

Prospective Study

Rationale for Prospective Assays of Intrathecal Mixtures Including Morphine, Ropivacaine and Ziconotide: Prevention of Adverse Events and Feasibility in Clinical Practice

Denis Dupouiron, MD¹, Catherine Devys, PharmD², Christophe Bazin, PharmD², Caroline Folliard, PharmD², Nathalie Lebre, MD¹, François Boré, MD¹, Pierre Yves Dubois, MD¹, and Hélène Kieffer, PharmD²

From: ¹Anesthesia and Pain Department, Institut de cancérologie de l'ouest - Paul Papin, Angers, France
²Pharmacy, Institut de cancérologie de l'ouest - Paul Papin, Angers, France

Address Correspondence:
Denis Dupouiron
Anesthesia and Pain Department
Institut de cancérologie de l'ouest - Paul Papin
2 rue Moll
49000 Angers France
E-mail:
denis.dupouiron@ico.unicancer.fr

Disclaimer: There was no external funding in the preparation of this manuscript.
Conflict of interest: Dr Dupouiron has received consultancy fees from Medtronic and EISAI.

Manuscript received: 01-08-2015
Revised manuscript received: 03-23-2015
Accepted for publication: 03-27-2015

Free full manuscript:
www.painphysicianjournal.com

Background: Use of intrathecal admixtures is widespread, but compounding these is sometimes challenging and may result in errors and complications causing super-potency or sub potency adverse events in patients or malfunctions in the pump itself.

Objective: The purpose of this study is to evaluate the accuracy of compounding of intrathecal admixtures through a prospective, systematic quantitative analysis of each component of the mixture before delivery to patients.

Study Design: Observational follow up prospective study of intrathecal mixtures components concentrations before refills.

Settings: Assays were performed on all intrathecal admixtures produced by the ICO-Paul Papin compounding pharmacy between January 2013 and October 2014 using Ultra High Performance Liquid Chromatography (U.H.P.L.C.). In addition, pH levels of admixtures have been measured since June 2014. When measured concentrations were 15% above or below the required concentrations, the mixture was excluded and compounded again.

Results: 1729 mixtures were analyzed. Mean deviation from theoretical values was $-1.17\% \pm 0.28\%$ for morphine, $-0.95\% \pm 1.07\%$ for ropivacaine, and $4.82\% \pm 0.6\%$ for ziconotide. Exclusion rates were 8.33% overall, but fell from 11.67% in 2013 to 4.97% in 2014. Most exclusions were caused by inaccuracy in the dose of ziconotide. Average mixture pH of the 603 tested admixtures was $4.83 \pm 0.6\%$.

Limitations: This study is monocentric and limitations include also its non-randomized nature with no clinical comparison of the rate of adverse events with a refill process without control of each component concentrations.

Conclusion: Prospective assays provide benefits in ensuring accuracy of intrathecal mixture compounding and in preventing overdosing or sub dosing, most notably concerning Ziconotide.

Key words: Intrathecal drug delivery, morphine, ziconotide, ropivacaine, prospective dosages, adverse events prevention, quality process

Pain Physician 2015; 18:349-357

Intrathecal analgesia has advanced considerably in the last 20 years, and numerous studies have proven its efficacy, especially in cancer treatment, as a credible alternative for patients suffering from refractory pain

(1,2). Over the years, certain associations of analgesics have shown synergistic effects (3-5) as well as greater efficacy (6) along with a reduction in side effects (4,7,8).

Use of analgesic admixtures is often necessary, particularly in oncology, for which it has been recommended by the most recent consensus conferences (9,10). The use of analgesic mixtures is sometimes challenging, however, as it can itself become a source of complications, because it requires accurate prescription of doses, and precise and aseptic mixture preparation while avoiding compounding errors and high stability of admixtures. Compatibility of mixtures with the pumps to deliver them must also be ensured.

In 2012, after a series of adverse events caused by pump failures, as a result of the use of intrathecal mixtures with a low pH, a manufacturer of intrathecal drug delivery systems published a warning concerning the use of intrathecal mixtures. In response, a panel of experts from the learned societies made recommendations on the prescription, preparation, and use of these analgesic admixtures (12,13).

Moreover, among these analgesics, ziconotide poses particular problems. On the one hand, it must be administered firstly in small doses with slow and steady increments in order to reduce adverse effects (14); this requires low doses in admixtures and highly accurate compounding of these mixtures, since the drug is initially highly concentrated. On the other hand, Ziconotide possibly decays in pumps when it is a constituent of admixtures (15-18).

BACKGROUND

In view of the above considerations and as part of our quality process, 2 years ago we implemented a system of production of intrathecal mixtures which includes computerized prescription, compounding under laminar flow hood in the department of pharmacy, and concentration analysis of each constituent drug to ensure conformance with prescription prior to delivery of refills.

