Laboratory Reports

Density determination of local anaesthetic opioid mixtures for spinal anaesthesia

Gregory M.T. Hare MD PhD,
Johnson C.S. Ngan MD PhD FRCPC

Purpose: To measure the density of hyperbaric and isobaric local anaesthetics before and after addition of neuroaxial opioids to define a method for calculating any local anaesthetic/opioid mixture density based on individual component densities.

Methods: Density was determined using a volumetric pycnometer (25.0281 ± 0.0013 ml). The density of local anaesthetics (bupivacaine, lidocaine), opioids (fentanyl, morphine) and multiple anaesthetic/opioid mixtures were measured in quadruplicate and expressed in $\text{g}\cdot\text{ml}^{-1}$, at 37°C (mean $\pm$ SD). Regression analysis was used to derive a formula for calculating the density of any anaesthetic/opioid mixture.

Results: Individual components had the following densities ($\text{g}\cdot\text{ml}^{-1}$): bupivacaine 0.75%; 1.0252 ± 0.0001 , lidocaine 5%; 1.0249 ± 0.0001 , bupivacaine 0.5%; 0.9994 ± 0.0001 , lidocaine 2%; 1.0000 ± 0.0001 , $50\text{ }\mu\text{g}\cdot\text{ml}^{-1}$ fentanyl; 0.9936 ± 0.0001 , and $0.5\text{ mg}\cdot\text{ml}^{-1}$ morphine; 1.0001 ± 0.0001 . Using regression analysis, linear relationships were demonstrated between density (D) of anaesthetic/opioid mixture and the proportion of anaesthetic in the mixture (fractional volume of anaesthetic) ($r = 0.9999$, $P < 0.001$). The following formula was derived;

$$\text{Density}_{\text{Mixture}} = (\text{D}_{\text{Local anaesthetic}} - \text{D}_{\text{Opioid}}) \times \text{Fractional Volume Anaesthetic} + \text{D}_{\text{Opioid}}$$

Comparison of calculated and measured densities for multiple clinically relevant anaesthetic/opioid mixtures showed a significant degree of correlation ($r = 0.9996$, $P < 0.001$).

Conclusion: Density of spinal anaesthetic/opioid mixtures can be calculated from the component densities and the proportion of anaesthetic in the mixture.

Objectif : Mesurer la densité de solutions d'anesthésiques locaux isobares et hyperbares avant et après addition d'opiacés neuraxiaux pour déterminer une méthode de calcul de la densité de tout mélange d'anesthésique local/opiacé basée sur les densités des composantes individuelles.

Méthodes : La densité a été déterminée au moyen d'un pycnomètre volumétrique ($25,0281 \pm 0,0013$ ml). La densité des anesthésiques locaux (bupivacaine, lidocaïne), des opiacés (fentanyl, morphine) et de multiples mélanges d'anesthésiques locaux/opiacés a été mesurée en quadruple et exprimée en $\text{g}\cdot\text{ml}^{-1}$ à 37°C (moyenne $\pm$ écart type). Une analyse de régression a été utilisée pour produire une formule permettant le calcul de la densité de tout mélange anesthésique local/opiacé.

Résultats : Les différentes composantes avaient les densités suivantes ($\text{g}\cdot\text{ml}^{-1}$): bupivacaine 0,75%: $1,0252 \pm 0,0001$; lidocaïne 5%: $1,0249 \pm 0,0001$; bupivacaine 0,5%: $0,9994 \pm 0,0001$; lidocaïne 2%: $1,0000 \pm 0,0001$; fentanyl $50\text{ }\mu\text{g}\cdot\text{ml}^{-1}$: $0,9936 \pm 0,0001$; morphine $0,5\text{ ml}^{-1}$: $1,0001 \pm 0,0001$. En utilisant une analyse de régression, des relations linéaires ont été démontrées entre la densité (D) du mélange anesthésique local/opiacé et la proportion de l'anesthésique local dans le mélange (volume fractionnel de l'anesthésique local) ($r \geq 0,9999$, $P < 0,001$). La formule suivante a été produite:

$$\text{Densité}_{\text{mélange}} = (\text{D}_{\text{anesth local}} - \text{D}_{\text{opiacé}}) \times \text{Volume fractionnel de l'anesthésique} + \text{D}_{\text{opiacé}}$$

La comparaison des densités mesurées et calculées pour de multiples mélanges anesthésique local/opiacé ayant une pertinence clinique a montré un excellent degré de corrélation ($N=0,9996$, $P < 0,001$).

