Accuracy of spinal anaesthesia drug concentrations in mixtures prepared by anaesthetists

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Abstract

Objective: Medication errors include the indirect dosing of drugs. For spinal anaesthesia mixtures of local anaesthetics and opioids are drawn from ampoules and combined in a syringe, according to clinical practice. We set out to determine the accuracy of the drug mixtures.

Methods: Physicians of our department were invited to prepare the mixture used for spinal anaesthesia for caesarean section, consisting of 10 mg hyperbaric bupivacaine (2 mL volume), 20 µg fentanyl (0.4 mL volume), and 100 µg morphine (0.1 mL volume). Concentrations of these drugs were determined by means of high performance liquid chromatography. Inter- and intraindividual variations were assessed.

Results: We analyzed 96 samples from 31 physicians. 51% of the measured bupivacaine concentrations were in +/- 10% deviation range of the intended concentration; 17% of the fentanyl and 24% of the morphine concentrations were in this range. 2.1% of the samples had a bupivacaine concentration corresponding to a dose ≤ 8 mg, and 11.5% of the samples had a morphine concentration corresponding to a dose ≥150 µg. Intraindividual variations were 10.9% for bupivacaine, 24.7% for fentanyl, and 38.9% for morphine.

Conclusions: Our results show a high deviation of the obtained from the intended concentrations. 2% of the samples had bupivacaine concentrations that probably result into an insufficient analgesia, 11% of the samples had morphine concentrations that according to guidelines would require a longer monitoring period than with the intended dose.

Key words: medication error, spinal anaesthesia, bupivacaine, fentanyl, morphine

Medication errors still pose a serious threat to patients undergoing anesthesia. In clinical practice different drugs are drawn from ampoules into syringes for further injection which may lead to inaccuracies in volume administered. This is particularly a problem when a dilution is prepared and when the volumes diluent and solvent may deviate[1] so that there is the risk of under- or overdosing of the drug. The most frequently used anaesthetic technique for Caesarean section is spinal anaesthesia[2,3] for which a combination of local anaesthetic and opioid is frequently used.[4] In line with current practice[5], in our institution we use hyperbaric bupivacaine in combination with fentanyl and morphine opioids which provide short and long-lasting postoperative analgesia. The use of three different drugs with different volumes multiplies the risk of under- or overdosing. This process of drawing up and mixing different drugs relies heavily on the individual skills and performance of the anesthesiologist. Surprisingly, little is known about the reliability of the process and the accuracy of the prepared drug doses.

We performed a study where spinal anaesthesia was prepared according to the standard protocol in our operating room and then analysed the concentrations of these three drugs by liquid chromatography coupled to mass spectromety. We hypothesized that the deviations from the intended concentration will be highest for the drug with the lowest volume. We present our results and discuss the clinical implications of either a too high or a too low dose.

METHODS

Preparation of combined drug samples

Both consultants and residents were invited to participate in this study. Participation was on a voluntary basis and data were blinded. Level of training was the only personal information registered with samples. The participants drew up 2 mL of hyperbaric bupivacaine 0.5% (10 mg) and 0.4 mL of fentanyl 50 µg /mL (20 µg) into a 5 cc syringe. Then they withdrew 0.1 mL of morphine into an insulin 1 ml syringe and subsequently transferred the contents from this syringe into the 5 mL syringe. Unfortunately, by error ampoules with a wrong concentration of morphine were used for this study (10 mg/mL instead of 1 mg/mL). Thus the final volume in the 5mL syringe was 2.5mL. Of the final mixture, 1.5 mL was transferred to a 1.5 mL vial which could be deep frozen for analysis at a different date. Physicians were asked to prepare several samples. Ethical approval was not required for this study.

Analysis of drug concentrations

Nowadays, compatibility and stability studies, therapeutic drug monitoring and analytical quality control of pharmaceutical drug preparations are done using high performance liquid chromatography coupled to ultraviolet detectors (HPLC-UV) or mass spectrometric analysis (HPLC-MS). Identification of molecules is done by chromatographic retention time comparison and/or matching fragmentation pattern of reference compounds. In selected carrier solutions, target analytes are selectively quantified against corresponding reference standards. Several reports are published showing the beneficial and ubiquitously applicable workflow of these instrumental procedures.[6,7,8]

Chemicals and reagents

Formic acid (FA), sodium chloride and analytical reference standards of morphin, fentanyl and bupivacaine were obtained from Sigma Aldrich (Buchs, Switzerland). Acetonitrile Optima LC/MS Grade was obtained from Thermo Fisher Scientific AG (Sunnyvale, CA, USA). Gibco™ PBS pH 7.4 (1X) was purchased from Life Technologies Limited (Paisley, UK). Pure water was obtained from an in-house water purification system from Labtec (Villmergen, AG, Switzerland). HPLC vials, screwcaps and inlets were purchased from BGB (Boeckten, Switzerland). For all experiments, Gilson pipettes and Gilson DIAMOND tips were used (Mettmenstetten, Switzerland).

