

Survey of pain specialists regarding conversion of high-dose intravenous to neuraxial opioids

Andrew W Gorlin
David M Rosenfeld
Jillian Maloney
Christopher S Wie
Johnathan McGarvey
Terrence L Trentman

Department of Anesthesiology, Mayo
Clinic Arizona, Phoenix, AZ, USA

Abstract: The conversion of high-dose intravenous (IV) opioids to an equianalgesic epidural (EP) or intrathecal (IT) dose is a common clinical dilemma for which there is little evidence to guide practice. Expert opinion varies, though a 100 IV:10 EP:1 IT conversion ratio is commonly cited in the literature, especially for morphine. In this study, the authors surveyed 724 pain specialists to elucidate the ratios that respondents apply to convert high-dose IV morphine, hydromorphone, and fentanyl to both EP and IT routes. Eighty-three respondents completed the survey. Conversion ratios were calculated and entered into graphical scatter plots. The data suggest that there is wide variation in how pain specialists convert high-dose IV opioids to EP and IT routes. The 100 IV:10 EP:1 IT ratio was the most common answer of survey respondent, especially for morphine, though also for hydromorphone and fentanyl. Furthermore, more respondents applied a more aggressive conversion strategy for hydromorphone and fentanyl, likely reflecting less spinal selectivity of those opioids compared with morphine. The authors conclude that there is little consensus on this issue and suggest that in the absence of better data, a conservative approach to opioid conversion between IV and neuraxial routes is warranted.

Keywords: intrathecal pump, epidural, cancer pain

Introduction

The delivery of neuraxial opioids to treat pain was first described in 1900 with a single injection of intrathecal (IT) morphine.¹ In 1983, Coombs et al published the first case series of a fully implantable drug delivery system to deliver neuraxial morphine to patients with intractable cancer-related pain.² Currently, implantation of IT opioid delivery systems is common therapy for the treatment of intractable malignant and nonmalignant pain. Morphine is the only opioid approved by the United States Food and Drug Administration (FDA) for IT use and is the most commonly prescribed IT opioid. Off-label use of neuraxial hydromorphone and fentanyl is also common.^{3,4} Implantation of epidural (EP) drug delivery systems is another method of administering neuraxial opioids, most commonly for short to intermediate palliation of malignant pain.⁵

Many patients who have IT or EP drug delivery systems implanted are highly opioid tolerant. Clinicians are often faced with the challenge of transitioning these patients from high-dose oral or parenteral opioids to neuraxial formulations after device implantation. Furthermore, reverse conversions (neuraxial to intravenous [IV]) are sometimes necessary if the system's reservoir runs out of medication or following explantation or malfunction. Although there are well-established guidelines for

Correspondence: Andrew W Gorlin
Department of Anesthesiology, Mayo
Clinic Arizona, 5777 West Mayo
Boulevard, Phoenix, AZ 85054, USA
Tel +1 480 342 2446
Fax: +1 480 342 2319
Email gorlin.andrew@mayo.edu

converting from oral to parenteral opioids, there is a lack of evidence-based guidelines to assist clinicians with conversion from parenteral to neuraxial opioids.⁶ Some authors suggest morphine conversion ratios of 100 mg IV: 10 mg EP: 1 mg IT; however, there is no firm scientific basis for those numbers.⁷ Guidelines for hydromorphone and fentanyl are even less established. In the absence of strong scientific data, clinical experience and expert opinion are the only available means to assist practitioners with IV:EP:IT conversions. Our objective is to survey pain physicians regarding how they convert high-dose IV to neuraxial opioids in order to add further substance to existing expert opinion on this clinical problem.