Conclusion : La densité d'un mélange anesthésique local/opiacé peut être calculée à partir de la densité des composants et de la proportion d'anesthésique local dans le mélange.

From the Department of Anaesthesia, Dalhousie University, Queen Elizabeth II Health Sciences Centre, 1278 Tower Road, Halifax, Nova Scotia, B3H 2Y9 Canada; Phone: 902-473-2331; Fax: 902-473-3820; E-mail: ghare@compuserve.com.
Presented in part at the meeting of the Canadian Anaesthetists' Society, Vancouver 1997.

Address correspondence to: Dr. Gregory M.T. Hare.

Accepted for publication December 6, 1997.

DENSITY is a major determinant of the distribution, duration and degree of the clinical block achieved in spinal anaesthesia.¹ Small changes in anaesthetic density may influence local anaesthetic distribution both experimentally and clinically.²⁻⁴ Bannister *et al.* demonstrated an increase in the average level of sensory block, from T₉ to T₇, as a result of increasing the local anaesthetic density by 0.0027 g·ml⁻¹, in the isobaric range.⁴

Baricity of an intrathecal agent is defined as the relative density of agent to that of cerebral spinal fluid (CSF) at specified temperatures.⁵ The density of human CSF has been determined by a number of authors, allowing local anaesthetic density to be defined as hypobaric, isobaric or hyperbaric relative to CSF density.⁵⁻⁷ Using mechanical oscillation resonance frequency techniques, Richardson *et al.*, have determined the density of human CSF to be 1.00064 ± 0.00012 g·ml⁻¹ for men and 1.00049 ± 0.00004 g·ml⁻¹ for premenopausal non-pregnant women, with an upper limit of hypobaricity of 1.00016–1.00037 g·ml⁻¹ at 37°C.⁷ Relative to CSF, some local anaesthetics, previously designated to be isobaric, are actually slightly hypobaric at 37°C.⁸⁻¹⁰

Addition of opioids to intrathecal local anaesthetics has become a popular method of enhancing analgesia associated with spinal anaesthesia.¹⁰⁻¹³ Opioid densities are lower than hyperbaric and, in some cases, isobaric local anaesthetics.¹⁰⁻¹³ While the effect of adding opioids to isobaric local anaesthetics has been examined,¹⁰ changes in the density of hyperbaric or isobaric local anaesthetics associated with opioid addition have not been defined in terms of the predictability of the final anaesthetic/opioid mixture density.

The purpose of this study was to measure changes in the density of isobaric and hyperbaric local anaesthetics after the addition of opioids and to determine a means of predicting the density of any anaesthetic/opioid mixture.

Methods

Density measurement

Density was determined to four significant figures using a volumetric pycnometer (Tercon, 25 ml, Fisher Scientific, Napean, Ontario). Before each measurement, the pycnometer was rinsed with deionised water followed by methanol and then dried with pressurised air. All measurements were performed in quadruplicate. Solutions were allowed to equilibrate to 37°C in

a water bath for 10 min before measurement. The temperatures of the solutions within the pycnometer were measured directly with a mercury manometer (Ertco #713, Ertco, West Paterson, New Jersey) to 37°C ± 0.1°C. Weights were determined to the nearest 0.0001 g using a weigh scale (Mettler H10, Mettler Toledo Inc., Burlington, Ontario).