Chromatographic conditions

All samples were analysed on a Waters Acquity UPLC system equipped with an autosampler, a binary pump and a column oven (Waters, Milford (MA), USA). Detection was done on a Thermo LTQ XL linear ion trap mass spectrometer (Thermo Scientific, San Jose (CA), USA). For all separations, water with 0.1% FA (solvent A) and ACN with 0.1% FA (solvent B) were used. Gradient elution was done on a VWR ACE Excel C8 column (2.1*30 mm, 2 µm). Chromatographic conditions were as follows: flow was set 0.4 ml/min; 0 - 1 min 98% A, 1 - 7.5 min to 100% B, 7.5 - 8.5 min 100% B, 8.5 - 9,0 min to 98% A, 9-10min, 98%A. Column oven temperature was set to 30 °C. Autosampler was kept at 10 °C and injection volume was 3 µl. Settings of the mass spectrometry (MS) detector are used as reported previously.[8] Analysis was done in ESI positive mode. Heated ESI II source was set to 150 °C. Sheath

gas 40 arbitrary units (AU); auxiliary gas 20 AU; source voltage 3.00 kV; ion transfer capillary 300 °C; capillary voltage 31 V; tube lens voltage 80 V. Automatic gain control was set to 15000 ions for full scan and 5000 for MSn. Collision induced dissociation (CID)- MS^n experiments were performed on precursor ions selected for MS1. Using information dependent acquisition. MS1 was performed in full scan mode (m/z 100-500). MS2 and MS3 were performed in the IDA mode: four IDA MS2 experiments were performed on the four most intensive signal from MS1 and additionally eight MS3 scan filters were chosen to record the most and second most ions from MS2.

Sample preparation

Calibration solutions (CAL) and quality control solutions (QC) were prepared from independent stock solutions in 0.9% (w/V) sodium chloride. Concentration of stock solutions were 400 µg/ml morphine, 40 mg/ml hyperbaric bupivacaine and 80 µg/ml fentanyl, respectively. For CAL, Stock solutions (1 mL each) were mixed and filled up to 10 mL with 0.9% sodium chloride solution to obtain final concentrations. QCs were prepared accordingly using 0.9 mL of stock solutions. **For analytical standard preparation, density differences of hyperbaric bupivacaine solutions were not taken into account.**[9] For analysis, 25 µL CAL, QC and therapeutic solutions were diluted with 975 µL mobile phase A. All samples were analyzed in independent duplicates and quantified against CAL solutions.

The concentration of therapeutically used morphine solution was given as 100 mg/mL of the corresponding hydrochloride trihydrate salt in the commercial available finished product. According to the diluting scheme, this results in a final concentration of 304 µg/mL of the free morphine base.

Data analysis

Descriptive statistics were used to analyze the data. We report mean, absolute and relative deviations from the target concentration. Samples were also classified in terms of their relative deviation from the target concentration (+/- 0-5% deviation; +/- 5-10% deviation; +/- 10-20% deviation; +/- 20-40% deviation; > +/- 40% deviation).

We also assessed intraindividual variations by analyzing the data of physicians who prepared ≥2 samples.

RESULTS

In total, 96 samples by 31 physicians were obtained. Up to six independent preparations per physician were investigated in detail.

Accuracy of the LC-MS procedure for morphine, bupivacaine and fentanyl was 98%, 101,5% and 100.5%. No matrix effects were observed for any target analyte. Overall recovery was higher than 97%. Autosampler stability was given for 48 h. Multianalyte Cal and QC samples were stable for at least two freeze thaw cycles.

Table 1 shows the deviations of observed from intended concentrations of the three drugs.

For bupivacaine (target concentration 4 mg/mL), the observed concentration was 3.7 mg/mL The mean absolute deviation was 0.47 mg/mL. Only 49 samples (51%) had maximum deviations of +/- 10 % of the targeted concentrations. Two samples (2.1%) had bupivacaine concentrations ≤ 3.2 mg/mL, which would correspond to a dose of 8 mg in 2.5 mL final volume. This is a clinically relevant cut-off for potential underdosing.

