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LABORATORY INVESTIGATIONS

Density of spinal anaesthetic solutions of bupivacaine, levobupivacaine, and ropivacaine with and without dextrose

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Background. Spread of intrathecal local anaesthetics is determined principally by baricity and position of the patient. Hypobaric solutions of bupivacaine are characterized by an unpredictable spread of sensory block whereas addition of dextrose 80 mg ml^{-1} provides a predictable spread but to high thoracic levels. In contrast, dextrose concentrations between 8 and 30 mg ml^{-1} have shown reliable and consistent spread for surgery. Hence, the aim of this study was to determine the density of bupivacaine, levobupivacaine, and ropivacaine with and without dextrose at both 23 and 37°C before embarking on clinical studies.

Methods. Density (mg ml^{-1}) was measured using the method of mechanical oscillation resonance, accurate to five decimal places on 1250 samples. 500 density measurements were performed in a randomized, blind fashion at 23 and 37°C on 10 plain solutions of bupivacaine (2.5, 5, and 7.5 mg ml^{-1}) levobupivacaine (2.5, 5, and 7.5 mg ml^{-1}) and ropivacaine (2, 5, 7.5, and 10 mg ml^{-1}). Following this, 750 density measurements were taken at 23 and 37°C on the 5 mg ml^{-1} solutions of bupivacaine, levobupivacaine, and ropivacaine with added dextrose (10, 20, 30, 50, and 80 mg ml^{-1}).

Results. There was a linear relationship between density and dextrose concentration for all three local anaesthetics (R^2=0.99) at 23 and 37°C. The mean density of levobupivacaine 5 mg ml^{-1} was significantly greater than the densities of bupivacaine 5 mg ml^{-1} and ropivacaine 5 mg ml^{-1} after adjusting for dextrose concentration using analysis of covariance. This difference existed both at 23 and 37°C. The mean (SD) density of levobupivacaine 7.5 mg ml^{-1} was 1.00056 (0.00003) mg ml^{-1}, the lower 0.5% percentile (1.00047 mg ml^{-1}) lying above the upper limit of hypobaricity for all patient groups.

Conclusions. The density of local anaesthetics decreases with increasing temperature and increases in a linear fashion with the addition of dextrose. Levobupivacaine 5 mg ml^{-1} has a significantly higher density compared with bupivacaine 5 mg ml^{-1} and ropivacaine 5 mg ml^{-1} at 23 and 37°C both with and without dextrose. Levobupivacaine 7.5 mg ml^{-1} is an isobaric solution within all patient groups at 37°C.

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The baricity of injectate and position of the patient primarily determine the spread of intrathecal local anaesthetics.[1] Baricity is a measure of the relative density of local anaesthetic solution when compared with cerebrospinal fluid (CSF) and accordingly, a hypobaric local anaesthetic is

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defined as a solution with a density more than 3 standard deviations (SD) below mean human CSF density.[2 3] Human CSF density is not uniform, however, and varies according to age, sex, pregnancy, and illness. Using the above definition, the upper boundary of hypobaricity, as defined by two studies using oscillometry, varies either from 1.00016 to 1.00037 mg ml^{-1} [4] or from 1.00003 to 1.00023 mg ml^{-1} [5] at 37°C according to patient population.

Plain solutions of bupivacaine with a density of 0.9993 g ml^{-1} at 37°C are hypobaric in all patients. Clinically, this manifests as an unpredictable median sensory block height with a large inter-individual spread[6] and is occasionally associated with block failure when the spinal block has not spread high enough for surgery.

Addition of dextrose to local anaesthetics increases the density of injectate and provides a predictable and consistently high sensory block.[7] Unfortunately, two problems arise with high spinal blocks. First, profound sympathetic block as a result of extensive spinal block may enhance vagal tone, precipitate cardiac ischaemia, and possible cardiac arrest,[8] and secondly, the duration of sensory block is significantly shortened.[9]

Several studies of spinal anaesthesia for lower limb, urological surgery, and Caesarian section with bupivacaine (8 mg ml^{-1} dextrose)[10] and ropivacaine (10 mg ml^{-1} dextrose)[11 12] have demonstrated that addition of a small amount of dextrose to local anaesthetics provides a reliable and sufficient sensory block within a small range of median maximal block height. The availability of new local anaesthetics such as levobupivacaine and ropivacaine and their increased use in practice as intrathecal agents, affords the opportunity of assessing the density and composition of new solutions with and without dextrose before embarking on clinical studies.

