Bupivacaine concentrations in lumbar cerebrospinal fluid in patients with failed spinal anaesthesia

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Background. Spinal anaesthesia (SA) has high success rates. However, inadequate block after SA has been reported even in the absence of technical problems. Various mechanisms for failed SA (FSA) have been proposed, but reports of cerebrospinal fluid (CSF) concentrations of local anaesthetics (LA) after FSA are scarce. We report lumbar CSF concentrations of bupivacaine in 20 patients in whom adequate block after subarachnoid injection failed to develop.

Methods. All patients with inadequate block after subarachnoid injection of plain bupivacaine 0.5% and in whom a second subarachnoid injection of LA was to be performed as a rescue technique were eligible for entry into this study. A CSF sample was withdrawn immediately before injection of the second dose of LA. Patients in whom failure was obviously due to technical problems or inadequate dosage were excluded. Bupivacaine concentrations were assessed with high-performance liquid chromatography.

Results. During the study period of 15 months, 2600 spinal anaesthetics were performed. The failure rate was 2.7% (71 patients). In 20 patients (0.77%), CSF concentrations of bupivacaine were determined, which ranged from 3.36 to 1020 μg ml⁻¹.

Conclusions. Inadequate CSF concentration of LA is a common reason for FSA. However, in 12 of our 20 patients, concentrations were above 73 μg ml⁻¹, a concentration that should lead to an adequate block. In these patients, maldistribution of bupivacaine could be responsible for FSA. In view of the absence of sufficient block, despite adequate lumbar CSF concentrations of bupivacaine, concerns about neurotoxicity with repeat injections may be warranted.
leading to an inappropriately high level of anaesthesia. In addition, reports of neurotoxic effects of LA10 and a correlation between the dose of LA and the risk for neurotoxicity11 call for cautious dosing when repeated subarachnoid injections of LA are performed. In fact, neurological deficits associated with repeated subarachnoid injection of LA after FSA have been reported,12 and the safety of this practice has been questioned.13

We measured lumbar bupivacaine cerebrospinal fluid (CSF) concentrations in patients with FSA to test the hypothesis that the primary reason for FSA is an inadequate concentration of LA in the CSF.

Methods
The study protocol was approved by the Regional Ethics Committee of the University Hospital Basel, Basel, Switzerland. The study lasted 15 months. For the purpose of this study, we defined FSA as inadequate sensory block for the planned procedure 15 min after subarachnoid injection of an adequate standardized dose of LA. All patients who fulfilled the definition of FSA and in whom SA had been performed with plain bupivacaine 0.5% (Carbostesin®, Astra Pharmaceutica AG, Dietikon, Switzerland) were eligible for entry into the study. However, of these patients, only those in whom the responsible anaesthesiologist decided to use a second subarachnoid injection of LA as a rescue technique were included, that is, no additional subarachnoid punctures were performed for study purposes only. Exclusion criteria were patient refusal, pregnancy, obvious technical difficulties during injection of the first dose, such as inability to aspirate CSF at the end of the injection, injection of less than the intended dose due to unexpected patient movement or inadvertent disconnection of the needle from the syringe during injection, and more than three attempts to enter the subarachnoid space.

After the injection of LA, the extent of the sensory block was assessed by cold-warm discrimination with an ether swab. If the patient fulfilled the entry criteria, oral informed consent for taking a CSF sample was obtained from the patient. The Regional Ethics Committee waived the need for written consent because no change in clinical management occurred and the volume of the test sample was less than that of the injected LA. During the second puncture, immediately before injection of the second dose of LA, a 1 ml sample of lumbar CSF was obtained and set aside. The sample was frozen immediately and stored at −20°C until analysis. CSF bupivacaine concentrations were measured after termination of the study period using high-performance liquid chromatography as previously described.14 The lower limit for quantification with this method is 0.05 µg ml⁻¹.

Discussion
We found a wide range of bupivacaine concentrations in the lumbar CSF of patients with FSA. An important point for the interpretation of our data is defining a threshold for lumbar bupivacaine CSF concentrations above which a sufficient block should be observed. On the basis of the available data15 and the fact that all our samples were obtained 15–45 min after the initial lumbar puncture, we assumed that a lumbar bupivacaine CSF concentration of ≥73 µg ml⁻¹ should lead to an adequate block. This concentration represents the 5th percentile of the concentrations sampled during the same time-span in 37 patients with adequate SA by Ruppen and colleagues.15 In our series of 20 patients with FSA, eight patients had a lumbar CSF bupivacaine concentration <73 µg ml⁻¹ and 12 patients a concentration >73 µg ml⁻¹ (Table 1). Interestingly, only one of six patients with a completely FSA had a bupivacaine concentration above this threshold (106 µg ml⁻¹). Resistance to bupivacaine, as suggested in
two reports, cannot explain the completely FSA in these six patients because they all developed adequate anaesthesia after the repeated injection. A more likely cause for completely or partially FSA is the failure to inject a sufficient dose of LA into the CSF as a result of unrecognized technical problems. Alternatively, an unanticipated large lumbar CSF volume could also explain inadequately low bupivacaine concentrations. A large variability (43–81 ml) of lumbosacral CSF volumes calculated from MRI sequences has been suggested as the most important factor contributing to the variability in spread of SA. However, this interpretation is questioned by the fact that exclusion of one of the 10 volunteers in that study would eliminate the statistical significance of the correlation between lumbosacral CSF volume and spread of SA. In an unfixed anatomic preparation of a human spinal column, Mollmann and colleagues were able to reproduce injection of LA into the subdural space in all preparations with a Sprotte needle but not with a Quincke needle. In our series, only three injections were performed with Sprotte needles, and only one of these patients had a CSF concentration below 73 μg ml⁻¹. Hence, this was not a major cause of FSA in our series. Maldistribution could be the most important explanation for the FSA in the 12 patients who had CSF bupivacaine concentrations (73 μg ml⁻¹).