After implementation, a study was carried out that observed the stability of each molecule of admixtures when stored in pumps (15). Secondly, conformance of mixtures has been verified systematically since January 2013, when a more powerful ultra-performance liquid chromatography (UPLC) unit was acquired, partly to meet a request from regional health authorities who asked for this control to authorize compounding for other hospitals in the region to ensure delivery of refills from our pharmacy closer to cancer patients' homes.

A database was created containing results of all assays performed on mixtures. The results are analyzed below.

Aims of the Study

The purpose of this study is to evaluate the accuracy of compounding of intrathecal admixtures during routine operations and thereby to determine rates of conformance with prescriptions. The study also aims to determine the number of compounding errors, including overdosing or underdosing issues of components that were avoided due to systematic concentration testing. It is also part of a continuing quality process designed to improve accuracy of preparation in order to reduce adverse effects from upstream dosing errors.

METHODS

Patients

Assays were performed on all mixtures produced for patients enrolled in intrathecal pain therapy, whether by internal pump or external pump, between January 2013 and October 2014 at the Institut de Cancérologie de L'Ouest - Paul Papin. This study has been authorized by the local Ethics Committee.

Medications

Mixtures were composed of at most 3 drugs, all from sterile commercially available solutions:

Morphine sulfate, without adjuvant, dilutions were prepared from 50 mg/mL vials (Lavoisier Pharmaceutical, Inc., Paris, France). The initial intrathecal (IT) morphine dosage was calculated from the patients' previous systemic opioid dosage by using an oral IT ratio of 300:1 (9).

Ropivacaine at a concentration of 10 mg/mL (Astra-Zeneca Pharmaceutical, Inc., London, United Kingdom) was utilized; local anesthetics: bupivacaine is generally preferred because of its long duration of action but is not available in France in the high concentrations required for intrathecal administration, and we consequently use ropivacaine instead.

Ziconotide was drawn from a 1-mL vial containing a concentration of 100 µg/mL (Eisai Pharmaceutical, Inc., Tokyo, Japan). Free L-methionine (50 µg/mL) is used as the vehicle for ziconotide because it is more easily oxidized compared to the methionine in ω-conotoxin.

The doses of each IT component used was determined to obtain the best pain relief following the latest recommendations of the experts (9).

Materials

Assays were performed on Ultra Performance Liquid Chromatography® UPLC Acquity H-Class (Waters)

equipment which includes an Acquity UPLC® BEH C18 1.7 µm 2.1x50mm column, quaternary solvent management, a Photo Diode Array detector, and a sample manager. All modules were controlled with Empower® software. The mobile phase was prepared using ultra-pure water (Elga Purelab DV25), acetonitrile, and trifluoroacetic acid (VWR®, Fontenay aux Roses, France), in gradient mode. The pH was determined with a glass micro-electrode connected to a pH meter model HI 2210 (Hanna, Tanneries, France).

Methods

The UPLC method consists of a gradient of ultra-pure water with 0.1% trifluoroacetic acid (Phase A) and acetonitrile with 0.1% trifluoroacetic acid (Phase B). The gradient used was as follows: T0 min 95:5 (A/B); T0.5 min 90:10 (A/B); T3.5 min 10:90 (A/B); T4 min 95:5 (A/B). The column is heated to 30°C. Injection volumes are 0.3 µl for simultaneous analysis of morphine and ropivacaine, and 10 µl for ziconotide. Each test takes 5 minutes. Total analysis time for samples containing morphine, ropivacaine, and ziconotide is 10 minutes. In these conditions, retention times are 0.95 minutes for morphine, 2.2 minutes for ropivacaine, and 1.78 minutes for ziconotide. UV spectra are analyzed between 200 and 400 nm. Detection wavelengths are 285 nm for morphine, 230 nm for ropivacaine, and 206 nm for ziconotide.

Statistical Analysis

Results were collated in an Access 2013 database (Microsoft Corporation, Redmond, WA) and were analyzed using the statistical software Winstat 7.0 (R. Fitch Software, Chicago, IL). Mean ziconotide errors were compared using the Mann-Whitney-Wilcoxon test at the 5% significance level. All data are presented as means ± standard deviation. Correlation was described using Pearson correlation coefficient.

Research Protocol

Withdrawal of oral analgesics is performed immediately after implantation of intrathecal device. The assessment of pain intensity before each refill is completed by the physician on a 0 – 10 numerical scale (0 = no pain, 10 = worst pain imaginable).

Then the intrathecal pump treatment is prescribed with the assistance of Anathec® (Accoss groupe ALMA Medical, Vitry sur Seine, France).

The prescription is then forwarded to the hospital

pharmacy where compounding is performed in sterile conditions under a laminar flow hood through a 0.2 micron low protein binding filter in polyethersulfone. In addition, to ensure sterility of the mixtures, preparations are made from sterile pharmaceutical products with sterile medical devices in a sterile environment. We can consider it a closed system. Controls consist of checking at set interval the environment and equipment.