For Fentanyl (target concentration 8 µg/mL), the mean observed concentration was 7.9 µg/mL. The mean absolute deviation was 2.09 µg/mL and 16 samples (17%) had concentrations within a +/- 10% deviation range of the target.

For morphine (target concentration 304 µg/mL) the observed concentration was 265.6 µg/mL. The mean absolute deviation was 102.03 µg/mL. Of the samples, 23 (24%) had deviations in morphine concentrations of +/- 10% of the target. However, 11 (11.5%) samples had morphine concentrations ≥456 µg/mL, this would correspond to a dose of ≥150 µg if we had not confused the 1 mg/mL ampoules with 10 mg/mL ampoules in the experiment.

2.1% of the samples had a deviation of more than 40% of the intended concentration of bupivacaine; this deviation was found for fentanyl in 17.7% and for morphine in 38.5% of the samples.

Figure 1 presents the distributions of observed concentrations relative to the intended concentrations for all three drugs.

Only one sample had all drugs within a +/- 0-5% deviation range. Contrary, in 25 samples (26.0%) all drugs deviated at least +/- 10 % of the targeted concentrations.

The intraindividual variations were 10.9% for bupivacaine, 24.7% for fentanyl, and 38.9% for morphine; individual data are given in Figure 2.

DISCUSSION

In our study, observed drug concentrations prepared as in routine practice for caesarean section deviated considerably from the intended concentrations. Our hypothesis that drug concentration deviations would be highest for the drug with the lowest volume (morphine) was clearly confirmed.

The clinical relevance of our study lies in the under- or overdosing of the components of our drug mixture. It has been shown in a meta-analysis[10] of randomized controlled trials that the dose of bupivacaine used for spinal anaesthesia in patients scheduled for caesarean section is important for the anaesthetic efficacy. In their analysis of 12 RCTs Arzola and Wieczorek[10] were able to demonstrate that doses of ≤8 mg bupivacaine were associated with a significantly increased need for analgesic supplementation during caesarean section compared with higher doses; the risk ratio was 3.76 (95% confidence interval 2.38, 5.92). This result was confirmed even after correcting for confounding variables. In our study, 2% of the samples contained a bupivacaine concentration corresponding to less than 8 mg. This suggests that insufficient anesthesia seems to a rather rare occasion.

Conversely, we also have to discuss the consequences of a drug dose that is higher than intended. This concern applies to morphine, a hydrophilic opioid that spreads cephalad in the cerebrospinal fluid. Morphine can reach the respiratory centers and cause a respiratory depression that can occur as long as 2 hours after the intrathecal administration.[11] There are reports of patients who suffered from respiratory depression requiring immediate treatment.[12,13] A systematic review of the available evidence on neuraxial opioids (including intrathecal and epidural application) found an incidence of clinically significant respiratory depression of 1.08 – 1.63/10,000 for clinically relevant doses of opioids.[14] In response, the American Society for Obstetric Anesthesia and Perinatology issued a consensus statement on the monitoring of obstetric patients who received neuraxial opioids[15] where the recommended monitoring periods depend upon the morphine dose. They suggested a tiered monitoring system; for 100 µg they recommended a monitoring period of 12 hours with blood pressure and sedation score examination every 2 hours whereas for doses ≥ 150 µg the monitoring period should be 24 hours with hourly checks for the first 12 hours and once every two hours for the next 12 hours. Our analysis showed that the morphine concentration was higher than 50% of the intended dose of 100 µg in 11 of the analyzed samples. Our study therefore reveals a serious safety concern with the standard procedure of preparing the spinal drug mixture in our institution. In a significant percentage of cases the applied morphine dose is 150 µg morphine instead of 100 µg but the monitoring period in our institution is that of 100 µg. Patients may be exposed to the risk of an opioid-induced respiratory depression and this may go unnoticed. Vital consequences for the patient may result as well as legal consequences for the anaesthetist. It is concerning that in more than one fourth of our samples, all drugs had a deviation of more than +/- 10% of the target concentration. However, from a human factor perspective, the outcome of our study is not surprising. The process of drawing different drugs from ampoules into syringes seems seriously error prone in itself. In particular, after the first drug has been injected into the syringe, multiple errors can potentiate and there is little chance or guidance for the clinician to check the concentrations produced. As a major conclusion from our study we think that the drug mixture should no longer be prepared by the anaesthetist but should be provided by the pharmacy or the drug manufacturer so that the risk of under- or overmedication can be avoided. **Previous study examined the stability of mixtures of bupivacaine with one opioid in polypropylene syringes and PVC cassettes.[16,17] We still need data on the stability of the mixture of hyperbaric bupivacaine, morphine, and fentanyl in the concentrations used in our study before ready-to-use mixtures can be recommended.**