Methods

Approval to conduct this study was obtained from the Mayo Clinic Institutional Review Board. All survey respondents were informed of the authors' intent to use their responses anonymously for academic publication. Focusing on morphine, hydromorphone, and fentanyl, a ten-question survey was developed to assess respondents' opinions regarding conversion of high-dose IV to both EP and IT opioids (Figure 1). We identified 724 pain medicine practitioners and obtained their contact information via personal contacts, Internet searches, and websites of pain organizations. The survey was formatted on surveymonkey.com® (Palo Alto, CA, USA), and the survey link was distributed to potential participants via email. Demographic and practice data were tabulated. The answers to questions 6–8 were transformed into ratios of IV:EP and IV:IT. These ratios were entered into standard graphical scatter plots (Figures 2–4).

Responses on the scatter plots are labeled as being either “aggressive” or “conservative”. We explain this using the following example. For question 6 (Figure 1), if the respondent answers 100 mg/24 h for EP and 10 mg/24 h for IT then the IV:EP and IV:IT ratios are 10:1 and 100:1, respectively. Because the 10:1 and 100:1 ratios are commonly cited in expert opinion (and were the most common answers in our survey), we defined these ratios as the neutral or average response. If the respondent answers 50 mg/24 h and 5 mg/24 h, then the calculated IV:EP and IV:IT ratios are 20:1 and 200:1, respectively. We call that a “conservative” response because the respondent is choosing a lower neuraxial dose of morphine, thus taking a more “conservative” approach. If the respondent answers 200 mg/24 h and 20 mg/24 h, then the IV:EP and IV:IT ratios will be 5:1 and 50:1, respectively. We label this an “aggressive” response because the respondent is choosing a higher neuraxial dose of morphine, thus taking a more “aggressive” approach.

1. How many intrathecal pumps do you manage (not necessarily implant) per year?
 - a. <5
 - b. 5–20
 - c. >20
2. For how many years have you been in practice?
 - a. <5
 - b. 5–20
 - c. >20
3. What is your practice type?
 - a. Academic
 - b. Private practice
 - c. Hybrid of academic and private practice
4. What is your primary specialty?
 - a. Pain management–anesthesiology
 - b. Pain management–physiatry
 - c. Neurosurgery
 - d. Other
5. Where do you practice?
 - a. US–northeast
 - b. US–south
 - c. US–midwest
 - d. US–west
 - e. Other
6. Your patient is on intravenous (IV) morphine 1,000 mg/24 h. In your opinion, what are the epidural and intrathecal equivalents of that dose (ie, the dose that will be equianalgesic after titration and equilibration)?
 - a. Epidural _____ mg/24 h
 - b. Intrathecal _____ mg/24 h
7. Your patient is on IV hydromorphone 100 mg/24 h. In your opinion, what are the epidural and intrathecal equivalents of that dose (ie, the dose that will be equianalgesic after titration and equilibration)?
 - a. Epidural _____ mg/24 h
 - b. Intrathecal _____ mg/24 h
8. Your patient is on IV fentanyl 2,000 µg/24 h. In your opinion, what are the epidural and intrathecal equivalents of that dose (ie, the dose that will be equianalgesic after titration and equilibration)?
 - a. Epidural _____ µg/24 h
 - b. Intrathecal _____ µg/24 h
9. I use an opioid calculator for converting IV opioids to epidural and intrathecal opioids.
 - a. Always
 - b. Sometimes
 - c. Never
10. Which opioid calculator do you most commonly use? _____

Figure 1 Ten question survey.

Results

Eighty-three respondents returned the survey (11% response rate). Data from questions 1–5 are presented in Table 1. There was an even distribution of the number of pumps managed, years of clinical practice, and geographic location. More respondents were in academic vs private

