In-Vitro Changes of Osmolality and Density of Spinal Anesthetic Solutions

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The purpose of this study was to determine: (1) osmolalities and densities at room and body temperature of the drugs currently marketed for intrathecal use; and (2) the rate at which injected drugs attained thermal and osmolal equilibrium with cerebrospinal fluid. Testing the drugs with a model of the spinal canal revealed changes that could be accounted for by physical factors alone. It was found that: (1) most solutions were isotonic; (2) anisotonic solutions rapidly reached isotonicity after injection; (3) dextrose 10 per cent and lidocaine 5 per cent with dextrose 7.5 per cent demonstrated persistent hypertonicity five minutes after being injected into the model; and (4) solutions injected at room temperature reached body temperature within 60 seconds. We concluded that premixing anisotonic solutions to bring them closer to physiologic isotonicity does not necessarily sacrifice the advantages of a weighted solution. Knowledge of a solution's osmolality and density at 37° C. is helpful in determining its appropriateness for intrathecal use in patients.

THE OSMOLALITIES of some solutions used intrathecally fall outside the normal range for human cerebrospinal fluid (CSF). A partial list of values was published by Sawinski *et al.*[1] The densities of some agents, many no longer marketed, have been studied by previous investigators,[2] but there is no recent information about currently used spinal anesthetic agents. The purpose of this study, therefore, was to determine: (1) the osmolalities and densities at room and body temperature of the drugs currently used intrathecally; (2) the rate at which solutions at room temperature reach body temperature after being injected into a model; and (3) the rate at which anisotonic drugs equilibrate with CSF when injected into the model.

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Accepted for publication August 21, 1967.

Methods

Osmolality was determined by the freezing point depression method using a Fiske osmometer equipped with a microadapter. The instrument was calibrated before and after use with standard solutions of NaCl containing 100, 300, 500 and 1,000 mosM/kg. water.[3]

Densities were obtained by measuring weight and volume of fluids contained in 0.5 ml. micropipettes. The exact volume of each pipette was established by determining the weight of sterile distilled water it would hold. Knowing these weights and the density of water at the pipetting temperature,[4] the volume of each pipette was determined (D =M/V). Pipetting was done at room temperature (23° C.) and in a large oven at body temperature (37° C.). A Sartorius electronic balance was used to weigh the micropipettes. At least six determinations were done on all solutions.

A model of the spinal canal was constructed (fig. 1),[5] which contained the approximate normal volume of CSF in the spinal canal. The composition of simulated CSF used to charge the model was calculated from published data.[5, 6] The solution had an osmolality of 280 mosM./kg. water, a *p*H of 7.3 and a specific gravity ($D^{37}/37$) of 1.0050. The stock solution was kept under oil, and the model was operated in a closed system to prevent escape of CO_2 and subsequent changes in *p*H. During a study spinal solutions were injected at the artificial L3–L4 interspace and samples were taken from various sites 60 seconds and five minutes post injection. Tests were done with the model in the horizontal and vertical positions. Osmolality determinations required only 0.2 ml., minimizing disturbances of the remaining solution. A needle thermocouple connected to a Sanborn multichannel optical recorder (model 560) was inserted into the simulated CSF for monitoring of temperature. The temperature was maintained at 37° C.

Results

The densities and specific gravities of solutions tested and limits of normal human CSF are listed in table 1. The differences in densities at room and body temperatures are compared with the density of normal CSF at 37° C. in figure 2. Figure 3 reveals how quickly the solutions reached body temperature after injection into the model. Solutions of tetracaine and dextrose caused a drop in the temperature at the site of injection to 31° C. in the first two seconds; within the next 60 seconds, the temperature rose to 37° C. When 10 ml. of light dibucaine were used, the temperature fell to 29° C., requiring approximately three minutes to return to body temperature.

Osmolalities of the solutions are shown in figure 4. Most agents were close to isotonicity; exceptions included distilled water, dibucaine 0.15 per cent, lidocaine 5 per cent with dextrose 7.5 per cent, dextrose 10 per cent and procaine 10 per cent.