Limitations: Because we present an observational study of a single group, a power calculation was not possible and therefore we could not draw conclusions on statistical significance. **In our study we erroneously used a concentration of morphine that is 10 times higher than the concentration we use in our clinical practice; however, we do not think that this fact has an impact on our conclusions.** The results of our study must be interpreted in clinical context. We think that our finding that 11 of the 96 samples showed a morphine dose that was ≥50% higher than what was intended is an impressive number. Whereas we cannot conclusively say whether this can be generalized and whether they would be found with participants from another anaesthesia department, we have no reason to believe that other physicians would perform significantly better than the participants in this study. A study limitation is that we did not assess association between experience (trainee versus specialist, specialist with several years versus specialist with only a few years of clinical experience) and accuracy of the drug preparation. We believed that our cohort was too small to have a sufficiently high number of participants in the various subgroups. Another complication that we did not address is bacterial contamination, a complication that can occur when physicians prepare medication. Our study mixtures were prepared under the same sterile conditions as during our daily clinical practice and in the last years we have not seen meningeal or other infection due to contamination of the drug mixture. This finding, however, does not preclude the fact that bacterial contamination can occur and may cause serious sequalae in patients at an increased risk of infection, eg immunocompromised patients.

CONCLUSIONS

We found a high percentage of samples that a concentration different from the intended concentration. The difference was the highest for the drug with the smallest volume. There was also considerable intraindividual variation. As a major conclusion from our study we think that the drug mixture should no longer be prepared by the anaesthetist but should be provided by the pharmacy or the drug manufacturer so that the risk of under- or overmedication can be avoided.

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Conflict of interests

All the authors report no conflicts of interest.

Authors contributions

MH: Designed the study, interpreted the data, drafted the manuscript.

CS: Performed the chemical and statistical analyses, interpreted the data.

PW: Designed the study, interpreted the data, drafted the manuscript.

DS: Designed the study, performed the statistical analyses, interpreted the data, drafted the manuscript.

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figures

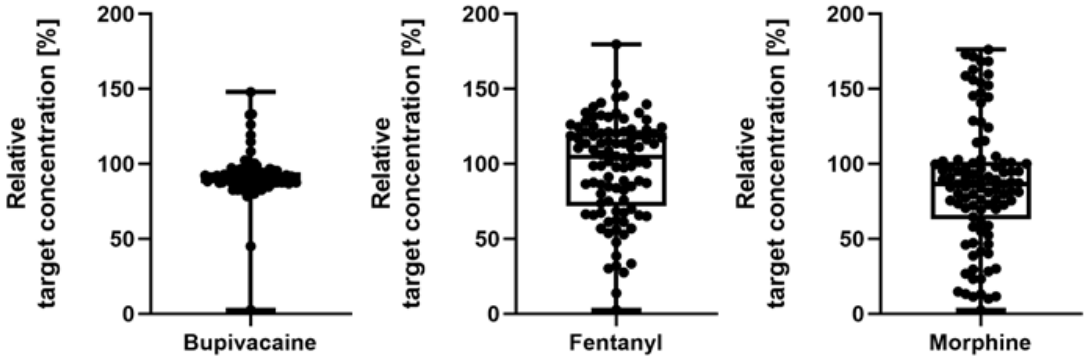

Figure 1: Box-plot representation for individual concentration of selected drugs.