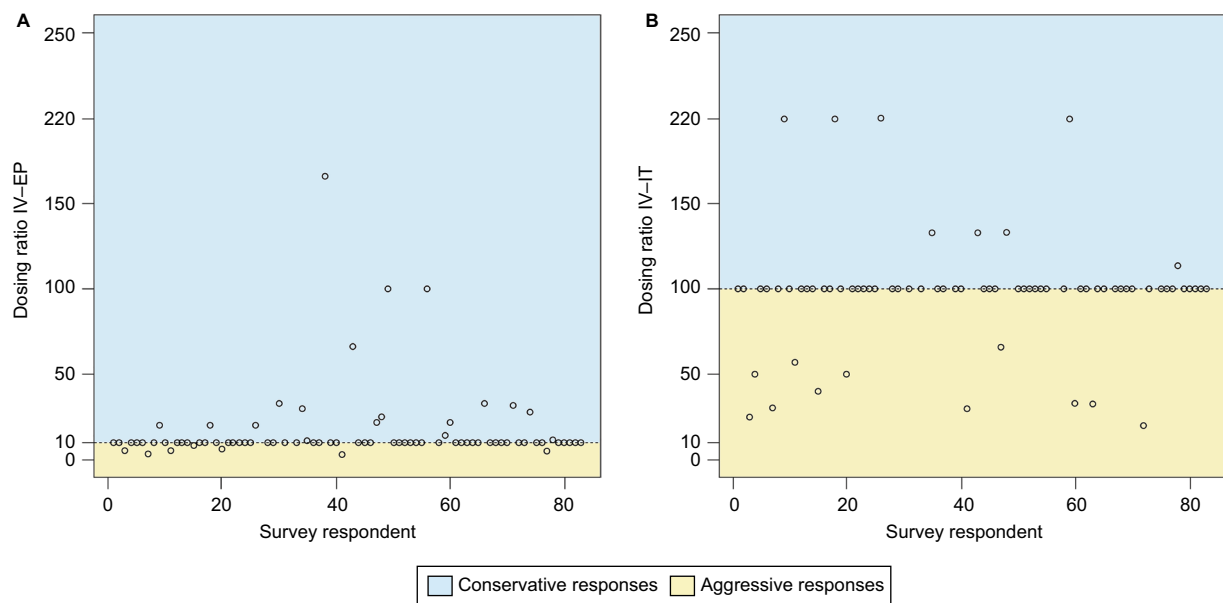


Figure 2 Morphine scatter plots.

Notes: Respondents' answers to survey question 6 were converted into IV:EP (A) and IV:IT (B) ratios. These ratios were entered into scatter plots. The most common response was 10:1 for the IV:EP (A) and 100:1 for the IV:IT (B). "Aggressive" and "conservative" answers are highlighted in blue and yellow shaded areas.

Abbreviations: EP, epidural; IT, intrathecal; IV, intravenous.

