The use of implantable intrathecal pumps has become increasingly more complex with clinicians’ combining opiates and local anesthetics such as morphine and bupivacaine. This technique produces heightened analgesia and is especially useful for the treatment of cancer-related neuropathic pain [1].

In this patient population, use of low-dose intrathecal bupivacaine does not appear to cause significant neurologic sequelae [2]. However, use of spinal catheters, with high concentrations of lidocaine, has been associated with cauda equina syndrome [3]. Recently, successful long-term use of intracisternal bupivacaine has been described for chronic facial pain [4,5]. It is conceivable that the combination of intrathecal bupivacaine and morphine might be useful in treating recalcitrant chronic regional pain syndromes such as reflex sympathetic dystrophy or causalgia.

Potential side effects of intrathecal local anesthetics including hypotension, bradycardia, and motor weakness should be evaluated [6]. In addition, the side effects of intrathecal opiates, such as respiratory depression, pruritus, and urinary retention must also be recognized [7]. If necessary, the reservoir and intrathecal catheter of these pumps can be easily drained.

The following sets of equations allow for readily available concentrations of both morphine and bupivacaine to be mixed so that a desired total daily dose of each can be administered. Two sets of equations will be described: one for pumps which are externally programmable, such as the Medtronic, and another for fixed-rate pumps, such as the Infusaid or Arrow. Table 1 provides a listing of terms and their definitions, along with appropriate units of measure.

**Determining Mixtures for Programmable Intrathecal Pumps**

Initially, a dimensionless constant R is defined which equals the ratio of the total daily dose of local anesthetic, $T_{LA}$, to the total daily dose of morphine, $T_{MSO}$. This constant is also equivalent to the ratio of the final concentration of local anesthetic, $C_{LA_{final}}$, to the final concentration of morphine, $C_{MSO_{final}}$:

$$R = \frac{C_{LA_{final}}}{C_{MSO_{final}}} = \frac{\text{Total daily dose of local anesthetic in mg/day}}{\text{Total daily dose of morphine in mg/day}} = \frac{T_{LA}}{T_{MSO}} \quad (1)$$

The final concentration of morphine, $C_{MSO_{final}}$, can then be determined using the initial concentration of local anesthetic, $C_{LA_{initial}}$, and the initial concentration of morphine, $C_{MSO_{initial}}$:

$$C_{MSO_{final}} = R \cdot C_{LA_{initial}} + \frac{1}{C_{MSO_{initial}}} \quad (2)$$

By using R and $C_{MSO_{final}}$ from equation 2, the final concentration of local anesthetic, $C_{LA_{final}}$, can be found:

$$C_{LA_{final}} = R \cdot C_{MSO_{final}} \quad (3)$$

The volumes of morphine, $Volume_{MSO_{initial}}$, and local anesthetic, $Volume_{LA_{initial}}$, to be drawn up, mixed, and infused into the pump reservoir are then calculated [8]:

$$Volume_{MSO_{final}} = C_{MSO_{final}} \cdot Volume_{reservoir} \quad (4)$$

and

$$Volume_{LA_{final}} = C_{LA_{final}} \cdot Volume_{reservoir} \quad (5)$$

The pump flow rate can then be determined:

$$\text{Pump flow rate in ml/day} = \frac{T_{MSO}}{C_{MSO_{final}}} \quad (6)$$

---

*The purpose of this section is to provide the reader with a series of tutorial lessons that may be used for self-study in pain medicine. CME credits will not be granted for the completion of this tutorial.
Table 1. List of terms.