Table 2 shows the changes in osmolality of fluid in the model after various isobaric or hyperbaric intrathecal agents were injected. They are presented in this manner because the post-injection sampling was at the site of in-

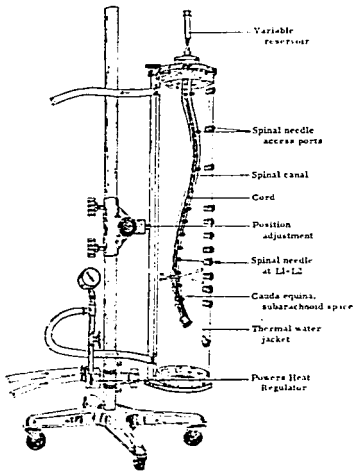

FIG. 1. Diagram of model. Capacity of filled canal was 30 ml. Spinal needles were introduced through access ports into the simulated subarachnoid space for injection and sampling. The variable reservoir maintained a closed system and permitted injection of fluid without causing pressure changes. Position adjustment allowed for operation in the horizontal and vertical positions.

TABLE 1. Densities and Specific Gravities at 23° C. and 37° C. of Various Solutions used Intrathecally

Code No.	Solution	Density at 23° C. Gm./ml.	Density at 37° C. Gm./ml.	Specific Gravity* D agent/D water
1	Distilled water	0.9976	0.9934	1.0000
—	Lower limits of CSF†	0.9987	0.9944	1.0014
2	Tetracaine 1%	0.9990	0.9947	1.0014
3	Procaine 1%	0.9995	0.9952	1.0019
4	Procaine 2%	1.0010	0.9967	1.0034
5	Dibucaine 0.15%	1.0012	0.9969	1.0036
6	Mepivacaine 4%	1.0022	0.9979	1.0047
7	Epinephrine 0.1%	1.0033	0.9991	1.0057
8	Dibucaine 0.5%	1.0035	0.9992	1.0060
9	Saline	1.0040	0.9997	1.0065
10	Phenylephrine 0.2%	1.0055	1.0012	1.0079
—	Upper limits of CSF†	1.0066	1.0023	1.0090
11	Ephedrine sulfate 5%	1.0075	1.0031	1.0099
12	Dibucaine 0.25%, dextrose 5%	1.0133	1.0093	1.0159
13	Procaine 10%	1.0151	1.0107	1.0176
14	Tetracaine 0.2%, dextrose 6%	1.0175	1.0132	1.0200
15	Tetracaine 0.3%, dextrose 6%	1.0205	1.0162	1.0230
16	Lidocaine 5%, dextrose 7.5%	1.0308	1.0265	1.0333
17	Dextrose 10%	1.0354	1.0309	1.0379

* Specific gravities at 23° C. ($D^{23}/23$) or 37° C. ($D^{37}/37$) do not differ more than ±0.0001.
† Limits of normal CSF. Davis and King.[7]

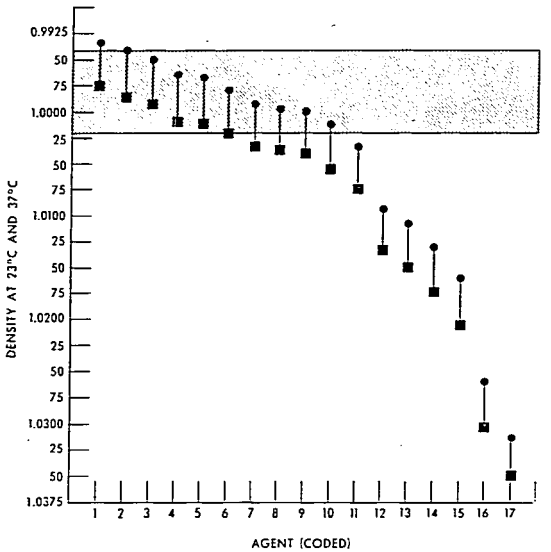

FIG. 2. Densities at 23° C. (■) and 37° C. (●) of intrathecal agents. Coded agent numbers correspond to those used in table 1. Horizontal shaded area represents the range of normal CSF at body temperature. Some agents which were hyperbaric at room temperature became isobaric when warmed to body temperature (*e.g.*, 7, 8, 9).

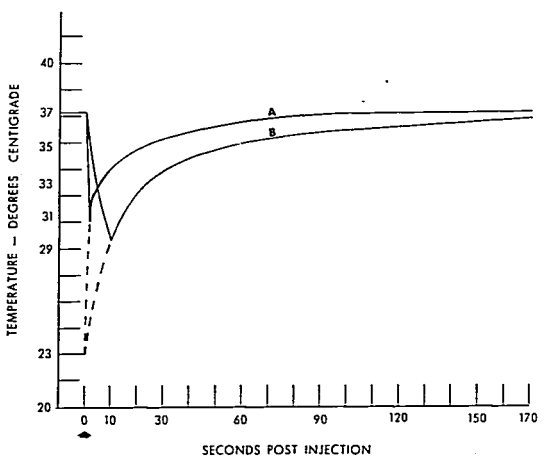

FIG. 3. Temperature changes at the site of injection of spinal solutions. Needle thermocouple sensitivity: 50° C./sec. Injection site and site of thermocouple placement: L3-L4 interspace. Rate of injection: 1 ml./sec. Line A: 2 ml. of equal parts of tetracaine 1 per cent and dextrose 10 per cent. Line B: 10 ml. of light dibucaine. Dotted lines were assumed.