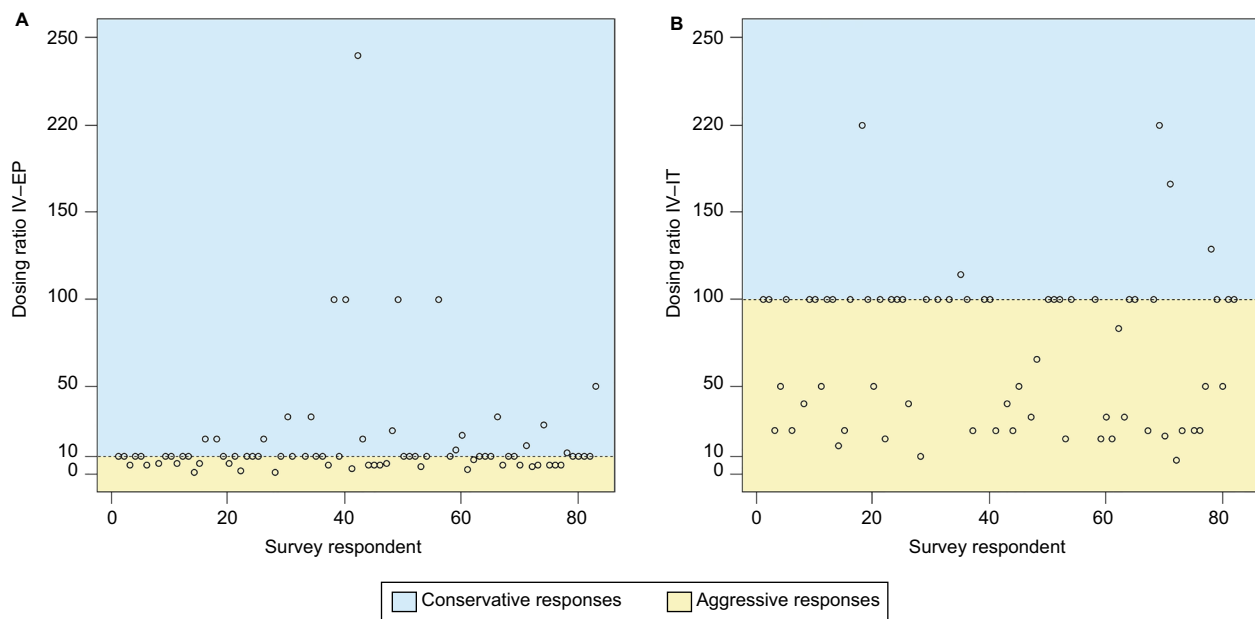


Figure 3 Hydromorphone scatter plots.

Notes: Respondents' answers to survey question 7 were converted into IV:EP (A) and IV:IT (B) ratios. These ratios were entered into scatter plots. The most common response was 10:1 for the IV:EP (A) and 100:1 for the IV:IT (B). "Aggressive" and "conservative" answers are highlighted in blue and yellow shaded areas.

Abbreviations: EP, epidural; IT, intrathecal; IV, intravenous.

practice (57% vs 36%). Ninety-two percent of respondents were trained in anesthesiology and pain medicine. Data from questions 9 and 10 are presented in Table 2. Only 20% of respondents always use an opioid calculator for IV to neuraxial dose conversion. The most popular opioid calculators mentioned were GlobalRph[®] (David McAuley, Detroit, MI, USA) and Cynergy[®] (DuPen, Poulsbo, WA, USA).

Data from questions 6–8 are presented in Figures 2–4 (scatter plots) and Table 3. Several trends are illustrated. First, an IV:EP ratio of 10:1 is most common for morphine (68% of respondents) and is also common for hydromorphone (42% of respondents) and fentanyl (40% of respondents). Second, an IV:IT ratio of 100:1 is most common for morphine (65% of respondents) and is also common for hydromorphone

