Cerebrospinal fluid catecholamine levels and duration of spinal anaesthesia

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The effects of catecholamines added to dibucaine on the duration of spinal anaesthesia and cerebrospinal fluid catecholamine levels were studied. Free norepinephrine levels increased from $0.107 \text{ ng}\cdot\text{ml}^{-1}$ before anaesthesia to $5.8 \text{ ng}\cdot\text{ml}^{-1}$ and $1,238 \text{ ng}\cdot\text{ml}^{-1}$ after $1.0 \text{ }\mu\text{g}$ or $100 \text{ }\mu\text{g}$ norepinephrine had been added to the local anaesthetic. The effects of $2.5 \text{ }\mu\text{g}$ of either norepinephrine or epinephrine added to dibucaine on the duration of motor blockade and sensory regression time were compared. The duration of both were significantly prolonged by added norepinephrine from $96 \pm 17 \text{ min}$ to $193 \pm 20 \text{ min}$ (sensory blockade) and from $116 \pm 14 \text{ min}$ to $204 \pm 34 \text{ min}$ (motor blockade), but were not changed by addition of epinephrine. These data suggest that a $2.5 \text{ }\mu\text{g}$ dose of norepinephrine is sufficient to prolong the duration of spinal anaesthesia and more effective than the same dose of epinephrine.

For many years vasopressors such as epinephrine (EP) and phenylephrine have been used to prolong the duration of action of various local anaesthetics following subarachnoid administration. Vasoconstrictors are believed to affect the absorption of local anaesthetics. However, animal studies have recently demonstrated that norepinephrine (NE) and phenylephrine elevate the nociceptive threshold to thermal stimuli,¹ and intrathecal administration of alpha adrenergic antagonists partially antagonises the analgesia produced by micro-injection of morphine in periaqueductal gray matter or the nucleus reticularis gigantocellularis.² Bedder *et al.*³ also reported that the alpha₂ adrenoceptor agonist clonidine was as effective as EP in prolonging tetracaine-induced spinal anaesthesia in dogs. These

results were characterized as a specific alpha adrenergic receptor interaction in the spinal anti-nociceptive system.¹

The main catecholamine (CA) in cerebrospinal fluid (CSF) is NE,⁴ and NE levels in the CSF are higher in patients with chronic pain⁵ than in surgical patients without pain undergoing spinal anaesthesia. These data suggest that endogenous spinal NE has direct effects on the spinal nociceptive system that modulate the central transmission of pain information. However, there are few reports of CA analysis in CSF during spinal anaesthesia. Moreover, there are few clinical reports on the effect of added NE on spinal anaesthesia.

We attempted to determine the effects of NE in prolonging the duration of spinal anaesthesia and to measure the concentration and the type of catecholamine in CSF following the administration of CA added to dibucaine. We administered small doses of CA to prevent the side effects of spinal anaesthesia with use of vasoconstrictive drugs, as the endogenous CA levels in the CSF are very low and more than 50 per cent is of the inactive, conjugated type. On the other hand, exogenous CAs administered with local anaesthetics will be the active, free types in the CSF.

Methods

Fifty-seven adult patients without neurological disorders scheduled for hernioplasty or orthopaedic surgery of their lower extremities were selected. They were classified as American Society of Anesthesiologist's physical status class I. With approval from our Committee on Human Research, all patients were informed of the nature of the experiment and their written consent was obtained. All operations started between 09:00 and 10:00 hours. Food and fluids were withheld from 21:00 hours the previous evening. Lactated Ringer's solution was administered at $500 \text{ ml}\cdot\text{h}^{-1}$ during the study, anaesthesia and surgery. No medication was given to any patient before or during the study period.

In Group 1 there were 27 patients (Table I); nine patients received 2 ml of hyperbaric dibucaine (0.3 per cent). Of the other 18 patients (Figures 1 and 2), each one or two patients were selected and anaesthetised with

Key words

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FIGURE 1 Correlation between the doses of added catecholamine (CA) to spinal anaesthesia and the CSF free CA levels.

dibucaine with NE or EP 1.0, 2.5, 5.0, 10.0, 50.0, or 100 µg. The subjects were studied in a level, lateral position and 2 ml of CSF were withdrawn just before and 3 min after the administration of the drug through a spinal needle that was inserted at the fourth lumbar interspace. Technical and ethical considerations made it impossible to take multiple sample collections at different levels of the subarachnoid space.

Following CSF collection the patients were maintained

FIGURE 2 Correlation between the doses of added catecholamine (CA) to spinal anaesthesia and the CSF conjugated CA levels.

in the supine position. CSF samples for determination of CA were collected into chilled silicon tubes and stored at -40°C until the levels of CA were determined. CA was selectively isolated from the samples by activated alumina as described by Anton and Sayre's method.⁶ Conjugated CA was hydrolysed in boiling water with 1 N HCl for 30 min. The elute for CA was determined by reverse phase high performance liquid chromatography (Waters Associates, model 701B) with electron capture detector (Bioanalytical System).