jection or lower. Most of these agents were also hypertonic, exceptions being agent 6 (isotonic) and agent 8 (hypotonic). The data demonstrate a rapid change towards isotonicity at the site of injection, within 60 seconds. Within five minutes, fluid at the site of injection was isotonic regardless of agent used. The fluid in the distal end of the model (S2), however, was still hypertonic after five minutes when agents 13, 16 and 17 were used. This was true when the model was operated in the vertical or horizontal position, although the tonicity was less in the horizontal position.

Table 3 shows changes in osmolality when hypobaric agents were injected into the model. Because of their lightness, sampling was done above the site of injection; both fluids were hypotonic. Sixty seconds after injection of 1 ml. distilled water into the model, fluid was slightly hypotonic near the site of injection. Five minutes post injection the fluid was isotonic at all sampled areas. Injection of 10 ml. of agent 5 (light dibucaine) resulted in an osmolality of 231 mosM./kg. at the site of injection within 60 seconds. After five minutes the osmolality below the site of injection was normal while the fluid above the site of injection remained slightly hypotonic.

Figure 5 compares the density at 37° C. and the osmolality of the agent studied with the normal range for human CSF. Shown are

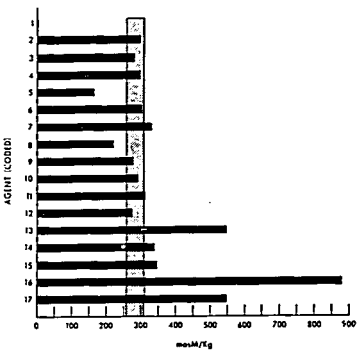

FIG. 4. Osmolality (mosM./kg. water) of solutions used intrathecally. Coded numbers correspond to those used in table 1. Shaded vertical column represents normal CSF range (Goldberg, *et al.*[8]).

the changes in osmolality and density that resulted from premixing lidocaine and dextrose solution with various amounts of distilled water. There was a linear relationship between percentage of dilution and distance away from the diluted agent. Lidocaine 5 per cent with dextrose 7.5 per cent was brought to isotonicity without completely sacrificing the advantage of a weighted solution.

TABLE 2. Change in Osmolality (mosM./kg. water) of CSF after Injection of Various Isobaric or Hyperbaric Intrathecal Solutions*

Model Position	Solution Injected†	Solution Osmolality	CSF Osmolality	60 Sec. Post Injection		5 Min. Post Injection	
				L3-L4	L4-L5	L3-L4	S2
Vertical	6	308	280	291	283	287	280
	8	219	280	268	261	271	280
	13	547	280	316	318	290	363
	15	345	280	281	283	280	282
	16	879	280	300	299	290	356
	17	547	280	291	295	286	318
Horizontal	13	547	280	327	315	294	322
	16	879	280	306	299	294	324
	17	547	280	296	304	295	319

* 1 ml. of solution injected at L3-L4 through 22-gauge spinal needle at 1 ml./sec.
† Solution code number refers to that used in table 1.

TABLE 3. Change in Osmolality (mosM/kg. water) of CSF after Injection of Hypobaric, Hypotonic Intrathecal Solution*

Solution† Injected	Solution Osmolality	CSF Osmolality	Amt. Injected (ml.)	60 Sec. Post Injection		5 Min. Post Injection		
				L3–L4	T10–11	T10–T11	S2	C3–C4
1	0	280	1	265	263	275	280	280
5	163	280	10	231	263	257	278	266

* Injected at L3–L4 through 22-gauge spinal needle at 1 ml/sec.
† Agent code number refers to that used in Table 1.
Model operated in vertical position.