Methods

Measurement

Density was measured using the method of mechanical oscillation resonance (DE50 density meter, Mettler-Toledo), controlled to 0.01°C by an electronic peltier thermostat. The physical principal involved is based on the electromagnetically induced oscillation of a glass tube. Each glass tube vibrates at a natural frequency that changes when filled with fluid; as mass increases, frequency decreases and the period of oscillation increases.

Calibration of the glass tube, otherwise known as factor (F) determination, was determined from the oscillation periods of desiccated air (ρ_A=0.99114 g ml^{-1}) and distilled deionized water (ρ_W=0.99333 g ml^{-1}) at 37°C according to the formula $F=(\rho_A-\rho_W)/(T_A^2-T_W^2)$ where T_A is the period of oscillation of air and T_W is the period of oscillation of water. Calculation of density (ρ_S) uses the formula $\rho_S=\rho_A-F(T_A^2-T_S^2)$ where T_S is the period of oscillation of the test solution.

Density measurements and calibration of the densitometer were performed by the University Department of Anaesthesia Research Nurse who established, before the study, a standardized technique. Local anaesthetic solutions with the same batch number were prepared by the author and the Research Nurse remained blind to the contents. Sixty millilitres of solutions were mixed (Table 1) within a sterile glass container with a tight fitting screw top, which was placed horizontally on to rollers within an electronic temperature controlled water bath set at either 23 or 37°C. These temperatures were chosen first to show the difference in density of local anaesthetics at room and body temperature and secondly to validate the methodology when measuring density at 37°C. The methodology involved automatically oscillating the solution within the water bath for 1 h in order to minimize microbubble formation. Microbubbles, invisible to the naked eye, are responsible for quite erroneous measurements of density. Following oscillation and de-gassing, five, 10 ml syringes were prepared by the author. Ten millilitre syringes allowed ease of injection of 2 ml samples into the port of the densitometer. Thus, 25 density measurements of each prepared solution were recorded to five decimal places by the research nurse.

Table 1 Preparation and composition of local anaesthetic solutions. All preparations mixed as 60 ml solutions, oscillated within water bath set to 23 and 37°C for 1 h to eliminate microbubbles, then aspirated into five 10 ml syringes for analysis

Dextrose (mg ml^{-1})	Volume (ml) of local anaesthetic 7.5 mg ml^{-1}	Volume (ml) of dextrose 5 mg ml^{-1}	Volume (ml) of dextrose 10 mg ml^{-1}	Volume (ml) of dextrose 50 mg ml^{-1}	Saline (ml)
10	40	12			8
20	40		12		8
30	40		18		2
50	40			6	14
80	40			9.6	10.4

Solutions

Bupivacaine was compared with two new long duration local anaesthetics, levobupivacaine and ropivacaine. A total of 1250 density measurements were performed in a randomized, double blind fashion on local anaesthetic solutions with and without dextrose at two temperatures, 23 and 37°C.

In the first part of the study, nine concentrations of commercially available plain local anaesthetics were measured at 23 and 37°C; 2.5, 5, and 7.5 mg ml^{-1} preparations of bupivacaine and levobupivacaine and 2, 7.5, and 10 mg ml^{-1} solutions of ropivacaine. As clinical intrathecal studies have been performed with dextrose containing solutions of 5 mg ml^{-1} ropivacaine[12] a preparation was made by a 50:50 dilution of 1 mg ml^{-1} ropivacaine with sterile saline. Thus, at each temperature, 250 measurements of density were made from 10 different plain local anaesthetics.

For the second part of the study, dextrose was added in concentrations of 10, 20, 30, 50, and 80 mg ml^{-1} using the above standardized technique (Table 1) in such a way that the concentration of local anaesthetic was 5 mg ml^{-1}. At each temperature, a total of 375 density measurements were made from 15 solutions of three local anaesthetics at five different concentrations of dextrose.

Statistical analysis

Repeated measures analysis of variance was initially used to compare the variability of measurement within each syringe to the variability between syringes. Changes in density as a result of increased concentration of plain local anaesthetic were compared using one way analysis of variance and the post-hoc Tukey–Kramer Multiple-Comparison Test. With regard to 5 mg ml^{-1} preparations of each local anaesthetic with and without added dextrose, linear regression analysis first determined the best approximation of a straight-line relationship between density and dextrose concentration, then an F ratio was calculated to determine if these slopes were equal. Subsequently, analysis of covariance (ANCOVA) was applied to the data to determine any differences in density between local anaesthetics while controlling for dextrose concentration. Similiarly, ANCOVA was used to measure difference in density between plain solutions while controlling for temperature. All recordings are presented as mean and 3 SD. Each commercial solution was also analysed in Ninewells Hospital Biochemistry Department for sodium, potassium ions, osmolality, and pH. Statistical analysis was performed using Number Cruncher Statistical Systems (NCSS), Hayes, Utah.