<table>
<thead>
<tr>
<th>Term</th>
<th>Meaning</th>
<th>Units</th>
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<tbody>
<tr>
<td>$C_{LA-initial}$</td>
<td>Initial concentration of local anesthetic</td>
<td>mg/ml</td>
</tr>
<tr>
<td>$C_{MSO_4-initial}$</td>
<td>Initial concentration of morphine</td>
<td>mg/ml</td>
</tr>
<tr>
<td>$C_{LA-final}$</td>
<td>Final concentration of local anesthetic</td>
<td>mg/ml</td>
</tr>
<tr>
<td>$C_{MSO_4-final}$</td>
<td>Final concentration of morphine</td>
<td>mg/ml</td>
</tr>
<tr>
<td>$V_{LA-initial}$</td>
<td>Initial volume of local anesthetic</td>
<td>ml</td>
</tr>
<tr>
<td>$V_{MPO_4-initial}$</td>
<td>Initial volume of morphine</td>
<td>ml</td>
</tr>
<tr>
<td>$V_{LA-final}$</td>
<td>Final volume of local anesthetic</td>
<td>ml</td>
</tr>
<tr>
<td>$V_{MPO_4-final}$</td>
<td>Final volume of morphine</td>
<td>ml</td>
</tr>
<tr>
<td>$T_{LA}$</td>
<td>Total daily dose of local anesthetic</td>
<td>mg/day</td>
</tr>
<tr>
<td>$T_{MPO_4}$</td>
<td>Total daily dose of morphine</td>
<td>mg/day</td>
</tr>
<tr>
<td>$F_p$</td>
<td>Flow rate for fixed-rate pumps</td>
<td>ml/day</td>
</tr>
<tr>
<td>$R$</td>
<td>CLA-final or $T_{LA}$ or $C_{MPO_4-final}$</td>
<td>dimensionless</td>
</tr>
<tr>
<td>Volumes</td>
<td>Volume of preservative-free normal saline</td>
<td>ml</td>
</tr>
</tbody>
</table>

Obviously, if $V_{LA-final}$ is less than zero, then either $C_{LA-initial}$ or $C_{MPO_4-initial}$ or both must be increased to reduce $V_{LA-initial}$ or $V_{MPO_4-initial}$ respectively.

Checking Accuracy

The above calculations, for both programmable and fixed-rate pumps, can be checked by multiplying the final concentrations, of the local anesthetic and morphine, by the pump flow rate.

$$C_{LA-final} \cdot (Pump \ flow \ rate) = T_{LA}$$ (14)

and

$$C_{MPO_4-final} \cdot (Pump \ flow \ rate) = T_{MPO_4}$$ (15)

The following equations are also necessary in accuracy checking:

$$C_{LA-initial} \cdot V_{LA-initial} = C_{LA-final} \cdot V_{LA-final}$$ (16)

and

$$C_{MPO_4-initial} \cdot V_{MPO_4-initial} = C_{MPO_4-final} \cdot V_{MPO_4-final}$$ (17)

Examples

Two calculations using the preceding formulas follow.

Example 1

It is desired to deliver 4 mg/day of intrathecal morphine with 5 mg/day of intrathecal bupivacaine via a programmable pump. The initial concentration of morphine, $C_{MPO_4-initial}$, is 25.0 mg/ml; and the initial concentration of bupivacaine, $C_{LA-initial}$, is 7.5 mg/ml. The pump reservoir has a capacity of 18 ml. Using Equation 1:

$$R = \frac{5}{4}$$

The final concentration of morphine, $C_{MPO_4-final}$, can be obtained from Equation 2:

$$C_{MPO_4-final} = \frac{1}{\left( \frac{5}{4} \right)} = 4.84 \text{ mg/ml}$$

Using Equation 3, the final concentration of bupivacaine can be found:

$$C_{LA-final} = R \cdot C_{LA-initial} = \frac{5}{4} \cdot (4.84) = 6.05 \text{ mg/ml}$$

The volumes of morphine and local anesthetic, to be drawn up and mixed, are determined from Equations 4 and 5:

$$V_{LA-final} = \frac{(4.84) \cdot 18}{25} = 3.48 \text{ ml}$$

$$V_{MPO_4-initial} = \frac{(6.05) \cdot 18}{7.5} = 14.52 \text{ ml}$$

The pump flow rate is then calculated from Equations 6 or 7:

$$\text{Pump flow rate} = \frac{4}{4.84} = \frac{5}{6.05} = 0.826 \text{ ml/day}$$
From Equation 8, the duration that the pump can be used until its reservoir needs to be refilled is:

\[
\text{Duration in days} = \frac{18}{0.826} = 21.8 \text{ days}
\]

The accuracy can be checked by using Equations 14 and 15 to verify the total daily dose of local anesthetic and morphine.

\[
\text{C}_{LA_{\text{final}}} \cdot \text{(pump flow rate)} = 6.05 \cdot 0.826 = 5 \text{ mg/day}
\]

and

\[
\text{C}_{MSO_{\text{final}}} \cdot \text{(pump flow rate)} = 4.84 \cdot 0.826 = 4 \text{ mg/day}
\]