Preparations are produced by pharmacy technicians who are qualified for this task. They are specialized in the realization of injectable preparations. Their specific training is performed by a referent and includes different steps, both practical and theoretical. The ability to perform intrathecal mixtures is delivered by the chief of the department after the examination of the performance, by the technician, of a mixture with key points.

The syringe containing the admixture is then packaged in a sterile sachet.

Prior to packaging, 1 mL is sampled from the admixture in order to test concentrations of each component drug; the results of this analysis are compared to the prescribed concentrations. All admixtures in which any constituent is found to differ by more than 15% from the prescribed concentration are rejected and compounded again. Given the lack of legal rules in France for this kind of assay, the results of a previous validation method allowed us to define the threshold for quantitative release to 15% between measured and theoretical concentration levels. This level represents the sum of the factors of extrinsic variation such that the concentration of industrial pharmaceutical drugs, the accuracy of syringes, and performance of the device. The refill is only delivered after validation of the assay by the managing pharmacist (Fig. 1).

Since June 2014, acquisition of a specific pH meter allowed for pH levels to also have been measured.

RESULTS

Exactly 1,729 consecutive mixtures for 153 patients were analyzed for concentrations of constituents from January 2013 to October 2014. Of the mixtures, 85.1% were prepared for Synchromed 2 Medtronic® internal pumps and 14.8% were prepared for patients with external pumps, catheters, and subcutaneous ports. Two patients were implanted with an intraventricular catheter. Mean prescribed concentrations are found in Table 1.

Analysis of Overall Conformance

Mean differences between observed concentrations and prescribed concentrations are $-1.17 \pm 0.28\%$ for morphine, $-0.952 \pm 1.07\%$ for ropivacaine, and $4.82 \pm 0.60\%$ for ziconotide. Accuracy is greater for

morphine and ropivacaine, and there was no change between 2013 and 2014. Inaccuracy rates are higher for ziconotide (Table 2).

Inaccuracy is higher for lower concentrations of ziconotide, as shown in Figs. 2-1, 2-2, and 2-3.

When inaccuracy rates are compared for ziconotide concentrations, a significant difference appears between 2 groups of ziconotide preparations: concentrations lower than $0.5\mu\text{g/mL}$ of ziconotide where the average difference between theoretical concentrations and observed concentration is $6.98\% \pm 0.94\%$, and concentrations equal to or greater than $0.5\mu\text{g/mL}$ where there is a mean difference of $1.47\% \pm 0.35\%$ ($P < 0.001$) (Fig. 3).

Concerning ropivacaine, not only is it the lower concentrated initially, but it also shows the least dispersion of values at low concentrations as well as the smallest differences.

Mixture Exclusions after Assay

The number of admixtures excluded after testing, i.e., showing the defined difference of 15%, is 8.3% overall, though it has improved considerably as compounding pharmacists have gained experience. The rate of exclusion was 11.69% in 2013, but has since fallen to 4.97% for the first 10 months of 2014 (Table 3).

Most exclusions have been caused by inaccuracy in ziconotide dosage, essentially during the first year of testing. In fact, in 2013, 118 out of 144 exclusions (81.9%) were due to inaccuracy in dilution of ziconotide, accounting for 70.3% (Table 4). Among excluded preparations caused by inaccuracy of ziconotide

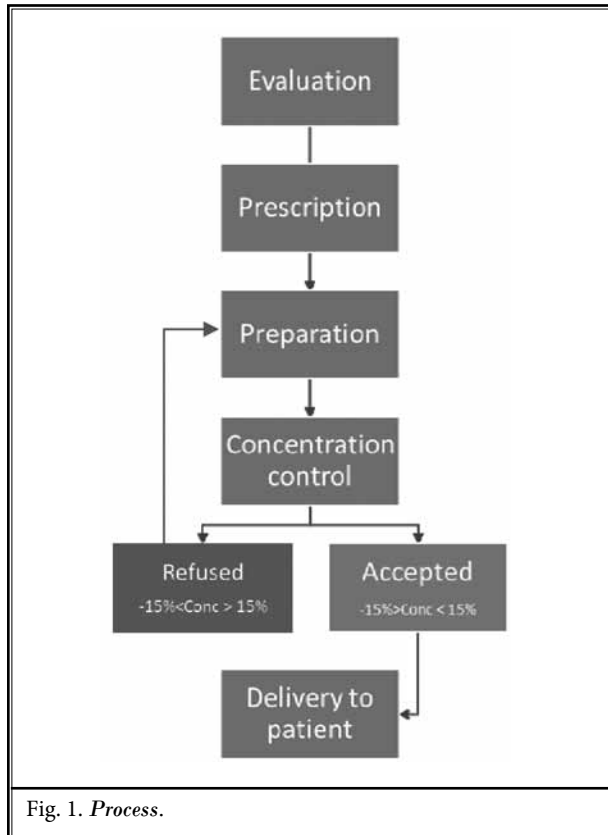


Fig. 1. Process.