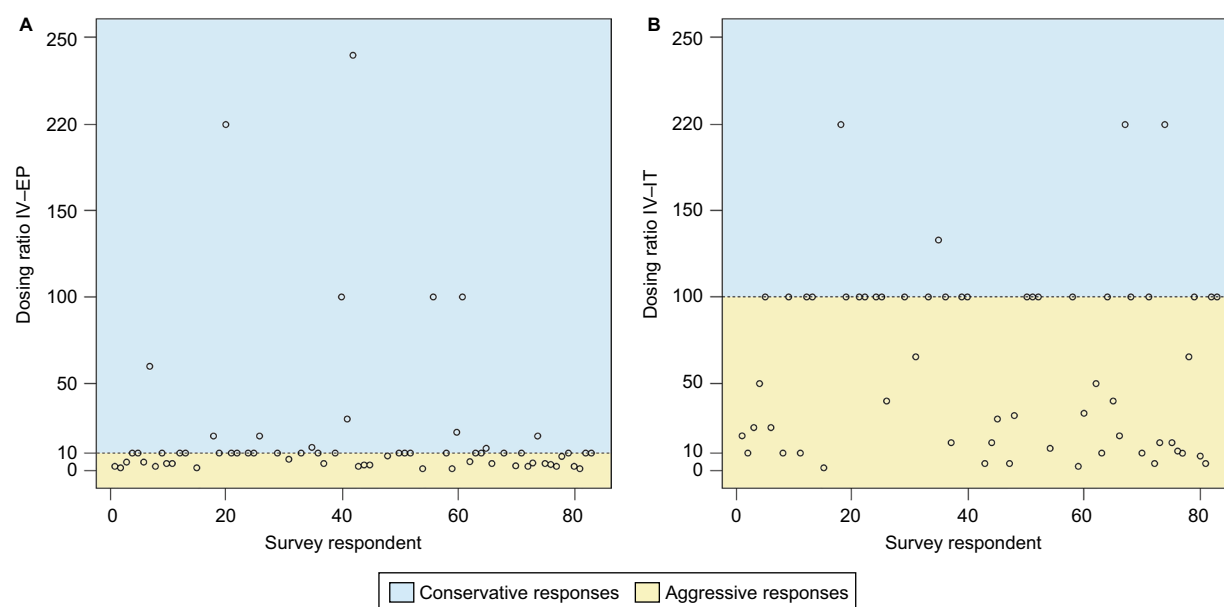


Figure 4 Fentanyl scatter plots.

Notes: Respondents' answers to survey question 8 were converted into IV:EP (A) and IV:IT (B) ratios. These ratios were entered into scatter plots. The most common response was 10:1 for the IV:EP (A) and 100:1 for the IV:IT (B). "Aggressive" and "conservative" answers are highlighted in blue and yellow shaded areas.

Abbreviations: EP, epidural; IT, intrathecal; IV, intravenous.

Table 1 Demographic data collected from the survey responses

How many IT pumps do you manage (not necessarily implant) per year?	
<5	25 (30%)
5–20	24 (29%)
>20	34 (41%)
For how many years have you been in practice?	
<5	38 (46%)
5–20	28 (34%)
>20	17 (20%)
What is your practice type?	
Academic	47 (57%)
Private	30 (36%)
Hybrid	6 (7%)
What is your specialty?	
Pain – Anes	76 (92%)
Pain – PMR	4 (5%)
Pain – other	2 (2%)
Neurosurg	1 (1%)
Where do you practice?	
US – northeast	25 (30%)
US – midwest	12 (14%)
US – south	20 (24%)
US – west	24 (29%)
Canada	1 (1%)
Other	1 (1%)

Note: Survey responses to questions 1–5.

Abbreviations: Anes, anesthesiology; IT, intrathecal; Neurosurg, neurosurgery; PMR, physical medicine and rehabilitation.

(42% of respondents) and fentanyl (40% of respondents). Third, for IV:EP and IV:IT morphine, there were more conservative responses (see "Methods" section for explanation) than aggressive responses. Finally, for IV:EP and IV:IT

Table 2 Use of opioid calculator collected from the survey responses

I use an opioid calculator for converting IV to epidural and intrathecal opioids	
Always	8 (20%)
Sometimes	42 (51%)
Never	31 (37%)
No response	2
Which opioid calculators do you most commonly use? ^a	
GlobalRph	9
Cynergy ^b	5
Johns Hopkins	3
Eopoid	1
Practicalpain-management.com	1

Notes: Survey responses to questions 9 and 10. ^a41/83 respondents answered this question. There were a range of free text answers and the majority of responses did not mention an actual calculator. ^b4/5 of these respondents reported "Mayo online", which is the Cynergy calculator.

Abbreviation: IV, intravenous.

hydromorphone and fentanyl, there were more aggressive responses than conservative responses.

Discussion

Converting high-dose IV opioids to appropriate EP and IT doses remains a common clinical dilemma and existing guidelines are based mostly on expert opinion. The primary aim of this survey study was to gain insight into how pain specialists manage these conversions by presenting respondents with three real-world examples of patients requiring EP and IT dose conversions from high-dose IV morphine, hydromorphone, and fentanyl. We show that there is wide variation in how pain

Table 3 Survey responses for questions 6–8 regarding conversion of IV to neuraxial opioids

IV opioid dose/24 h	Equivalent epidural dose/24 h	Responses, n (%)	Equivalent intrathecal dose/24 h	Responses, n (%)
Morphine 1,000 mg (n80)	100 mg (most common)	54 (68)	10 mg (most common)	52 (65)
	>100 mg (aggressive)	7 (8)	>10 mg (aggressive)	11 (14)
	<100 mg (conservative)	19 (24)	<10 mg (conservative)	17 (21)
Hydromorphone 100 mg (n77)	10 mg (most common)	32 (42)	1 mg (most common)	32 (42)
	>10 mg (aggressive)	24 (31)	>1 mg (aggressive)	30 (39)
	<10 mg (conservative)	21 (27)	<1 mg (conservative)	15 (19)
Fentanyl 2,000 µg (n67)	200 µg (most common)	27 (40)	20 µg (most common)	27 (40)
	>200 µg (aggressive)	27 (40)	>20 µg (aggressive)	30 (45)
	<200 µg (conservative)	13 (19)	<20 µg (conservative)	10 (15)