The initial and final concentrations and volumes can also be checked by using Equations 16 and 17.

\[
\text{C}_{LA_{\text{initial}}} \cdot \text{Volume}_{LA_{\text{initial}}} = 7.5 \cdot 14.52 = 109 \text{ mg}
\]

\[
\text{C}_{LA_{\text{final}}} \cdot \text{Volume}_{LA_{\text{final}}} = 6.05 \cdot 18 = 109 \text{ mg}
\]

and

\[
\text{C}_{MSO_{\text{initial}}} \cdot \text{Volume}_{MSO_{\text{initial}}} = 25 \cdot 3.48 = 87 \text{ mg}
\]

\[
\text{C}_{MSO_{\text{final}}} \cdot \text{Volume}_{MSO_{\text{final}}} = 4.84 \cdot 18 = 87 \text{ mg}
\]

**Example 2**

It is desired to deliver 7 mg/day of intrathecal morphine and 5 mg/day of intrathecal bupivacaine via a fixed-rate pump with a reservoir volume of 50 ml. The pump has a preset flow rate of 2 ml/day. The initial concentration of local anesthetic, \( C_{LA_{\text{initial}}} \), is 7.5 mg/ml; and the initial concentration of morphine, \( C_{MSO_{\text{initial}}} \), is 10.0 mg/ml.

The final concentrations of morphine and local anesthetic can be determined from Equations 9 and 10.

\[
\text{C}_{MSO_{\text{final}}} = \frac{7}{2} = 3.5 \text{ mg/ml}
\]

and

\[
\text{C}_{LA_{\text{final}}} = \frac{5}{2} = 2.5 \text{ mg/ml}
\]

The initial volumes of local anesthetic and morphine to be drawn up and mixed can be determined using Equations 11 and 12.

\[
\text{Volume}_{LA_{\text{initial}}} = \frac{5 \cdot 50}{2 \cdot 7.5} = 16.67 \text{ ml}
\]

and

\[
\text{Volume}_{MSO_{\text{initial}}} = \frac{7 \cdot 50}{2 \cdot 10} = 17.5 \text{ ml}
\]

The volume of preservative-free normal saline to be drawn up and mixed to the above volumes is determined from Equation 13.

\[
\text{Volume}_{NS} = 50 - (16.67 + 17.5) = 15.83 \text{ ml}
\]

The accuracy can be checked by using Equations 14 and 15 to verify the total daily dose of local anesthetic and morphine.

\[
\text{C}_{LA_{\text{final}}} \cdot \text{(pump flow rate)} = 2.5 \cdot 2.0 = 5 \text{ mg/day}
\]

and

\[
\text{C}_{MSO_{\text{final}}} \cdot \text{(pump flow rate)} = 3.5 \cdot 2.0 = 7 \text{ mg/day}
\]
Table 2. Software program, written in Microsoft QBasic, executes the described equations for programmable intrathecal pumps.

CLS
format$ = "##.##"
INPUT "Enter the total daily dose of local anesthetic in mg"; TDLA
INPUT "Enter the total daily dose of morphine in mg"; TDMS
INPUT "Enter the initial concentration of local anesthetic in mg/ml"; CLAI
INPUT "Enter the initial concentration of morphine in mg/ml"; CMSI
INPUT "Enter the volume of the pump reservoir in ml"; VolRes

R = TDLA / TDMS
CMSF = 1 / ((R / CLAI) + (1 / CMSI))
CLAF = R * CMSF
VolMS = (CMSF * VolRes) / CMSI
VolLA = (CLAF * VolRes) / CLAI
PumpflowrateLA = TDMS / CLAF
PumpflowrateMS = TDMS / CMSF

LPRINT "Enter the total daily dose of local anesthetic in mg: "; USING format$; TDLA
LPRINT "Enter the total daily dose of morphine in mg: "; USING format$; TDMS
LPRINT "Enter the initial concentration of local anesthetic in mg/ml: "; USING format$; CLAI
LPRINT "Enter the initial concentration of morphine in mg/ml: "; USING format$; CMSI
LPRINT "Enter the volume of the pump reservoir in ml: "; USING format$; VolRes