Table 1. Mean concentration of each component.

	N	Mean Concentration	Minimum Concentration	Maximum Concentration
Morphine concentration	1729	3.34 ± 2.32 mg/mL	0.05 mg/mL	23.9 mg/mL
Ropivacaine concentration	1712	7.54 ± 2.33 mg/mL	0.4 mg/mL	9.8 mg/mL
Ziconotide concentration	1681	0.98 ± 0.03 $\mu\text{g/mL}$	0.04 $\mu\text{g/mL}$	5.8 $\mu\text{g/mL}$

Table 2. Mean variation of drug concentration.

	N	Mean	Confidence interval (\pm)
% Mean variation M	1729	-1.172%	0.28%
% Mean variation R	1712	-0.952%	1.07%
% Mean variation Z	1681	4.822%	0.604%

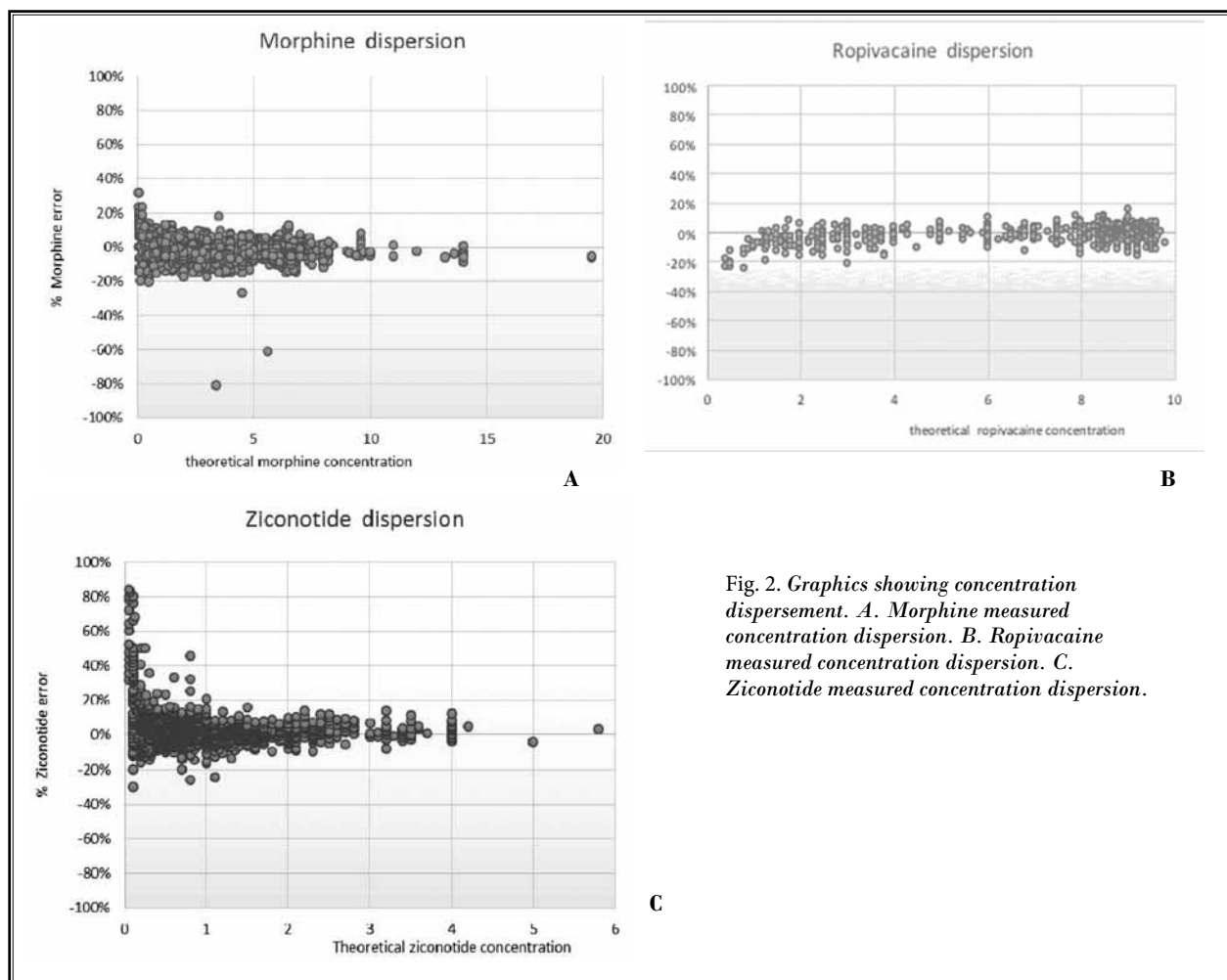


Fig. 2. Graphics showing concentration dispersement. A. Morphine measured concentration dispersion. B. Ropivacaine measured concentration dispersion. C. Ziconotide measured concentration dispersion.