The pycnometer volume was determined daily before measuring sample densities. Briefly, the pycnometer was filled with deionised water at room temperature and the tight fitting lid was applied. The pycnometer lid contained a central capillary channel to allow for overflow as the liquid content expanded upon heating to 37°C. The pycnometer volume was calculated by dividing the weight (g) of deionised water contained in the pycnometer at 37°C by the known density of water at 37°C (0.9933 g·ml⁻¹)¹⁴ using Formula #1.

Experimental solution densities were then determined in a similar manner. The weight of each solution (g) was determined at 37°C. The density was then determined by dividing the weight of the solution by the volume of the pycnometer (ml) using Formula #2.

Density determination of local anaesthetics

The following commercially available anaesthetics and opioids were used for density determination; hyperbaric bupivacaine 0.75% (containing dextrose 82.5 mg·ml⁻¹), isobaric bupivacaine 0.5% (Marcaine, Sanofi Winthrop, Markham, Ontario), hyperbaric lidocaine 5% (containing glucose 75 mg·ml⁻¹), isobaric lidocaine 2% (Xylocaine, Astra Pharma Inc., Mississauga, Ontario), isobaric tetracaine 1%, hypobaric tetracaine 0.1% (Pontocaine, Sanofi Winthrop, Markham, Ontario), preservative free 0.5 mg·ml⁻¹ morphine (Sabex Inc., Boucherville, Quebec), 50 µg·ml⁻¹ fentanyl (Abbott Laboratories Ltd., Toronto, Ontario) and 50 µg·ml⁻¹ sufentanil (Janssen Pharmaceutica Inc., Markham, Ontario).

Formula for determining opioid/local anaesthetic mixture density

Hyperbaric bupivacaine 0.75%, isobaric bupivacaine 0.5% and hyperbaric lidocaine 5% were each combined with water in six different dilutions with final local anaesthetic components of 0, 20, 40, 60, 80 and 100% by volume. Water was initially used, for practical reasons, because its density (0.9933 g·ml⁻¹) is very similar to that of both fentanyl (0.9936 g·ml⁻¹) and

$$\text{FORMULA 1} \quad \text{Volume (ml)} = (\text{Weight}_{\text{Pycnometer full}} - \text{Weight}_{\text{Pycnometer empty}}) (\text{g}) / .9933 (\text{g} \cdot \text{ml}^{-1})$$

$$\text{FORMULA 2} \quad \text{Density (g} \cdot \text{ml}^{-1}) = (\text{Weight}_{\text{Pycnometer full}} - \text{Weight}_{\text{Pycnometer empty}}) (\text{g}) / \text{Pycnometer Volume (ml)}$$

sufentanil ($0.9935 \text{ g}\cdot\text{ml}^{-1}$). The effect of additives on the density of local anaesthetics were then tested using opioids. Hyperbaric bupivacaine 0.75% and isobaric bupivacaine 0.5% were each combined with preservative free $0.5 \text{ mg}\cdot\text{ml}^{-1}$ morphine in four different dilutions with final local anaesthetic components of 0, 20, 60 and 100% by volume. In addition, preservative free $0.5 \text{ mg}\cdot\text{ml}^{-1}$ morphine was combined with $50 \mu\text{g}\cdot\text{ml}^{-1}$ fentanyl in four different dilutions with final morphine components of 0, 20, 60 and 100% by volume. The proportion of anaesthetic by volume was expressed as a fraction between 0 and 1.0 or 0% to 100% local anaesthetic by volume. This proportion was defined as the fractional volume of anaesthetic (FVA). Dilutions were performed using a $5.0 \pm 0.02 \text{ ml}$ graduated pipette to a final volume of 30 ml, prior to density determination.

The relationship between mixture density and fractional volume of anaesthetic was determined by plotting density (y axis) against the fractional volume of anaesthetic (x axis) (Figure 1). The slope (m), y intercept (b), r value and P values were determined by linear regression analysis (SigmaStat, Version 2, Jandel Scientific Software, San Rafael, California). In each case a linear relationship was defined by the equation $y = m(x) + b$, where y was the density (D), m was the slope of the line, x was the fractional volume of anaesthetic and b was the density at which the line intercepted the y axis. The slope (m) was defined by the change in density divided by the change in fractional volume of an aesthetic (see Formula #3).