Discussion

According to Dormandy,[9] homeostatic maintenance of osmolality is more vigorously and successfully controlled than any other aspect of our internal environment, including hydrogen ion concentration. The changes in osmolality that occurred in the *in vitro* system developed for this study were mostly the result of dilution and mixing. Minor changes in *p*H that resulted when an acidic intrathecal solution was injected into the mildly basic CSF may have caused some precipitation and decrease in osmolality. However, there was no adsorption or absorption of the drugs by nerves or blood vessels, and no movement of water across membranes. The data demonstrated only the change that could be expected from physical factors alone. These factors caused rapid return to isotonicity of all agents except the hyperbaric hypertonic agents such as dextrose 10 per cent and lidocaine 5 per cent with dextrose 7.5 per cent. Premixing of anisotonic solutions brought them closer to physiologic isotonicity, but also changed their densities.

Density values were used in preference to specific gravity in this study because there is an opportunity for confusion when the latter term is used. Density is the weight in grams of a liquid divided by its volume in milliliters at any given temperature ($D = M/V$). Specific gravity is a comparison of two densities (D of liquid in question/D of water). As Macintosh[10] points out, the temperature of reference water frequently is not mentioned. It could be 4° C., 20° C., 37° C. or the same temperature as the liquid in question. Thus, the use of density values at different temperatures results in different specific gravities. Unless the temperatures of both liquids are stated, specific gravities afford no means of comparing weights of different fluids. The problem in using specific gravity in comparisons of baricity is that most specific gravity values furnish no temperature references or incomplete ones. Density, therefore, is emphasized in this paper because of the confusion surrounding the term "specific gravity." Table 1 shows that the specific gravities ($D^{23}/23$ or $D^{37}/37$) of the various solutions were almost the same. This was because they had approximately the same water content. Their densities, however, varied with temperature, and their baric movement probably should be considered at the density of body temperature. In the model, 2 ml. of solution (at room temperature) approached body temperature within seconds.

Summary

Osmolalities and densities at room and body temperatures of solutions used intrathecally during spinal anesthesia were determined. A model of a human spinal canal was constructed and *in vitro* studies were done of changes in osmolality when anisotonic solutions were injected. Most solutions were isotonic. Osmolality of anisotonic solutions rapidly changed towards that of normal CSF as the injected agent was displaced from the site of injection. The notable exceptions to this were the hyperbaric hypertonic solutions—dextrose 10 per cent and lidocaine 5 per cent with dextrose 7.5 per cent. *In vitro*, these solutions demonstrated mild hypertonicity in the distal portion of the model. Premixing with distilled water brought the tonicity closer to physiologic range without completely sacrificing the advantage of the weighted solution.

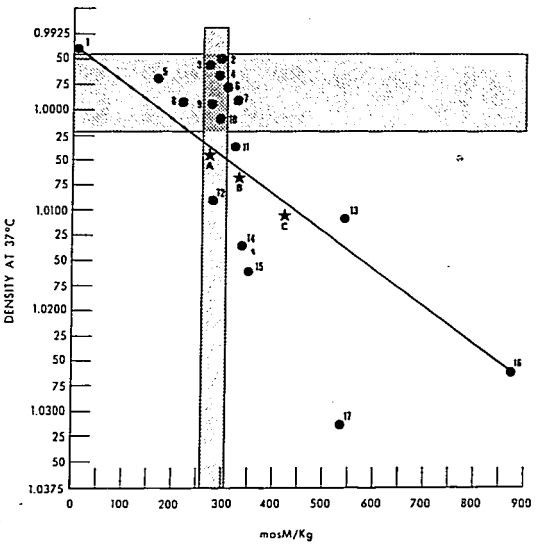

FIG. 5. Comparison of densities and osmolalities of various intrathecal agents. Coded agent numbers correspond to those in table 1. Shaded areas represent ranges of normal CSF. A line connecting agents 1 (distilled water) and 16 (lidocaine 5 per cent with dextrose 7.5 per cent) illustrates the change in density and osmolality when various proportions of these agents were mixed. Point A: 2 ml. distilled water, 1 ml. lidocaine with dextrose (66 per cent dilution). Point B: 1.5 ml. distilled water, 1 ml. lidocaine with dextrose (60 per cent dilution). Point C: 1 ml. distilled water, 1 ml. lidocaine with dextrose (50 per cent dilution). The percentage of dilution multiplied by the length of line 1-16 was the approximate distance between the value for the agent diluted 16, and that for distilled water. (*E.g.*, the distance of point A from 16 = (66 per cent) × (length of line 1-16).)

The author wishes to thank Dr. Ralph Nelson for his valuable assistance and advice. The technical assistance of Arlene McKinnell, Helene Vohnout, Robert Marbury and Anthony Niederst is gratefully acknowledged. The pharmaceutical companies, Ciba, Winthrop, Astra, and Abbott, contributed drugs used in this study.

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