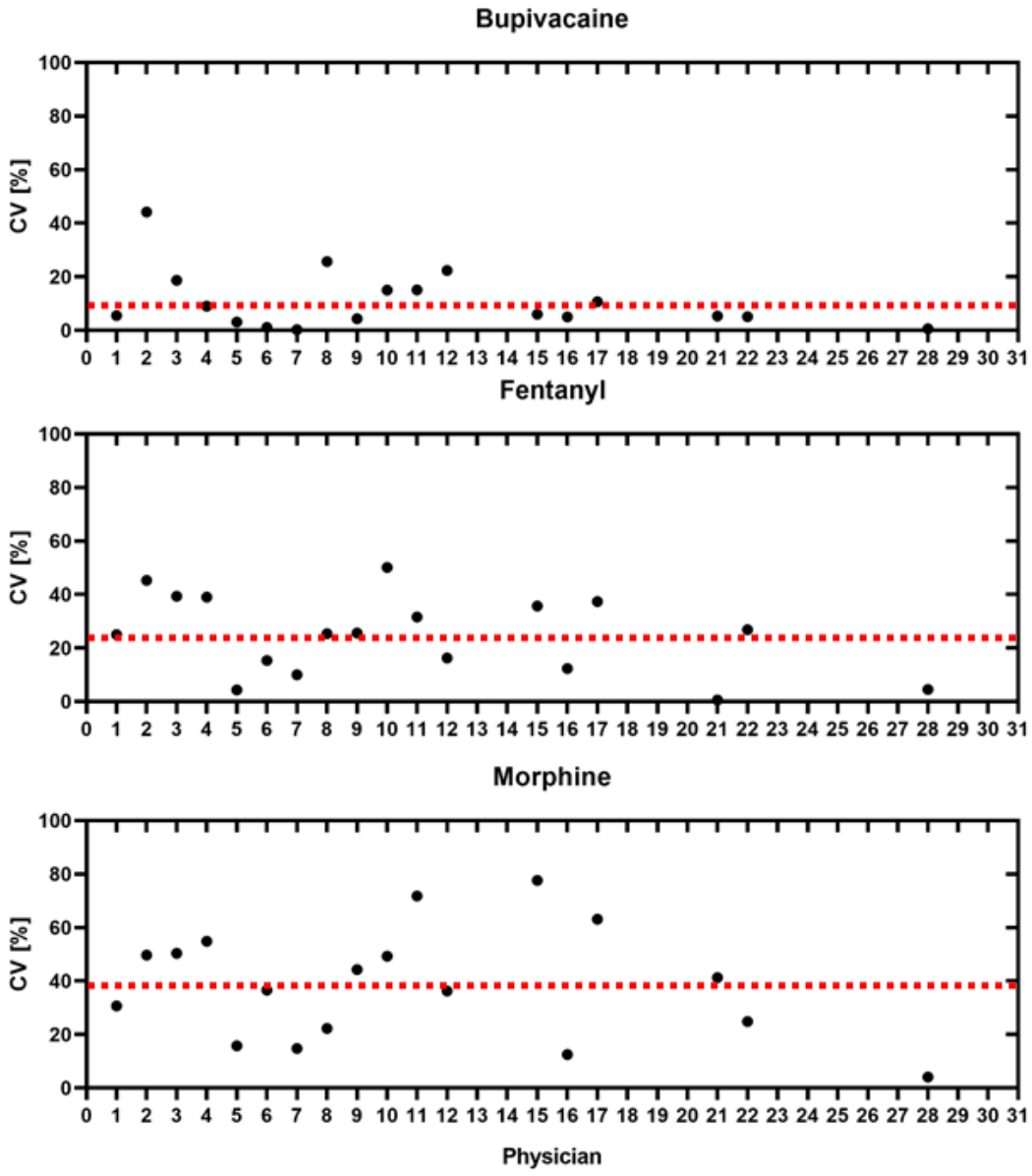

Figure 2: Intraindividual variations for anesthesiologists preparing more than two mixtures. Dashed line indicates the mean intraindividual variation.

Table 1. Deviations of observed from intended concentrations of the three drugs.

	Bupivacain [mg/mL]	Fentanyl [µg/mL]	Morphin [µg/mL]
Intended concentration	4	8	304
Observed concentration, Mean (SD) [range]	3.7 (0.49) [1.8-5.9]	7.9 (2.56) [1.1-14.4]	265.6 (125.59) [30.7-535.8]
% of intended concentration, mean	92.19%	98.44%	87.38%
Mean absolute deviation	0.47 [mg/mL]	2.09 [µg/mL]	102.03 [µg/mL]
n (%) samples with +/- 0-5% deviation	20 (20.8%)	11 (11.5%)	16 (16.7%)
n (%) samples with +/- 5-10% deviation	29 (30.2%)	5 (5.2%)	7 (7.3%)
n (%) samples with +/- 10-20% deviation	41 (42.7%)	29 (30.2%)	17 (17.7%)
n (%) samples with +/- 20-40% deviation	4 (4.2%)	34 (35.4%)	19 (19.8%)
n (%) samples with > +/- 40% deviation	2 (2.1%)	17 (17.7%)	37 (38.5%)