Substituting the other values into the general equation produces an equation (see Formula #4) for determining the density of any anaesthetic/opioid mixture (Figure #1).

Similarly, the equation for the density of a mixture of two opioids can be written as shown in Formula #5.

Formula confirmation by comparing measured and calculated densities

Sample mixtures of anaesthetics and opioids ($n = 12$ determinations) were then prepared and the densities measured to determine if the values obtained by the calculated formulas were comparable to the actual measured densities. Morphine and fentanyl were added

FIGURE 1 Graphic representation of the formula for deriving the density of any local anaesthetic/opioid mixture based upon the density of the individual components and the relative proportion of anaesthetic (fractional volume anaesthetic). The density of the mixture changes from hyperbaric to isobaric below the density of cerebral spinal fluid (CSF).

FIGURE 2 Comparison of mixture density and fractional volume of anaesthetic for hyperbaric bupivacaine 0.75%, diluted with water or morphine. Note the significant linear relationship in both cases.

FORMULA 3 $m = (D_{\text{local anaesthetic}} - D_{\text{opioid}}) / (1.0 - 0) = (D_{\text{Local anaesthetic}} - D_{\text{Opioid}})$

FORMULA 4 $\text{Density}_{\text{Mixture}} = (D_{\text{local anaesthetic}} - D_{\text{opioid}}) \times \text{Fractional volume anaesthetic} + D_{\text{Opioid}}$

FORMULA 5 $\text{Density}_{\text{Opioid mixture}} = (D_{\text{opioid \#1}} - D_{\text{opioid \#2}}) \times \text{Fractional volume opioid \#1} + D_{\text{Opioid \#2}}$

$$\text{FORMULA 6 } \text{Density}_{\text{Mixture}} = (D_{\text{local anaesthetic}} - D_{\text{Opioid}}) \times \text{Fractional volume anaesthetic} + D_{\text{Opioid}}$$

separately, or in combination, to bupivacaine 0.75% and 0.5%, and lidocaine 5% and 2%, in amounts appropriate for clinical use. Four determinations were made per sample and densities reported in $\text{g}\cdot\text{ml}^{-1}$ (mean $\pm$ SD).

Results

The calibrated volume of the pycnometer was 25.0281 ± 0.0013 ml at 37°C , based on eight determinations performed on separate days. The densities of the commercially available local anaesthetics and opioids, as determined by volumetric pycnometer, are presented in Table I.

The linear relationships between anaesthetic mixture density and the fractional volume of anaesthetic are depicted in Table II. In Figure 2, the relationship between density of hyperbaric bupivacaine 0.75%, and the proportion of anaesthetic relative to water or morphine is depicted. The density of the anaesthetic mixture decreases in a linear fashion as the fractional volume of anaesthetic is reduced by adding a larger

proportion of water or opioid (Figure 2). In each case, the slope of the line represents the difference between the density of the pure anaesthetic (fractional volume of anaesthetic = 1.0) and the density of the opioid or water additive (fractional volume of anaesthetic = 0) (Table II, Figures 1, 2). The y intercept represents the density of 100% opioid or water additive (fractional volume of anaesthetic = 0). In every case the r values are highly significant ($P < 0.001$) (Table II). Dilution of morphine with fentanyl yields a similar linear relationship (Table II, $P < 0.001$).

Sample local anaesthetic/opioid mixtures, prepared to test the accuracy of the predictive formula, had measured densities between 0.9983 ± 0.0001 and 1.0177 ± 0.001 (Table III, fractional volume of anaesthetic between 0.2 and 0.8). In each case the calculated density was within $0.0006 \text{ g}\cdot\text{ml}^{-1}$ of the measured values. This was also the case when a combination of morphine and fentanyl were added to the anaesthetic (Table III). Comparison of measured density and calculated density produced a significant linear relationship (Figure 3, $r = 0.9996$, $P < 0.001$).