Table 2 Density of plain solutions of bupivacaine, levobupivacaine, and ropivacaine at 23 and 37°C. Data represent mean (3 SD)

Solution	Density at 23°C mg ml^{-1}	Density at 37°C mg ml^{-1}
Bupivacaine 2.5 mg ml^{-1}	1.00345 (0.00003)	0.99921 (0.00009)
Bupivacaine 5 mg ml^{-1}	1.00376 (0.00002)	0.99944 (0.00012)
Bupivacaine 7.5 mg ml^{-1}	1.00369 (0.00002)	0.99938 (0.00017)
Levobupivacaine 2.5 mg ml^{-1}	1.00418 (0.00001)	0.99985 (0.00002)
Levobupivacaine 5 mg ml^{-1}	1.00419 (0.00002)	1.00024 (0.00009)
Levobupivacaine 7.5 mg ml^{-1}	1.00482 (0.00002)	1.00056 (0.00010)
Ropivacaine 2 mg ml^{-1}	1.00372 (0.00002)	0.99960 (0.00006)
Ropivacaine 5 mg ml^{-1}	1.00380 (0.00002)	0.99953 (0.00013)
Ropivacaine 7.5 mg ml^{-1}	1.00380 (0.00003)	0.99953 (0.00014)
Ropivacaine 10 mg ml^{-1}	1.00381 (0.00002)	0.99950 (0.00010)

Results

The variability of density measurement either within or between all 50 syringes was negligible. Therefore, mean density and SD was calculated from all 25 measurements from the batch of five syringes corresponding to each local anaesthetic concentration.

Plain solutions

Increasing the concentration of bupivacaine and levobupivacaine from 2.5 to 5 mg ml^{-1} and 7.5 mg ml^{-1} significantly increased the density of the latter solutions using one way analysis of variance F-ratio 191.4, $P<0.01$ for bupivacaine and F-ratio 4329.9, $P<0.01$ for levobupivacaine $P<0.01$. Increasing the concentration of ropivacaine up to 10 mg ml^{-1} also significantly increased density, F-ratio 34.8, P,0.01. The exception was between 5 and 7.5 mg ml^{-1} ropivacaine for which no difference in density was observed.

Effect of temperature

Mean (SD) density of each local anaesthetic solution was significantly different; higher at 23 compared with 37°C (Table 2). The slope of the reduction in density with increasing temperature was equivalent for all plain local anaesthetics, F-ratio for equality of slope=62.9, $P<0.01$. For every increase in temperature by 1°C between 23 and 37°C the density of all plain solutions fell by 0.0003 mg ml^{-1}. ANCOVA using density as the independent variable and temperature as the covariate, showed that the adjusted means (for temperature) of local anaesthetics to be significantly different F-ratio=63.1, $P<0.01$.

Effect of dextrose

Density increased significantly and in a linear fashion with addition of dextrose to 5 mg ml^{-1} preparations of local anaesthetic. Using linear regression analysis, the best-fit slope was 0.0003, R^2=0.99 for all local anaesthetics at both 23 (Table 3) and 37°C (Table 4). The F-ratio for equality of slopes was 20.7, $P<0.01$ at 23°C and 3.7, P=0.02 at 37°C indicating no difference in slope gradient between local anaesthetics with increasing dextrose concentrations. ANCOVA using density as the independent variable and dextrose concentration as the covariate, showed that the adjusted means (for dextrose) of local anaesthetics to be

Table 3 Density of 5 mg ml^{-1} solutions of bupivacaine, levobupivacaine, and ropivacaine with respect to dextrose concentration at 23°C. Slope, intercept and R^2 line best fitting data. Data represent mean (3 SD)