Notes: Survey responses to questions 6–8. Number of survey responses is given along with the percentage of responses in parentheses. The data were broken down into most common, aggressive, and conservative.

Abbreviation: IV, intravenous.

management specialists convert IV to neuraxial opioids, which suggests a lack of good scientific evidence to guide practice as well as a lack of consensus with respect to existing expert opinion. Nonetheless, two trends were identified that deserve further exploration. First, a 100 IV:10 EP:1 IT conversion ratio was a common response for all three opioids, especially morphine. Second, more aggressive conversion ratios were more common for hydromorphone and fentanyl.

What is the basis for the customary 100:10:1 conversion ratio? Most of the data on parenteral to neuraxial opioid conversion have focused on morphine probably because it is the most commonly prescribed neuraxial opioid and is currently the only opioid that is approved for neuraxial administration by the FDA. The package insert for preservative-free morphine used for neuraxial delivery (Duramorph, West-Ward Pharmaceuticals, Eatontown, NJ, USA) states that the EP:IT conversion ratio is 10:1, although there is no reference cited.⁸ Sylvester et al contacted one manufacturer of Duramorph (Elkins-Sinn, Inc, Cherry Hill, NJ, USA) and were advised that the 10:1 conversion ratio in the package insert was based on anecdotal reports rather than any actual data.⁶ The Duramorph package insert makes no comment on IV:EP or IV:IT conversion. Krames reports an 100 IV:10 EP:1 IT ratio but cites no reference, simply describing it as the conversion he uses in practice.⁹ This 100 IV:10 EP:1 IT conversion ratio is also recommended in a cancer pain manual published by the American Pain Society (APS) as well as the Cynergy calculator developed by DuPen but, again, no evidence-based reference is cited.^{10,11}

There are some data suggesting that the 100 IV:10 EP:1 IT morphine conversion ratios may not be correct. In a randomized, double-blinded trial of patients undergoing cesarean section, Sarvela et al report similar analgesic outcomes among patients receiving morphine 100 µg IT vs 200 µg IT vs 3 mg EP.¹² This study suggests that, at least for a single dose,

the EP:IT conversion ratio for morphine could be as high as 30:1. However, the study population was relatively opioid-naïve and not clinically comparable to patients who typically receive implantable opioid delivery devices. In a randomized, blinded study of ten subjects with cancer pain, patients were allowed to self-administer morphine until they felt adequate analgesia.¹³ The median patient controlled analgesia doses of EP and subcutaneous morphine that the patients received were 372 and 106 mg, respectively, leading the authors to suggest that the average subcutaneous to EP conversion ratio is roughly 3:1. Though it is a small study and it is uncertain whether this conversion ratio translates to IV morphine, this study provides some empirical evidence for an equianalgesic conversion ratio of 3:1 between parenteral and EP morphine. In addition, in an online review of IT drug delivery, DuPen and DuPen reference 4 years of unpublished data from their clinic in support of an IV:EP morphine conversion ratio of 3:1.¹⁴ The Cynergy calculator utilizes an IV:EP ratio of 3:1 for morphine as well. Nonetheless, despite some evidence and expert opinion to the contrary, the 100 IV:10 EP:1 IT conversion ratio for morphine appears to be the most commonly recommended approach and this is reflected in our survey data.