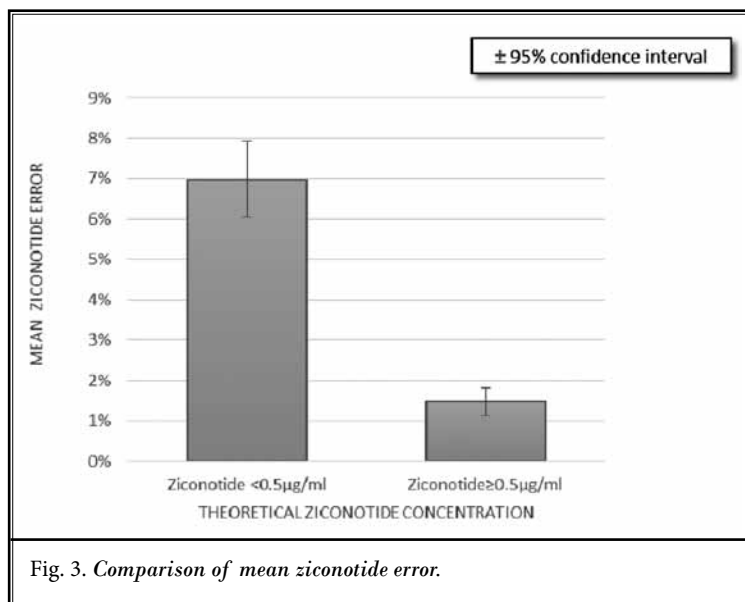


Fig. 3. Comparison of mean ziconotide error.

Table 3. Numbers and rate of mixture exclusions per year.

Year	N	Total exclusions	% exclusions
2013	864	101	11.69%
2014	865	43	4.97%
Total	1729	144	8.33%

Table 4. Number of exclusions per year. M = Morphine, R = Ropivacaine, Z = Ziconotide.

Year	N dosages	N exclusions	% exclusions	Z alone	M alone	N alone	Z+ M+N	Z+ M	Z+ R	M+R
2013	864	101	11.69%	69	8	10	0	11	3	0
2014	865	43	4.97%	33	4	1	1	1	0	3
Total	1729	144	8.33%	102	12	11	1	12	3	3

Table 5. Number of exclusions per drug.

	N	Max diff	Min diff	Mean
Morphine	28	32.00%	-80.80%	18.00%
Ropivacaine	18	922.50%	-25.00%	16.72%
Ziconotide	118	203.50%	-30.00%	23.80%

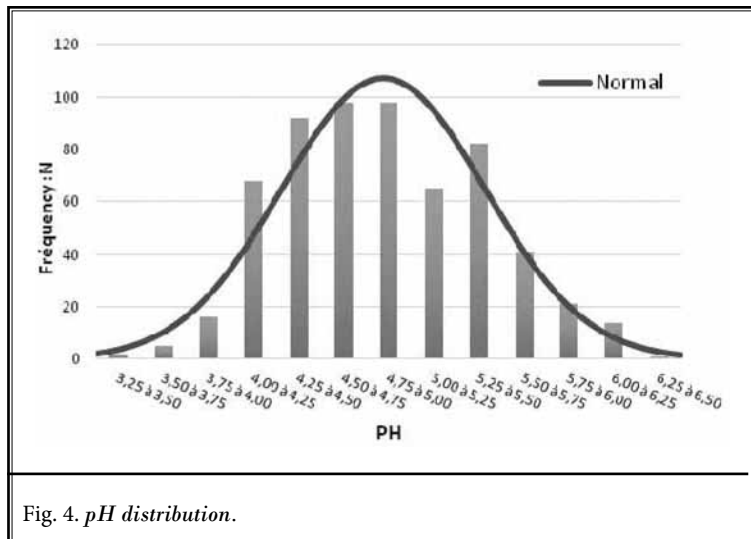


Fig. 4. pH distribution.

Systematic Measurement of pH

Since the implementation of a program of systematic measurement of pH, 603 consecutive admixtures have been verified. The mean pH is 4.83 ± 0.5 with a maximum of 6.31 and a minimum of 3.33 (Fig. 4). A search for factors explaining this variation in pH reveals that it is strongly correlated with morphine concentration (Pearson Coefficient = 0.77) (Fig. 5).

DISCUSSION

Accuracy of Intrathecal Mixtures

These prospective concentration analyses of intrathecal mixtures demonstrate the difficulty involved in obtaining accurate concentrations of each component of mixtures. However, the 8% of all prepared admixtures showing an error 15% greater than the prescribed concentration were rejected, thus avoiding potential adverse events.