Solution	10 mg ml^{-1}	20 mg ml^{-1}	30 mg ml^{-1}	50 mg ml^{-1}	80 mg ml^{-1}	Slope (10^{-4})	Intercept	R^2
Bupivacaine	1.00755 (0.00007)	1.00986 (0.00008)	1.01300 (0.00009)	1.01984 (0.00026)	1.02890 (0.00051)	3.13	1.00390	0.99
Levobupivacaine	1.00785 (0.00008)	1.01092 (0.00034)	1.01408 (0.00022)	1.02054 (0.00112)	1.03042 (0.00026)	3.23	1.00448	0.99
Ropivacaine	1.00679 (0.00005)	1.00998 (0.00005)	1.01317 (0.00010)	1.01949 (0.00019)	1.02980 (0.00060)	3.34	1.00350	0.99

Table 4 Density of 5 mg ml^{-1} solutions of bupivacaine, levobupivacaine, and ropivacaine with respect to dextrose concentration at 37°C. Slope, intercept, and R^2 line best fitting data. Data represent mean (3 SD)

Solution	10 mg ml^{-1}	20 mg ml^{-1}	30 mg ml^{-1}	50 mg ml^{-1}	80 mg ml^{-1}	Slope (10^{-4})	Intercept	R^2
Bupivacaine	1.00254 (0.00017)	1.00564 (0.00031)	1.00874 (0.0026)	1.01490 (0.00029)	1.02424 (0.00163)	3.10	0.99944	0.99
Levobupivacaine	1.00325 (0.00004)	1.00642 (0.00042)	1.00945 (0.00016)	1.01577 (0.00202)	1.02487 (0.00348)	3.09	1.00022	0.99
Ropivacaine	1.00260 (0.00015)	1.00572 (0.00006)	1.00876 (0.00027)	1.01528 (0.00086)	1.02450 (0.00168)	3.13	0.99984	0.99

Table 5 Molar concentration, electrolyte composition, osmolality, pH, and H^+ concentration of plain solutions of bupivacaine, levobupivacaine and ropivacaine at 37°C

	Local anaesthetic (mmol $litre^{-1}$)	Sodium (mmol $litre^{-1}$)	Potassium (mmol $litre^{-1}$)	Osmolality (mosmol kg^{-1})	pH	H^+ (nmol $litre^{-1}$)
Bupivacaine 2.5 mg ml^{-1}	7.7	133	<0.5	272	6.96	109
Bupivacaine 5 mg ml^{-1}	15.4	134	<0.5	287	6.74	182
Bupivacaine 7.5 mg ml^{-1}	23.1	125	0.8	281	6.57	269
Levobupivacaine 2.5 mg ml^{-1}	8.7	149	<0.5	308	6.42	379
Levobupivacaine 5 mg ml^{-1}	17.3	151	<0.5	322	6.04	914
Levobupivacaine 7.5 mg ml^{-1}	26.0	151	0.9	334	5.85	1413
Ropivacaine 2 mg ml^{-1}	6.4	143	<0.5	292	6.82	152
Ropivacaine 7.5 mg ml^{-1}	24.1	126	<0.5	287	6.65	222
Ropivacaine 10 mg ml^{-1}	32.2	120	<0.5	291	6.22	599

significantly different at 23°C, F-ratio 99.0, $P<0.01$ and at 37°C, F-ratio 12.8, $P<0.01$.

Electrolyte composition

Analysis of electrolyte composition, osmolarity, and pH showed levobupivacaine to have a higher sodium content osmolarity and H^+ ion concentration compared with either bupivacaine or ropivacaine. Table 5 shows that as the molar concentration of levobupivacaine is increased, sodium ion concentration is held constant, thus increasing osmolality. In contrast, as the concentration of bupivacaine and ropivacaine is increased, sodium concentration is reduced, maintaining osmolality between 272 and 292 mmol kg^{-1}.

Discussion

This study has demonstrated several differences in the composition and density of currently available long acting local anaesthetics. First, as the temperature of bupivacaine, levobupivacaine, or ropivacaine increases, density decreases. Secondly, addition of dextrose concentration increases the density of all three local anaesthetics (R^2=0.99). Thirdly, using ANCOVA, the density of levobupivacaine 5 mg ml^{-1} with and without dextrose was significantly greater than the corresponding densities of bupivacaine 5 mg ml^{-1} and ropivacaine 5 mg ml^{-1} at both 23 and 37°C. Finally, the mean (SD) density of levobupivacaine 7.5 mg ml^{-1} was 1.00056 (0.00003) mg ml^{-1}, the lower 0.5% percentile (1.00047 mg ml^{-1}) lying above the upper limit of hypobaricity for all patient groups and thus can be regarded as an isobaric solution.