For hydromorphone and fentanyl there are even less data and expert opinion to guide practice. Our survey suggests that many practitioners adhere to the 100 IV:10 EP:1 IT ratio for fentanyl and hydromorphone, though less so than for morphine. In addition, our data suggest that many clinicians take a more aggressive approach with fentanyl and hydromorphone (ie, lower IV:neuraxial conversion ratios). This is consistent with the pharmacologic differences between morphine, hydromorphone, and fentanyl. In general, lipophilic opioids such as fentanyl (hydromorphone is intermediate between morphine and fentanyl) are less spinally selective when given in the EP or IT space compared with hydrophilic opioids

such as morphine.¹⁵ Morphine stays in the IT space longer and gains better access to both spinal and supraspinal opioid receptors when compared with more lipophilic opioids. In addition, there is evidence that morphine distributes preferentially to the more cellular gray matter of the spinal cord (where opioids exert their effects) compared with fentanyl, which tends to distribute into the lipid filled white matter.^{16–18}

The only clinical data we have to guide neuraxial dosing of fentanyl come from the anesthesia literature and, though these data may not apply to highly opioid-tolerant patients with chronic pain, these studies do merit review. Glass et al and Loper et al demonstrate that IV and EP fentanyl administered at the same dose result in very similar plasma levels following bolus and infusion and achieve equivalent analgesic effects.^{19,20} These authors posit that EP fentanyl has no significant spinal action and that it behaves pharmacokinetically the same as when it is given intravenously. Another study from the obstetric anesthesia literature suggests that there may be some minor spinally mediated effects of EP fentanyl infusions, at least when given in combination with a local anesthetic.²¹ IT fentanyl does have a significant spinally mediated analgesic effect. Palmer et al report a dose-dependent analgesic and duration effect with 5–45 µg of IT fentanyl administered to females with acute labor pain.²²

Citing anecdotal and consensus opinion, the Cynergy calculator suggests that the IV:EP conversion ratio for fentanyl is 10:7. For IT fentanyl, Cynergy does not provide a specific conversion but instead cites “obstetric literature” and recommends a starting dose of 100–150 µg/day with µg titration to effect. The APS suggests that for a single dose, typical fentanyl doses will be 25–100 µg EP and 5–25 IT.¹⁰ The APS suggests an EP infusion rate for fentanyl of 25–100 µg/h but has no recommendation for IT fentanyl infusion dosing.

Unlike fentanyl, there is no debate as to whether EP hydromorphone provides significant spinally mediated analgesia.^{15,23} Furthermore, at least in the perioperative setting, IT hydromorphone is comparable in its analgesic efficacy to morphine.^{15,24} Because hydromorphone is between morphine and fentanyl in terms of lipophilicity (octanol–water partition coefficient of 525 compared with one and 955 of morphine and fentanyl, respectively), the IV to neuraxial dose conversions might be predicted to fall somewhere in between those of morphine and fentanyl.¹⁵ Despite that, the Cynergy calculator utilizes a dose conversion strategy identical to that of morphine; that is, IV:EP 3:1 and EP:IT 10:1.

Review of the literature and the highly variable data from this survey suggest that the true equianalgesic ratios for IV and neuraxial opioids are still uncertain. Though based on small

and methodologically limited studies, IV:oral opioid conversion strategies are well established in various guidelines.¹⁰ The basic concept of IV:oral conversion is rational and is based on differences in speed of delivery and bioavailability between the different routes. In the case of parenteral to neuraxial dose conversions, the dosing differences are due not only to pharmacokinetic differences but to mechanistic differences as well. To put it simply, opioids work differently when given neuraxially. Spinally administered opioids exert much of their analgesic effect on opioid receptors in the spinal cord (and to varying degrees in the supraspinal opioid receptors in the brainstem depending on the lipophilicity of the opioid); whereas, parenteral opioids act largely in the brainstem.²⁵ Due to these mechanistic differences, equianalgesic dose ratios between parenteral and neuraxial routes may not even be a valid concept.