TABLE I Density of individual local anaesthetics and opioids.

Local anaesthetic or opioid	Designated baricity	Density, $\text{g}\cdot\text{ml}^{-1}$, 37°C
		Mean $\pm$ SD (n = 4)
Bupivacaine 0.75%	Hyperbaric	1.0252 ± 0.0001
Lidocaine 5%	Hyperbaric	1.0249 ± 0.0001
Bupivacaine 0.5%	Isobaric	0.9994 ± 0.0001
Lidocaine 2%	Isobaric	1.0000 ± 0.0001
Tetracaine 1%	Isobaric	1.0003 ± 0.0001
Tetracaine 0.1%	Hypobaric	0.9936 ± 0.0001
Morphine 0.5 $\text{mg}\cdot\text{ml}^{-1}$	Isobaric	1.0001 ± 0.0001
Fentanyl 50 $\mu\text{g}\cdot\text{ml}^{-1}$	Hypobaric	0.9936 ± 0.0001
Sufentanil 50 $\mu\text{g}\cdot\text{ml}^{-1}$	Hypobaric	0.9935 ± 0.0001

Discussion

In this study, a general formula for calculating the final density of any anaesthetic/opioid mixture was derived from density (D) measurements of local anaesthetics diluted with water or morphine, using linear regression analysis (see Formula #6) the formula was validated by comparing the measured and calculated densities of a number of clinically applicable local anaesthetic/opioid combinations. In all cases, the measured and calculated values were similar to within $0.0006 \text{ g}\cdot\text{ml}^{-1}$ with a highly significant correlation coefficient ($r = 0.9996$, $P < 0.001$) confirming that the density of

TABLE II Regression analysis derived data describing the linear relationships between anaesthetic/opioid mixture density and proportion of local anaesthetic. Density changes in a linear fashion as the proportion of additive to anaesthetic is increased with multiple dilutions

Anaesthetic or Opioid	Additive	Number of dilutions	Slope (m)	Y intercept (b)	r value
Bupivacaine 0.75%	Water	6	0.0319	0.9933	1.0000
Lidocaine 5%	Water	6	0.0317	0.9934	0.9999
Bupivacaine 0.5%	Water	6	0.0059	0.9936	0.9999
Bupivacaine 0.75%	Morphine	4	0.0250	0.9999	0.9999
Bupivacaine 0.5%	Morphine	4	-0.0004	0.9999	-0.9820
Morphine 0.5 $\text{mg}\cdot\text{ml}^{-1}$	Fentanyl	4	0.0062	0.9936	0.9998

r value; $P < 0.001$ in each case

TABLE III Comparison of measured and calculated anaesthetic/opioid mixture densities. Addition of morphine and/or fentanyl to local anaesthetics in variable proportions resulted in measured densities very close to the calculated values

<i>Anaesthetic</i>	<i>Opioid additive</i>	<i>Fractional volume of anaesthetic</i>	<i>Calculated density, g·ml⁻¹</i>	<i>Measured density, mg·ml⁻¹</i>	<i>Difference mg·ml⁻¹</i>
Bupivacaine 0.75%	Morphine	0.60	1.0149	1.0150 ± 0.0001	0.0001
Bupivacaine 0.75%	Morphine	0.20	1.0049	1.0048 ± 0.0001	0.0001
Bupivacaine 0.75%	Fentanyl	0.76	1.0178	1.0175 ± 0.0001	0.0003
Lidocaine 5%	Morphine	0.71	1.0175	1.0177 ± 0.0002	0.0002
Lidocaine 5%	Fentanyl	0.76	1.0178	1.0175 ± 0.0001	0.0003
Lidocaine 5%	Fentanyl	0.50	1.0093	1.0090 ± 0.0001	0.0003
Bupivacaine 0.5%	Morphine	0.60	0.9996	0.9997 ± 0.0001	0.0001
Bupivacaine 0.5%	Fentanyl	0.70	0.9983	0.9983 ± 0.0001	0.0000
Lidocaine 2%	Fentanyl	0.80	0.9987	0.9988 ± 0.0001	0.0001
Bupivacaine 0.75%*	Morphine	0.61	1.0141	1.0135 ± 0.0001	0.0006
	Fentanyl				
Lidocaine 5%*	Morphine	0.61	1.0141	1.0140 ± 0.0001	0.0001
	Fentanyl				
Bupivacaine 0.5%*	Morphine	0.61	0.9987	0.9989 ± 0.0002	0.0001
	Fentanyl				