LPRINT "Volume of morphine to be drawn up in ml: "; USING format$; VolMS
LPRINT "Volume of local anesthetic to be drawn up in ml: "; USING format$; VolLA
LPRINT "Final concentration of morphine to be infused in mg/ml: "; USING format$; CMSF
LPRINT "Final concentration of local anesthetic to be infused in mg/ml: "; USING format$; CLAF
LPRINT "Pump flow rate in ml/day: "; USING format$; PumpflowrateLA
LPRINT "Pump flow rate in ml/day (check): "; USING format$; PumpflowrateMS
LPRINT "Duration of mixture in reservoir in days: "; USING format$; (VolRes / PumpflowrateLA)

LPRINT "Check: Total daily dose of local anesthetic = CLAF * Pump flow rate = "; CLAF * PumpflowrateLA; "mg"
LPRINT "Check: Total daily dose of morphine = CMSF * Pump flow rate = "; CMSF * PumpflowrateMS; "mg"
LPRINT "Check: CLAI * VolLA = "; CLAI * VolLA; "mg"
LPRINT "Check: CMSF * VolRes = "; CMSF * VolRes; "mg"
LPRINT "Check: VolMS = "; VolMS; "mg"
LPRINT "Check: VolLA = "; VolLA; "mg"

CHR$(12)
SYSTEM
END

Table 3. Software program, written in Microsoft QBasic, executes the described equations for fixed-rate intrathecal pumps.

CLS
format$ = "##.##"
INPUT "Enter the total daily dose of local anesthetic in mg"; TDLA
INPUT "Enter the total daily dose of morphine in mg"; TDMS
INPUT "Enter the initial concentration of local anesthetic in mg/ml"; CLAI
INPUT "Enter the initial concentration of morphine in mg/ml"; CMSI
INPUT "Enter the volume of the pump reservoir in ml"; VolRes
INPUT "Enter the flow rate of the pump in ml/day"; FRP

CMSF = TDMS / FRP
CLAF = TDMS / FRP
VolMS = (CMSF * VolRes) / CMSI
VolLA = (CLAF * VolRes) / CLAI
VolNS = VolRes - (VolMS + VolLA)

LPRINT "Enter the total daily dose of local anesthetic in mg: "; USING format$; TDLA
LPRINT "Enter the total daily dose of morphine in mg: "; USING format$; TDMS
LPRINT "Enter the initial concentration of local anesthetic in mg/ml: "; USING format$; CLAI
LPRINT "Enter the initial concentration of morphine in mg/ml: "; USING format$; CMSI

(Table continues on next page)
Table 3. Software program, written in Microsoft QBASIC, executes the described equations for fixed-rate intrathecal pumps. (Continued)

LPRINT "Enter the volume of the pump reservoir in ml: "; USING format$; VolRes
LPRINT "Enter the flow rate of the pump in ml/day: "; USING format$; FRP
LPRINT
LPRINT "Volume of morphine to be drawn up in ml: "; USING format$; VoIMS
LPRINT "Volume of local anesthetic to be drawn up in ml: "; USING format$; VoILA
LPRINT "Volume of normal saline to be drawn up in ml: "; USING format$; VolNS
LPRINT "Final concentration of morphine to be infused in mg/ml: "; USING format$; CMSF
LPRINT "Final concentration of local anesthetic to be infused in mg/ml: "; USING format$; CLAF
LPRINT "Duration of mixture in reservoir in days: "; USING format$; (VolRes / FRP)
LPRINT
LPRINT "Check Total daily dose of local anesthetic = CLAF * pump flow rate ="; CLAF * FRP; "mg"
LPRINT "Check Total daily dose of morphine = CMSF * pump flow rate ="; CMSF * FRP; "mg"
LPRINT "Check CLAF*VoILA ="; CLAF * VoILA; "mg "; "CLAF*VolRes ="; CLAF * VolRes; "mg"
LPRINT "Check CMSI*VoIMS ="; CMSI * VoIMS; "mg "; "CMSF*VolRes ="; CMSF * VolRes; "mg"
LPRINT CHR$(12)
SYSTEM
END

\[
Volume_{LA_{\text{initial}}} = \frac{T_{LA}}{F_p} \cdot \frac{Volume_{reservoir}}{C_{LA_{\text{initial}}}} \quad (10)
\]

and

\[
Volume_{MSO_{\text{initial}}} = \frac{T_{MSO}}{F_p} \cdot \frac{Volume_{reservoir}}{C_{MSO_{\text{initial}}}} \quad (11)
\]

Summary

The clinician will find the preceding sets of equations useful in the day-to-day management of morphine and local anesthetic combinations for administration via implantable intrathecal pumps. Other opiate and local anesthetic combinations, with the appropriate changes in concentrations and nomenclature, can be substituted. In addition, the software programs in Tables 2 and 3, written in Microsoft QBASIC, allow for the rapid computation of the necessary final parameters.