In addition, such analyses led, over time, to improvements in accuracy, since the exclusion rate fell from 11% in 2013 to 5% in 2014. Thus, following the results of this study, the imprecision acceptable rate will be decreased to $\pm 10\%$.

This improvement is due primarily to a reduction in inaccuracy rates for ziconotide concentrations, due to an improvement in the preparation as well as in the qual-

concentrations, 22 (1.2% of analyses) presented concentrations 50% greater than the prescribed dose with a maximum of 203% difference; 18 of these greater-than-50% of prescription errors occurred in 2013 (Table 5).

In addition, among those exclusions caused by an inaccurate dosage of ziconotide, 12 were accompanied by a significant error in morphine concentrations, 11 by a significant error in ropivacaine dosage, and one involved all 3 components of the mixture.

Exclusions caused by morphine inaccuracies are rarer, and observed differences are smaller; only 28 (1.8% of assays) significant differences were observed, with differences ranging from -80% to +32%. Here too, 68% of these errors were found in 2013.

Errors in ropivacaine dosage are occasional: 18 (1.3%); however, for one of those errors, the difference was considerable, 923%, which is nearly 10 times the prescribed dose.

ity of homogenization and sampling. Indeed, ziconotide showed the highest rate of inaccuracy in concentrations following the implementation of systematic assays. This information is crucial, because dosage errors most likely explain a significant percentage of the side effects (14,19-21) caused by ziconotide. Indeed, ziconotide is a particularly powerful drug and its therapeutic index is low; adverse effects may occur at low doses (1 µg/day) (7). The accuracy of the injected dose is therefore vital, but as of today, no other clinical study has checked concentrations of ziconotide really infused.

In addition, a significant difference in inaccuracy rates between mixtures containing low concentrations of ziconotide (< 0.5 µg/mL) and those containing the highest concentrations (≥ 0.5 µg/mL) was observed. As ziconotide is initially concentrated at 100 µg/mL, it is easy to reach such levels of inaccuracy. Low concentrations are often necessary, because it is recommended that ziconotide treatment start at 0.5 µg/day and should increase by small increments (22). In France, for ziconotide, only the formulation 100 µg/mL is available, so an assay of concentrations therefore seems essential to ensure a safe incremental increase in treatment dosage.

Similarly, another important finding of this study is that the greatest accuracy is obtained from the commercial dilutions which are as close as possible to prescribed doses as in, for example, ropivacaine (10 µg/mL). However, if ropivacaine is used in France it is primarily because 40 µg/mL bupivacaine is not available in the country. Moreover, such commercial dilutions also present the disadvantage of requiring more frequent refilling of pumps.

Prevention of Super-Potency

The major dosage errors observed here may cause serious overdose accidents (23,24). In our series of analyses, the error involving overdosing of ropivacaine of more than 900% was, fortunately, detected, thus preventing most likely a serious accident. Similarly, the large errors of more than 50% in the dosage of ziconotide that led to rejection of refills would probably have caused serious side effects. It is worthy of note that during the period of the study, no serious adverse effects, of the kind requiring a report

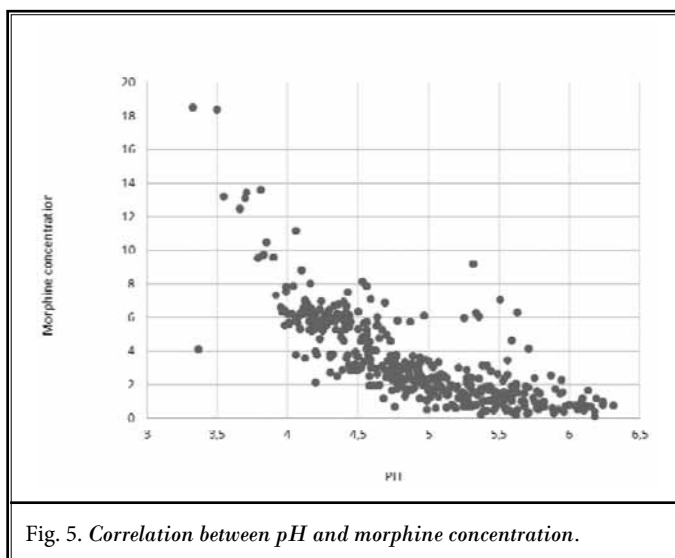


Fig. 5. Correlation between pH and morphine concentration.

to authorities, were observed in any of the 153 patients who benefited from the systematic assay of their medication. Functional accuracy of pumps has been widely studied (25), but the current study shows that inaccuracy in dosage of medications is perhaps another important factor in mortality. Mortality caused by overdose in intrathecal analgesia is unclear (24). In a retrospective study of mortality in intrathecal treatment, Coffey et al (26) found that overdosing was a credible factor in 28% of cases. However, measurement of morphine concentrations had been performed in only 3 out of 88 cases. In our experience, a patient was hospitalized 48 hours after a pump refill delivered by another hospital without mixture preparation by the pharmacy and without any prospective dosing for a morphine overdose syndrome. Assay confirmed the diagnosis of morphine overdose, with a concentration 10 times higher than the prescribed dose of morphine.