*Local anaesthetic (2 ml) + morphine 0.4 mg (0.8 ml) + fentanyl 25 µg (0.5 ml)

an anaesthetic/opioid combination can be calculated from the individual component densities and the proportion of local anaesthetic in the mixture.

The clinical utility of this relationship can be exemplified by determining the final density of an anaesthetic/opioid mixture containing 15 mg hyperbaric bupivacaine 0.75% (2 ml), 0.4 mg morphine (0.8 ml) and 25 µg fentanyl (0.5 ml). The density changed from 1.0252 ± 0.0001 g·ml⁻¹, for the anaesthetic alone, to 1.0135 ± 0.0001 g·ml⁻¹, for the final mixture, representing a change of 0.0117 g·ml⁻¹ (Table III). This could have important clinical implications since a change in anaesthetic density of 0.0027 g·ml⁻¹ has been demonstrated to change the sensory block by about two dermatomes.⁴ Addition of opioid to 100 mg hyperbaric lidocaine 5% had a similar effect on density (Table III). Conversely, addition of opioids to isobaric local anaesthetics produced much smaller changes in density (Table III).

Richardson *et al.*, demonstrated that the density of isobaric local anaesthetic/opioid mixtures is proportional to the densities of the individual components.¹⁰ However, they did not measure the effect of addition of opioids on the density of hyperbaric anaesthetic/opioid mixtures or provide a means of calculating the expected mixture density. In this study, we confirmed these findings with respect to isobaric anaesthetics and demonstrated that addition of opioids to hyperbaric

anaesthetics changes the density of the mixture in a predictable manner. The proposed novel formula provides an easy means for calculating the final density of any anaesthetic/opioid mixture.

FIGURE 3 The significant linear relationship between measured and calculated density of anaesthetic/opioid mixtures confirms the accuracy of the predictive formula for determining the density of any anaesthetic/opioid mixture (n = 12 determinations).

Recently, Money *et al.*¹⁵ have compared changes in density associated with the addition of opioids to local anaesthetics with movement of anaesthetic/opioid mixtures within a glass spinal cord model, further characterising the importance of density changes on local anaesthetic/opioid mixture distribution.

Density measurements in this study were accurate to four decimal places ($0.0001 \text{ g}\cdot\text{ml}^{-1}$) with a high degree of reproducibility and small standard deviations. Using a glass spinal cord model, it has been estimated that very small density changes may influence flow of local anaesthetic.^{2,10,15} Larger changes in density ($0.0027 \text{ g}\cdot\text{ml}^{-1}$) are required to demonstrate different levels of sensory block achieved clinically.⁴ Density measurements of individual local anaesthetics and opioids in this study concur with other studies⁸⁻¹⁰ and should be sensitive enough to detect changes in density of local anaesthetic/opioid combinations relevant to clinical practice.

Density measurements were determined at 37°C because anaesthetic solutions likely equilibrate to body temperature very rapidly.^{9,10} The density of bupivacaine 0.5%, changes very little ($0.00015 \text{ g}\cdot\text{ml}^{-1}$) between 36.8°C and 37.2°C ,¹⁰ demonstrating that small variations in water bath temperature ($37 \pm 0.1^\circ\text{C}$) would have a negligible effect on density measurements in this study.

In summary, the density of any local anaesthetic/opioid mixture can be determined from the known density of the individual components and the proportion of anaesthetic in the mixture. With an increasing number of drugs being proposed for intrathecal administration, including clonidine,¹⁶ midazolam,¹⁷ magnesium sulfate¹⁸ and neostigmine,¹⁹ this principal could also be applied to determine the density of other anaesthetic/drug combinations.

