported converting a patient from IT morphine to intravenous morphine and from intravenous morphine to oral methadone without any adverse effects. They employed an equianalgesic conversion ratio of 1 mg IT morphine to 100 mg of parenteral morphine published by Krames (Table 2).

Conclusion

In spite of 35 years of experience with the intraspinal administration of morphine, equianalgesic dose ratios for converting to oral dosage regimens remain to be validated. This is only the second case report to describe the conversion of a patient from IT to an oral opioid regimen. The conversion to an oral morphine regimen beginning with a dosage regimen in the range recommended for opioid-naïve patients was successful. Two weeks after the termination of her IT infusion, the oral morphine dosage for the patient in this study stabilized at 150 mg/d. This dose was substantially less than estimated equianalgesic doses ranging from 1,125 mg/d to 3,750 mg/d that were calculated using current equianalgesic guidelines. Further study is needed to validate safe and effective methods for converting patients from IT to oral morphine. Pending further validation, we recommend caution when applying existing equianalgesic ratios to patients being converted from IT to oral morphine.

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