Conformance with Recommendations

Medtronic's 2012 warning (11) highlighted the difficulties involved in using drug admixtures in intrathecal pumps. In their response, the specialist panel recommended that preparation of mixtures be carried out in "compounding pharmacies" with testing of constituent quality and of admixture pH levels (9,12,13). Our process meets those recommendations and goes beyond them by quantifying concentrations of constituents.

Cost of Equipment

The initial cost of the equipment for UHPLC is € 70,000 and each test is evaluated at € 50. The additional cost of these assays is acceptable given the price of reimbursement of each refill by health insurance. In addition, this assessment does not

take into account the savings achieved by preventing overdoses. However, these considerations are applicable only in France and cannot be implemented given the reimbursement differences in each country.

Limitations

This study is monocentric and limitations include its non-randomized nature with no clinical comparison of the rate of adverse events with a refill process without control of each component concentration.

CONCLUSION

There is no equivalent study in the literature. This evaluation of prospective assay in intrathecal mixtures demonstrates the benefits of such a process which may be easily made part of daily practice, to better ensure the accuracy of dosages and the prevention of overdosing and underdosing, thus improving the quality and the safety of these techniques. This quantitative analysis limits dosage errors and, by extension, overdosing, par-

ticularly for ziconotide. Moreover, the method seems to be becoming a requirement of medical authorities to obtain approval for "off label" admixtures. Finally, it should allow greater numbers of institutions to dispense reliable mixtures. Thanks to these assays, we recently obtained from the regional health administration, the first authorization in France to produce IT mixtures for a hospital that does not have these production facilities and who could not use the IT treatment previously. In this way, refills of pumps may be dispensed at home or as close as possible to the patient's home, thus limiting the difficulties of travel for cancer patients at an advanced stage of the disease and also reducing the costs of refills from travel. It appears to be a major factor in the future development of intrathecal drug delivery.

Acknowledgments

The authors would like to thank Michael Hyde for medical editorial assistance.

REFERENCES

- Smith T, Staats P, Deer T, Stearns L, Rauck R, Boortz-Marx R, Buchser E, Catala E, Bryce D, Coyne P, Pool G. Randomized clinical trial of an implantable drug delivery system compared with comprehensive medical management for refractory cancer pain: Impact on pain, drug-related toxicity, and survival. *J Clin Oncol* 2002; 20:4040-4049.
- Wang J, Nauss L, Thomas J. Pain relief by intrathecally applied morphine in man. *Anesthesiology* 1979; 50:149-151.
- Alicino I, Giglio M, Manca F, Bruno F, Puntillo F. Intrathecal combination of ziconotide and morphine for refractory malignant pain: A rapidly acting and effective choice. *Pain* 2011; 153: 245-249.
- Wallace M, Rauck R, Deer T. Ziconotide combination intrathecal therapy: Rationale and evidence. *Clin J Pain* 2010; 26:635-644.
- Wang Y, Gao D, Pettus M, Phillips C, Bowersox S. Interactions of intrathecally administered ziconotide, a selective blocker of neuronal N-type voltage-sensitive calcium channels, with morphine on nociception in rats. *Pain* 2000; 84:271-281.
- van Dongen R, Crul B, van Egmond J. Intrathecal coadministration of bupivacaine diminishes morphine dose progression during long-term intrathecal infusion in cancer patients. *Clin J Pain* 1999; 15:166-172.
- Dupoiron D, Bore F, Lefebvre-Kuntz D, Brenet O, De bourmont S, Dixmieras F, Buisset N, Lebrec N, Monnin D. Ziconotide adverse events in patients with cancer pain: A multicenter observational study of a slow titration, multidrug protocol. *Pain Physician* 2012; 15:395-403.
- Wallace MS, Kosek PS, Staats P, Fisher R, Schultz DM, Leong M. Phase II, open-label, multicenter study of combined intrathecal morphine and ziconotide: Addition of ziconotide in patients receiving intrathecal morphine for severe chronic pain. *Pain Med* 2008; 9:271-281.
- Deer TR, Prager J, Levy R, Rathmell J, Buchser E, Burton A, Caraway D, Cousins M, De Andres J, Diwan S, Erdek M, Grigsby E, Huntoon M, Jacobs M, S. Kim P, Kumar K, Leong M, Liem L, McDowell GC, Panchal S, Rauck R, Saulino M, Sitzman BT, Staats P, Stanton-Hicks M, Stearns L, Wallace M, Willis KD, Witt W, Yaksh T, Mekhail N. Polyanalgesic Consensus Conference—2012: Recommendations for the management of pain by intrathecal (intraspinial) drug delivery: report of an interdisciplinary expert panel. *Neuromodulation* 2012; 15:436-464.
- Deer TR, Smith HS, Burton AW, Pope JE, Doleys DM, Levy RM, Staats PS, Wallace MS, Webster LR, Rauck RL, Cousins M. Comprehensive consensus based guidelines on intrathecal drug delivery systems in the treatment of pain caused by cancer pain. *Pain Physician* 2011; 14:283-312.
- Medtronic. Increased Risk of Motor Stall and Loss of or Change in Therapy with Unapproved Drugs Formulations. 2012. http://professional.medtronic.com/wcm/groups/mdtcom_sg/@mdt/@neuro/documents/documents/risk-motor-stall.pdf
- Rezai A, Kloth D, Hansen H, Schultz D, Thomson S, Deer T, Caraway D. Physician response to medtronic's position on the use of off-label medications in the synchromed pump. *Neuromodulation* 2013; 16:398-400.
- Rezai A, Kloth DS, Hansen H, Schultz D, Thomson S, Deer T, Caraway D. Physician response to medtronic's position on the use of off-label medications in the synchromed pump. *Pain Physician* 2013; 16:415-417.
- Rauck RL, Wallace MS, Leong MS, Minehart M, Webster LR, Charapata SG, Abraham JE, Buffington DE, Ellis D, Kartzinel R. A randomized, double-blind, placebo controlled study of intrathecal ziconotide in adults with severe chronic pain. *J Pain Symptom Manage*