Acknowledgments

We would like to acknowledge the help of Andrew P. Rodenhiser and Dr. Jan. C.T. Kwak for their assistance in performing this study, Marilyn LeBlanc for technical assistance and Drs. Coonan, Hall, Hung and Muir for their critical appraisal of the manuscript.

References

- Greene NM. Distribution of local anesthetic solutions within the subarachnoid space. *Anesth Analg* 1985; 64: 715-30.
- Stienstra R, Gielen M, Kroon JW, van Poorten F. The influence of temperature and speed of injection on the distribution of a solution containing bupivacaine and methylene blue in a spinal canal model. *Reg Anesth* 1990; 15: 6-11.
- Stienstra R, van Poorten JF. The temperature of bupivacaine 0.5% affects the sensory level of spinal anesthesia. *Anesth Analg* 1988; 67: 272-6.
- Bannister J, McClure JH, Wildsmith JAW. Effect of glucose concentration on the intrathecal spread of 0.5% bupivacaine. *Br J Anaesth* 1990; 64: 232-4.
- Davis H, King WR. Densities of cerebrospinal fluid of human beings. *Anesthesiology* 1954; 15: 666-72.
- Levine E, Muravchick S, Gold MI. Density of normal human cerebrospinal fluid and tetracaine solutions. *Anesth Analg* 1981; 60: 814-7.
- Richardson MG, Wissler RN. Density of lumbar cerebrospinal fluid in pregnant and nonpregnant humans. *Anesthesiology* 1996; 85: 326-30.
- Nicol ME, Holdcroft A. Density of intrathecal agents. *Br J Anaesth* 1992; 68: 60-3.
- Horlocker TT, Wedel DJ. Density, specific gravity and baricity of spinal anesthetic solutions at body temperature. *Anesth Analg* 1993; 76: 1015-8.
- Richardson MG, Wissler RN. Densities of dextrose-free intrathecal local anesthetics, opioids, and combinations measured at 37°C . *Anesth Analg* 1997; 84: 95-9.
- Abuzaid H, Prys-Roberts C, Wilkins DG, Terry DMS. The influence of diamorphine on spinal anaesthesia induced with isobaric 0.5% bupivacaine. *Anaesthesia* 1993; 48: 492-5.
- Singh H, Yang J, Thornton K, Giesecke AH. Intrathecal fentanyl prolongs sensory bupivacaine spinal block. *Can J Anaesth* 1995; 42: 987-91.
- Ferouz F, Norris MC, Arkoosh VA, Leighton BL, Boxer LM, Corba RJ. Baricity, needle direction, and intrathecal sufentanil labour analgesia. *Anesthesiology* 1997; 86: 592-8.
- Lentner C. (Ed.). Geigy Scientific Tables. Units of Measurement, Body Fluids, Composition of the Body, Nutrition. CIBA-GEIGY. 1981; 1: 50.
- Money P, Milne B, Parlow J, Raymond J. Density of various local anaesthetic-opioid solutions and their spread in an *in vitro* model of the spinal canal. *Can J Anaesth* 1997; 44: A28.
- Gentili M, Bonnet F. Spinal clonidine produces less urinary retention than spinal morphine. *Br J Anaesth* 1996; 76: 872-3.
- Bahar M, Cohen ML, Grinshpon Y, Chanimov M. Spinal anaesthesia with midazolam in the rat. *Can J Anaesth* 1997; 44: 208-15.
- Bahar M, Chanimov M, Grinspun E, Koifman I, Cohen ML. Spinal anaesthesia induced by intrathecal magnesium sulfate. An experimental study in a rat model. *Anaesthesia* 1996; 51: 627-33.
- Rose G, Xia Z, Tong C, Eisenach JC. Spinal neostigmine diminishes, but does not abolish, hypotension from spinal bupivacaine in sheep. *Anesth Analg* 1996; 83: 1041-5.