The rank order of density of bupivacaine, levobupivacaine, or ropivacaine is the same at temperatures of 23 and 37°C and is consistent over the range of dextrose concentrations used in clinical practice. Analysis was performed at 23 and 37°C to illustrate the relationship between densities of local anaesthetic formulations before and after clinical intrathecal injection. As thermal equilibrium occurs quickly within CSF, it is highly unlikely that density at 23°C has any relevance to spread. However, the consistency of measurement of adjusted means and slope over a range of dextrose concentrations at 37°C was similar to measurement at 23°C and justifies our rigorous methodology for de-gassing of solutions by oscillation in a water bath heated to 37°C for 1 h. Initial pre-study measurements of density were highly variable and sometimes unrecordable at 37°C as microbubbles are responsible for erroneous measurements of density. This is the first study to describe this phenomenon with regard to measurement of local anaesthetic density.

A linear relationship existed between the density of bupivacaine, levobupivacaine, or ropivacaine and increasing dextrose concentration at 23 and 37°C. The F ratio for equality of slopes was 20.7, $P<0.01$ at 23°C and 3.7, $P=0.02$ at 37°C. The derived slope (3.1×10^{-4} to 3.3×10^{-4}) is in agreement with a study by Hare and colleagues[13] in which density was measured using multiple dilutions but is higher than that calculated by Hallworth and colleagues[14] albeit using solutions up to 10 mg ml^{-1} dextrose. With incremental addition of dextrose to 5 mg ml^{-1} bupivacaine, levobupivacaine, and ropivacaine, consistent and significant differences existed between local anaesthetics at 23°C, F ratio 99.0, $P<0.01$ and 37°C, F ratio 12.8, $P<0.01$.

All concentrations of bupivacaine and ropivacaine were hypobaric when measured at 37°C. These results compare

favourably with laboratory studies performed with bupivacaine and ropivacaine using the same oscillometric technology accurate to five decimal places.[4 5 14] In contrast, the mean (SD) density of levobupivacaine 7.5 mg ml^{-1} was 1.00056 (0.00003) mg ml^{-1}, the lower 0.5% percentile (1.00047 mg ml^{-1}) lying above the upper limit of hypobaricity for all patient groups and thus can be regarded as an isobaric solution. Levobupivacaine 5 mg ml^{-1} (1.00024 (0.00003) mg ml^{-1}) is slightly hypobaric according to the definition of Richardson and Wissler[4] but may be regarded as isobaric within males and postmenopausal women according to the results of Lui and colleagues.[5]

The increased density of levobupivacaine may be attributable to its higher sodium ion content and higher osmolality compared with bupivacaine and ropivacaine. As the concentration of levobupivacaine is increased, sodium concentration is held constant, whereas as the concentration of bupivacaine and ropivacaine is increased, sodium concentration is reduced. In addition, there is a 13% additional contribution to osmolality by levobupivacaine compared with bupivacaine. Ampoules of levobupivacaine contain 7.5 mg ml^{-1} free base (26.0 mmol $litre^{-1}$) whereas corresponding ampoules of bupivacaine contain 6.66 mg ml^{-1} free base (23.1 mmol $litre^{-1}$) and ampoules of ropivacaine 6.63 mg ml^{-1} (24.1 mmol $litre^{-1}$).

Although mathematically the lower limit of hyperbaricity may be defined as 3 SD above the mean, the actual density at which local anaesthetics behave consistently as a hyperbaric solution is not known. Other determinants of spread include patient posture, composition of solution, type of needle, level and speed of injection, volume,[15] viscosity, and protein content of CSF,[5] and in pregancy, inferior vena cava obstruction.[11]

Furthermore, opioids are often added to spinal preparations of local anaesthetics to improve anaesthesia and prolong post-operative analgesia. Opioids such as fentanyl are hypobaric (0.9933 mg ml^{-1}) and when added to a local anaesthetic will render the subsequent mixture even more hypobaric. The degree to which this occurs is proportional to the respective densities and volumes of individual drugs.[13] Although changes in density may seem minimal and clinically unnnecessary, a change in density as low as 0.0006 mg ml^{-1} may influence spread of local anaesthetic.[2]

In conclusion, this study has shown that the density of bupivacaine, levobupivacaine, and ropivacaine fell with increasing temperature and increased with added dextrose in a predictable, linear fashion. Significant differences existed between all three local anaesthetics when added to dextrose at both 23 and 37°C. Levobupivacaine 7.5 mg ml^{-1} is isobaric in all patient groups.

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