- 2006; 31:393-406.
15. Dupouiron D, Richard H, Chabert-Desnot V, Devys C, Leynia P, Boisdron-Celle M. In vitro stability of low-concentration ziconotide alone or in admixtures in intrathecal pumps. *Neuromodulation* 2014; 17:472-482.
 16. Shields D, Montenegro R. Chemical stability of ziconotide-clonidine hydrochloride admixtures with and without morphine sulfate during simulated intrathecal administration. *Neuromodulation* 2007; 10:6-11.
 17. Shields D, Montenegro R, Aclan J. Chemical stability of an admixture combining ziconotide and bupivacaine during simulated intrathecal administration. *Neuromodulation* 2007; 10:1-5.
 18. Shields DE, Liu W, Gunning K, Montenegro R. Statistical evaluation of the chemical stability of ziconotide solutions during simulated intrathecal administration. *J Pain Symptom Manage* 2008; 36:4-6.
 19. Sanford M. Intrathecal ziconotide: A review of its use in patients with chronic pain refractory to other systemic or intrathecal analgesics. *CNS Drugs* 2013; 27:989-1002.
 20. Schmidtko A, Lotsch J, Freynhagen R, Geisslinger G. Ziconotide for treatment of severe chronic pain. *Lancet* 2010; 375:1569-1577.
 21. Staats PS, Yearwood T, Charapata SG, Presley RW, Wallace MS, Byas-Smith M, Fisher R, Bryce DA, Mangieri EA, Luther RR, Mayo M, McGuire D, Ellis D. Intrathecal ziconotide in the treatment of refractory pain in patients with cancer or AIDS: A randomized controlled trial. *JAMA* 2004; 291:63-70.
 22. Prager J, Deer T, Levy R, Bruel B, Buchser E, Caraway D, Cousins M, Jacobs M, McGlothlen G, Rauck R, Staats P, Stearns L. Best practices for intrathecal drug delivery for pain. *Neuromodulation* 2014; 17:354-372.
 23. Horlocker TT, Burton AW, Connis RT, Hughes SC, Nickinovich DG, Palmer CM, Pollock JE, Rathmell JP, Rosenquist R, Swisher JL, Wu CL. Practice guidelines for the prevention, detection, and management of respiratory depression associated with neuraxial opioid administration. *Anesthesiology* 2009; 110:218-230.
 24. Coffey R, Owens M, Broste S, Dubois M, Ferrante F, Schultz D, Stearns L, Turner M. Medical practice perspective: Identification and mitigation of risk factors for mortality associated with intrathecal opioids for non-cancer pain. *Pain Med* 2010; 11:1001-1009.
 25. Wesemann K, Coffey R, Wallace M, Tan Y, Broste S, Buvanendran A. Clinical accuracy and safety using the SynchroMed II intrathecal drug infusion pump. *Reg Anesth Pain Med* 2014; 39:341-346.
 26. Coffey R, Owens M, Broste S, Dubois M, Ferrante F, Schultz D, Stearns L, Turner M. Mortality associated with implantation and management of intrathecal opioid drug infusion systems to treat noncancer pain. *Anesthesiology* 2009; 111:881-891.