Chromatograms were recorded on a Waters 703 Data Module set in the peak height mode. An internal standard dihydrobenzylamine (10 ng) was included in the sample

TABLE 1 Patients' age, body weight and highest level of spinal anaesthesia

Group	n	Age	Body weight	Highest level of anaesthesia	Drugs
1	9	45.7 $\pm$ 4.9	56.1 $\pm$ 3.2	Th7 $\pm$ 1	Dibucaine alone
	9	46.3 $\pm$ 5.7	53.2 $\pm$ 2.9	Th7 $\pm$ 1	Dibucaine + EP 1-100 µg
	9	44.9 $\pm$ 6.1	54.5 $\pm$ 2.7	Th6 $\pm$ 1	Dibucaine + NE 1-100 µg
2	10	45.9 $\pm$ 4.0	51.5 $\pm$ 1.8	Th7 $\pm$ 1	Dibucaine alone
3	10	44.4 $\pm$ 6.8	54.1 $\pm$ 3.8	Th7 $\pm$ 1	Dibucaine + EP 2.5 µg
4	10	47.8 $\pm$ 5.2	55.6 $\pm$ 3.1	Th6 $\pm$ 1	Dibucaine + NE 2.5 µg

to accommodate dilution of CSF and determination of CA recoveries. The recovery of CA analysis was 83 ± 4 per cent. Conjugated CA levels were determined from the total CA value minus the free CA value.

In 30 patients the effects of added 2.5 μg EP or 2.5 μg NE on the duration of anaesthesia were evaluated in Groups 3 and 4 and compared with Group 2 patients who were anaesthetised with 2 ml plain dibucaine (Tables I and II). The randomized double-blind study was designed to measure the duration of anaesthesia for hernioplasty in Groups 2, 3 and 4. All observations were made by an independent physician not involved in the study. The added dose of CA (2.5 μg) was based on preliminary studies and the results of Group 1 patients. We felt that 2.5 μg of NE should be enough to prolong the duration of spinal anaesthesia, from the data in Group 1.

Duration of anaesthesia was evaluated every 10 min by ice cold stimuli, until the beginning of sensory regression. A decrease in the level of temperature sensation of two dermatomes was defined as the beginning of sensory regression. Motor block was assessed by the method described by Bromage⁷ and determined by the recovery of knee joint movements, with ability to lift over 5 cm. When asymmetry in the quality of motor block existed the value for the lower leg in the lateral position for induction of spinal anaesthesia was used. Ankle and foot movement was not observed as some patients did not have complete paralysis of ankles and toes.

Patients who needed additional drugs for complete analgesia and/or for maintaining blood pressure in the operating room were excluded from the study.

All results are expressed as means $\pm$ SEM, unless otherwise indicated. Changes were considered significant when $p < 0.05$.

Results

In Group 1 there were no significant differences in preanaesthetic CSF free NE levels between patients who received plain dibucaine ($0.104 \pm 0.014 \text{ ng}\cdot\text{ml}^{-1}$), added EP ($0.110 \pm 0.033 \text{ ng}\cdot\text{ml}^{-1}$) or added NE ($0.107 \pm 0.028 \text{ ng}\cdot\text{ml}^{-1}$). Free NE levels increased after the drug adminis-

tration in patients who received plain dibucaine ($0.170 \pm 0.052 \text{ ng}\cdot\text{ml}^{-1}$) or added EP ($0.174 \pm 0.046 \text{ ng}\cdot\text{ml}^{-1}$), but there was no statistically significant change.

Free CSF EP levels were undetectable ($<10 \text{ pg}\cdot\text{ml}^{-1}$) in every patient and conjugated CSF EP levels were also undetectable in half of the patients, except for the data presented in Figures 1 and 2 which was obtained from the patients who were anaesthetised with EP added to dibucaine.

As seen in Figure 1 CSF free CA levels increased logarithmically, due to the addition of CA to the dibucaine in Group 1 patients. The mean free CSF CA level was $1,428 \text{ ng}\cdot\text{ml}^{-1}$ in patients who received the usual dose of NE or EP ($<100 \mu\text{g}$). It was more than 10,000 times the preanaesthetic free CA level.

Conjugated CA levels were also increased after drug administration (Figure 2). The free/conjugated ratio of NE increased to 93 ± 20 from 0.59 ± 0.17 following NE addition.

There were no significant differences with regard to patients' age and body weight between Groups 1, 2, 3 and 4 (Table I). The duration of sensory anaesthesia was significantly longer in Group 4 compared with Group 2 and Group 3 (Table II). The duration of motor blockade was significantly longer in Group 4 compared with Group 2. No differences were found in the highest dermatome blocked in Groups 2, 3 or 4 (Table I).

There were no side effects in any patients during anaesthesia.

Discussion

We have shown that small doses of NE significantly prolong the duration of sensory and motor block, compared with the effects of plain dibucaine, and are more useful than EP in the same doses for prolonging the duration of spinal anaesthesia.