Maldistribution needs to be discussed with an understanding of the factors determining intrathecal drug spread. The distribution of plain bupivacaine is somewhat unpredictable. In an extensive review, Hocking and Wildsmith discuss characteristics of the injected LA, clinical

<table>
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<th>Weight (kg)</th>
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<th>Dose (mg)</th>
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Effects of needle type and direction of needle opening have, to our knowledge, not been investigated with plain bupivacaine. Although these factors may explain some of the heterogeneity of our data, they are unlikely to fully explain FSA. In contrast, individual anatomical factors including the configuration of the spinal column (kyphosis, lumbar lordotic curvature) may influence distribution of the LA or even cause maldistribution.\cite{21} If SA with plain bupivacaine is repeated on a second occasion, using exactly the same technique, a block with an extent similar to the first SA results.\cite{22,23} Two of our patients had a history of FSA. Other anatomical factors that may limit the distribution of the injected LA are fibrous attachments and membranous structures in the subarachnoid space. Fibrous attachments were found between nerve roots, between nerve roots and the arachnoid membrane at one or more spinal levels in 16 of 26 autopsy subjects studied using endoscopy, or both. In another three subjects, a membranous structure was identified in the posterior midline of the subarachnoid space.\cite{24} By limiting the distribution of the injected LA, these fibrous attachments and membranes may be associated with a variation in the extent of SA.

The single patient with a very high (1020 μg ml\(^{-1}\)) bupivacaine CSF concentration warrants special attention. This concentration is higher than the concentrations reported by Ruppen and colleagues\cite{15} and led to an incomplete block (L3 left, T12 right). Injection into a low lumbar CSF volume could be assumed: 17.5 ml would be appropriate to achieve this concentration with the used dose of 17.5 mg. However, such a CSF volume is far below the values that were found in an MRI study.\cite{6} Moreover, such a small CSF volume alone would not explain the FSA. Some other factor, probably anatomical, leading to maldistribution must have been present. Injection into a (congenital) spinal arachnoid\cite{25} or s.c. cyst\cite{29} has been proposed but seems unlikely in view of the normal neurological presentation of the patient.

Our findings might support concerns about neurotoxicity after repeated injections of bupivacaine into the subarachnoid space. Although our data do not allow drawing any conclusion on this issue, a correlation between bupivacaine dose and neurotoxicity has been demonstrated in dogs.\cite{11} Considering that more than half of the measured CSF concentrations in our patients were in a range that should have led to an adequate block, we agree with Drasner and Rigler\cite{13} that if a second dose is to be considered, careful testing including the sacral dermatomes should precede the injection. We suggest that if any sensory anaesthesia is present, the second injection should not be performed as maldistribution may be present. On the other hand, some of the doses we used were rather large and it may be inappropriate to extrapolate our suggestion to patients who receive lower doses of bupivacaine. An alternative approach would be to use repeat injections, provided the total amount administered

![Fig 1 Bupivacaine concentrations in the lumbar CSF and the number of blocked segments. Bilateral segments are counted separately and were counted as follows: starting from S5, each blocked segment was added to the number of blocked segments, for example, a patient with a block level of L5 on the right side and a level of L3 on the left side would be represented by 14 blocked segments (right: S5, S4, S3, S2, S1, L5 and left: S5, S4, S3, S2, S1, L5, L4, L3, i.e. 6+8 segments). Dotted line: 73 μg ml\(^{-1}\).](image-url)
Failed spinal anaesthesia

does not exceed a dose that the clinician would consider reasonable as a single injection.

Two limitations of our protocol need consideration: in order to avoid unnecessary lumbar punctures for study purposes only, sampling of CSF did not always take place at the same interspace as the primary injection of LA had taken place. On the basis of experimental data from an upright spinal canal model, LA concentrations should not be markedly influenced by choosing a modestly distant interspace. However, models of the spinal canal lack a representation of the spinal cord and the cauda equina, which may act as baffles to the generation of fluid currents. We cannot exclude that some of our measurements represent local values. On the other hand, inadequately high local concentrations of LA in the subarachnoid space are not influenced by the interspace at which the sample was obtained. The second problem is the variable time-lag between the injection of bupivacaine and sampling for determination of the CSF concentration, as bupivacaine concentrations change during this time.

In summary, we report CSF concentrations of plain bupivacaine in 20 patients with FSA. Patients in whom obvious technical problems or insufficient dosage of LA could explain FSA were excluded. We found a wide range of CSF concentrations with more than half of the values in a range where adequate block should have been present. Inadequately low CSF concentration of bupivacaine due to failure to realize technical problems during injection of the LA is the most likely explanation for FSA when low concentrations are present. Maldistribution due to anatomical factors is probably the most frequent cause of FSA in cases with adequate CSF concentrations, but further studies are needed to clarify the cause of FSA in such patients. Although our data provide no evidence for a relationship between repeated subarachnoid injections of LA and neurotoxicity, we suggest that a second injection of LA after FSA should only be performed in patients with complete failure or if a repeat injection is performed in a patient with incomplete failure, the total amount of LA administered should not exceed a dose that the clinician would consider reasonable as a single injection.

Acknowledgements

We thank K. Censier for performing the analysis of the CSF samples. A. Dwileski’s support in preparing this manuscript is also gratefully acknowledged.

Funding

This study was funded exclusively by the Department of Anaesthesia, University Hospital Basel, Basel, Switzerland.

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