References

For a *programmable* intrathecal pump, it is desired to deliver 3 mg per day of bupivacaine and 5 mg per day of morphine. The pump reservoir has a capacity of 18 ml. The initial concentration of local anesthetic, $C_{LA,\text{initial}}$, is 7.5 mg/ml and the initial concentration of morphine, $C_{MSO,\text{initial}}$, is 25.0 mg/ml.

1. Using Equation 1, determine $R$.
   a. 0.4
   b. 0.5
   c. 0.6
   d. 0.7

2. Find the final concentration of morphine, $C_{MSO,\text{final}}$, from Equation 2.
   a. 7.33 mg/ml
   b. 8.33 mg/ml
   c. 9.33 mg/ml
   d. 10.33 mg/ml

3. Calculate the final concentration of local anesthetic, $C_{LA,\text{final}}$, from Equation 3.
   a. 2 mg/ml
   b. 3 mg/ml
   c. 4 mg/ml
   d. 5 mg/ml

4. Using Equation 4, find the initial volume of morphine, $V_{MSO,\text{initial}}$.
   a. 6.0 ml
   b. 7.0 ml
   c. 8.0 ml
   d. 9.0 ml

5. Using Equation 5, determine the initial volume of local anesthetic, $V_{LA,\text{initial}}$.
   a. 10 ml
   b. 11 ml
   c. 12 ml
   d. 13 ml

6. Calculate the pump flow rate from Equations 6 or 7:
   a. 0.4 ml/day
   b. 0.5 ml/day
   c. 0.6 ml/day
   d. 0.7 ml/day

7. Find the duration of the mixture in the reservoir from Equation 8.
   a. 25 days
   b. 30 days
   c. 35 days
   d. 40 days

8. Use Equation 16 to determine that the initial and final amounts of local anesthetic, in milligrams, are equivalent.
   a. 70 mg
   b. 80 mg
   c. 90 mg
   d. 100 mg

9. Use Equation 17 to determine that the initial and final amounts of morphine, in milligrams, are equivalent.
   a. 130 mg
   b. 140 mg
   c. 150 mg
   d. 160 mg

For a *fixed-rate* intrathecal pump, it is desired to deliver 3 mg per day of bupivacaine and 5 mg per day of morphine. The pump has a flow rate of 2 ml/day and a reservoir capacity of 50 ml. The initial concentration of local anesthetic, $C_{LA,\text{initial}}$, is 7.5 mg/ml and the initial concentration of morphine, $C_{MSO,\text{initial}}$, is 10 mg/ml.

10. Find the final concentration of morphine, $C_{MSO,\text{final}}$, from Equation 9.
    a. 2.5 mg/ml
    b. 3.5 mg/ml
    c. 4.5 mg/ml
    d. 5.5 mg/ml

11. Calculate the final concentration of local anesthetic, $C_{LA,\text{final}}$, from Equation 10.
    a. 0.5 mg/ml
    b. 1.5 mg/ml
    c. 2.5 mg/ml
    d. 3.5 mg/ml

12. Using Equation 11, determine the initial volume of local anesthetic, $V_{LA,\text{initial}}$.
    a. 7.0 ml
    b. 8.0 ml
    c. 9.0 ml
    d. 10.0 ml

13. Using Equation 12, find the initial volume of morphine, $V_{MSO,\text{initial}}$.
    a. 10.5 mg
    b. 11.5 mg
    c. 12.5 mg
    d. 13.5 mg

14. Determine the volume of preservative-free normal saline, $V_{NS}$, to add to the combination...
Appendix: Continuing Medical Education Questions—Continued

15. Use Equation 16 to determine that the initial and final amounts of local anesthetic, in milligrams, are equivalent.

- a. 75 mg
- b. 85 mg
- c. 95 mg
- d. 105 mg

16. Use Equation 17 to determine that the initial and final amounts of morphine, in milligrams, are equivalent.

- a. 110 mg
- b. 115 mg
- c. 120 mg
- d. 125 mg
Answers to CME Questions for Tutorial 24, Vol. 6, Issue 3

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