Our survey data, in addition to the existing opinions in the literature, suggest that using a 100 IV:10 EP:1 IT conversion strategy is consistent with what many practitioners actually do, at least for highly opioid tolerant patients requiring neuraxial opioid infusions for pain. Ultimately, however, the old axiom of “start low and go slow” may be the most sensible approach when initiating neuraxial opioid administration. This practice is reflected in survey data published by Hassenbusch and Portenoy, which shows that the average starting dose of IT morphine is 1.5 mg/day regardless of the preexisting systemic opioid requirements.⁴ The 2012 Polyanalgesic Consensus Conference suggested starting IT doses of morphine (0.1–0.5 mg/day), hydromorphone (0.02–0.5 mg/day), and fentanyl (25–75 µg/day) without reference to preexisting opioid requirements.²⁶ In addition, this panel recommended trialing patients prior to implantation which, in addition to establishing efficacy and toleration of therapy, may help guide clinicians on initial neuraxial dosing.²⁵ Finally, it should be noted that the survey queried respondents about “equianalgesic dose after titration and equilibration” not “starting dose”. It is possible that if we had asked about starting dose the answers would have been substantially more conservative.

Limitations

There are several limitations of this study. First, although we were able to obtain over 80 responses, the survey response rate was low (11%) and it is possible that our data are not representative of the larger pain management community. The relatively high percentage of respondents in academic practice as opposed to private practice is another concern. Nonetheless, the total number of respondents (83) is a reasonably high number in a small specialty such as pain management. Furthermore, the respondents were evenly

distributed in terms of geographic location, years in practice, and volume of pumps managed.

Second, most patients who are candidates for neuraxial opioid infusion devices are highly opioid tolerant and may have different and unpredictable responses to both IV and neuraxial opioids when given at various doses. In our survey, we queried the conversion practices for a single high dose of each of the three opioids. However, we recognize that the responses might have been quite different had we asked about lower doses of opioids. Furthermore, opioids are often given along with local anesthetics and other adjuncts such as clonidine, which act synergistically with opioids and may significantly reduce the required neuraxial opioid dose.

Further, there may be patient-specific factors that can influence the IV:neuraxial opioid conversion. In fact, DuPen and Williams propose a conversion tool for this problem that takes into account not only the patient's systemic morphine requirements but also factors such as pain severity, age, and the existence of neuropathic pain when determining the appropriate starting neuraxial opioid dose.²⁷ To our knowledge, this tool has not been validated, but it raises legitimate questions about whether one can reasonably apply a universal dose conversion ratio to all patients.

Another limitation of the survey is that we only asked about dose conversion in one direction, that is, IV–EP and IV–IT. We did not ask respondents about how they might convert neuraxial to parenteral opioids. If we accept that 100 IV:10 EP:1 IT conversion is safe, can we apply the same ratio in reverse when converting neuraxial to IV? Sylvester et al suggest that the 100 IV:10 EP:1 IT conversion strategy may result in significant and potentially dangerous overestimates of parenteral or oral opioid requirements when used to convert patients from neuraxial morphine to parenteral or oral morphine.⁶ We believe that clinicians should exercise caution and common sense when converting neuraxial to parenteral or oral opioids and that the 100 IV:10 EP:1 IT ratio may not apply to all conversions. In future studies, we intend to examine the issue of bidirectional conversion.

Conclusion

Converting high-dose IV opioids to an equianalgesic EP or IT dose in highly opioid tolerant patients remains a clinical problem guided mainly by expert opinion. A 100 IV:10 EP:1 IT conversion ratio is commonly cited in various guidelines and opioid conversion calculators. This study suggests wide variability in how pain specialists estimate equianalgesia when converting opioids from IV to neuraxial routes. We also showed that the 100 IV:10 EP:1 IT ratio is commonly

applied for morphine and, to a lesser extent, hydromorphone and fentanyl. Further, our data suggest that some clinicians may apply more aggressive conversion strategies for fentanyl and hydromorphone, possibly because of the higher lipophilicity and lower degree of spinal selectivity of these drugs compared to morphine. We conclude that conversion ratios suggested by this survey and expert opinion are estimates and should be used with caution when making clinical decisions.

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Disclosure

The authors report no conflicts of interest in this work.

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