Meagher *et al.*⁸ reported that the alpha adrenoceptor stimulant phenylephrine caused a significantly greater prolongation of the time of regression of sensory anaesthesia than EP. Recently, Caldwell *et al.*⁹ also found that phenylephrine prolongs the duration of sensory anaesthesia to a greater extent than EP. In contrast, Concepcion *et al.*¹⁰ reported the result of a double blind comparison of the effects of EP (0.2 ~ 0.3 mg) and phenylephrine (1 ~ 2 mg) on the duration of tetracaine spinal anaesthesia. Both drugs prolonged the duration of sensory and motor block compared with the effects of plain tetracaine, but no significant difference was found between the degree of prolongation caused by the vasoconstrictors. They concluded that in "equivalent" or equipotent doses (1 mg EP = 10 mg phenylephrine) the effect of EP and phenylephrine were not different. However, it is difficult to conclude

TABLE II Duration of spinal anaesthesia

Group	Duration of sensory blockade (min)	Duration of motor blockade (min)
2. Dibucaine	96 $\pm$ 17	116 $\pm$ 14
3. Dibucaine + EP 2.5 μg	136 $\pm$ 23	147 $\pm$ 26
4. Dibucaine + NE 2.5 μg	193 $\pm$ 20**	204 $\pm$ 34*

* $p < 0.02$, ** $p < 0.01$; compared with Group 2 data (mean $\pm$ SEM, $n = 10$).

which dose of phenylephrine is optimal and equipotent to EP because phenylephrine is not an endogenous CA, and there is a large difference in their potencies.

The classic explanation for the prolongation of spinal anaesthesia by CA is that alpha-adrenergic mediated vasoconstriction decreases the uptake of local anaesthetics. However, EP does not inhibit the washout of tetracaine¹¹ or lidocaine¹² from the CSF, and neither EP nor phenylephrine added to spinal anaesthetic solutions affect the distribution of local anaesthetics within the subarachnoid space.¹³ Further, Bedder *et al.*³ reported that the alpha₂ adrenoceptor stimulant clonidine is as effective as epinephrine in prolonging spinal anaesthesia in dogs. The main endogenous CA in the CSF is NE, and is increased in patients with chronic pain compared with surgical patients without pain, during spinal anaesthesia.⁵ Takagi *et al.*¹⁴ reported that noxious stimuli increase spinal levels of the NE metabolite normetanephrine in rats. These reports suggest the main mechanism of prolonging spinal anaesthesia by added vasoconstrictors may be a direct effect on the spinal nociceptive system.

In this study, we only examined the effects of 2.5 µg CA on the duration of spinal anaesthesia in order to avoid the side effects of added CA, but CSF free NE levels increased to 10 ng·ml⁻¹ with use of 2.5 µg NE. This is almost 100 times the normal CSF free NE level and is 80 times the CSF NE level of patients with chronic pain.⁵ The duration of spinal anaesthesia in Group 1 patients was not reported, because 2 ml of CSF were withdrawn 3 min after the administration of the drug. CSF NE levels increased to 1800 ng·ml⁻¹, more than 10,000 times the preanaesthetic value, in patients who received 100 µg of NE added to dibucaine. We therefore continued the study with small doses of CA's. However, we suspect that there were no significant differences between the patients receiving 2.5 µg of NE and those receiving more than 50 µg of NE, from Group 1 data. From these data, we suggest that addition of 2.5 µg NE is enough to prolong the duration of spinal anaesthesia. The dose of added CA to the spinal anaesthetic solution should be severely restricted, to prevent ischaemic damage to the spinal cord caused by abnormally high levels of CSF CA during spinal anaesthesia.

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Résumé

L'effet des catécholamines ajoutées la dibucaïne sur la durée de l'anesthésie rachidienne et le taux de catécholamines dans le liquide céphalorachidien sont étudiés. Le taux de norépinéphrine libre augmenta de $0.107 \text{ ng}\cdot\text{ml}^{-1}$ avant l'anesthésie à $5.8 \text{ ng}\cdot\text{ml}^{-1}$ et $1.238 \text{ ng}\cdot\text{ml}^{-1}$ après $1 \text{ }\mu\text{g}$ ou $100 \text{ }\mu\text{g}$ de norépinéphrine ajouté à l'anesthésie locale. Les effets de $2.5 \text{ }\mu\text{g}$ de norépinéphrine ou d'épinéphrine ajouté à la dibucaïne sur la durée du bloc moteur et le temps de régression sensorielle furent comparés. Les deux temps furent significativement prolongés par l'addition de norépinéphrine, de $96 \pm 17 \text{ min}$ à $193 \pm 20 \text{ min}$ (blocage sensoriel) et de $116 \pm 14 \text{ min}$ à $204 \pm 34 \text{ min}$ (blocage moteur), mais ne furent pas altérés par l'addition d'épinéphrine. Ces données suggèrent qu'une dose de $2.5 \text{ }\mu\text{g}$ de norépinéphrine suffit pour prolonger la durée de l'anesthésie rachidienne et qu'elle est plus efficace qu'une même dose d'épinéphrine.