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Baclofen Stability up to One Year in In Vivo Intrathecal Infusion Pumps

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ABSTRACT

Objectives: Commercial intrathecal baclofen treatment (ITBT) infusion pumps are recommended to be refilled within a maximum of 180 days, thus necessitating at least twice-yearly outpatient visits and refill injections. In particular, pumps with 40-mL reservoir volumes would allow much longer refill intervals. We investigated baclofen stability in active implanted ITBT infusion pumps in vivo with refill intervals up to 367 days to study the feasibility of lengthening refill intervals beyond six months.

Materials and Methods: We obtained 25 baclofen samples from 19 patients receiving ITBT with varying pump refill intervals. All patients had a baclofen infusion system delivering undiluted 2 mg/mL baclofen at continuous rates of 96.1 to 673.7 μg/d with a concentration of 2.002 mg/mL. Baclofen concentrations of the infusate samples acquired during the refill procedures were analyzed using a validated high-performance liquid chromatography with diode-array detection (HPLC-DAD) assay, later complemented with repeat assay with pH and physical measurements. We also present the validation data of the HPLC-DAD assay.

Results: During the mean refill interval of 247 days (SD 90, range 54–367 days), the mean change in baclofen concentration was −0.0156 mg/mL (−0.8%, SD 0.14, range −0.30 to 0.32 mg/mL, paired *t*-test $p = 0.57$, $t_{24} = 0.57$). Only a low negative correlation was found between the baclofen concentration and the refill interval (Pearson's $r = -0.32$, $p = 0.12$).

Conclusions: We could not show a significant change in baclofen concentration over the time studied; 2 mg/mL baclofen ITBT refill intervals could be lengthened to up to one year—the theoretical maximum refill interval in our cohort would have been 489 days. Further studies with larger sample sizes and other baclofen brands are warranted.

Keywords: Concentration, HPLC-DAD, intrathecal baclofen therapy, spasticity, stability

INTRODUCTION

Spasticity, a common sequela of central nervous system disease, is a significant cause of disability that may be alleviated with intrathecal baclofen therapy (ITBT) in select cases. The incidence of disease amenable to ITBT has been estimated to be 4.6 to 5.7 per million population.[1] According to unpublished manufacturer data, approximately 100 ITBT systems are implanted annually in Finland, with a population of 5.6 million. In the United States, >80,000 ITBT systems have been implanted.[2] Worldwide, hundreds of thousands of ITBT-related appointments and refill procedures are thus carried out yearly.

ITBT pump refill procedures carry risks of inadvertent subcutaneous baclofen injection, subcutaneous hematoma, bowel perforation, infection leading to infusion system removal, mechanical complications leading to catheter malfunction, and human errors in medicine preparation and in system programming.[3–5] In a home-based setting, adverse events occurred in 1.5% of all ITBT-related appointments,[4] and in another study, 0.6% of pump refills caused infections.[5] Furthermore, recurring appointments may be a significant quality-of-life issue in this moribund patient group, which is exacerbated by long geographic distances in our setting. Pump refill procedures should therefore be minimized.

Extending refill intervals would be a cost-effective means of reducing appointments, procedures, and complications arising from ITBT pump refills. However, in keeping with manufacturer recommendations, pump refill intervals are commonly kept <180 days.[6–8] Theoretically, refill intervals could exceed six months in many cases, especially with 40-mL infusion systems. Clinical interest in extending refill intervals has arisen in our practice. We aimed to examine the stability of intrathecally administered baclofen in active in vivo ITBT pump systems with extended refill intervals that predominantly exceeded six months.

MATERIALS AND METHODS

Patient Population

Between June 1, 2020, and January 31, 2022, we identified 19 patients receiving ITBT with varying pump refill intervals, from whom 25 samples were obtained (Fig. 1). Data on patient demographics and pump refills were extracted from the Oulu University

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Hospital patient records. All the patients had Synchromed IIintrathecal infusion systems (Medtronic, Inc, Minneapolis, MN) delivering undiluted 2 mg/mL b-(aminomethyl)-p-chlorohydrocinnamic acid (baclofen) solution (brand name: Baclofen Sintetica, manufacturer: Sintetica SA, Mendrisio, Switzerland) at continuous rates with no boluses. Patients receiving any drug other than 2 mg/mL Baclofen Sintetica were excluded from the current study.

Sample Acquisition and Analysis

The baclofen infusate extracted during the refill procedure was visually evaluated for turbidity and particles, aseptically injected into a sealed vacuum container, protected from light, stored at 6 °C, and sent to baclofen concentration analysis in an independent laboratory. The samples were kept in an aseptic plastic container protected from sunlight in 2 to 8 °C and analyzed within five days of receipt (initial analysis). Concentration analysis was conducted using high-performance liquid chromatography with diode-array detection (HPLC-DAD) (VWR International, Radnor, PA) with a 120 × 4 mm column (Knauer GmbH, Berlin, Germany). The mobile phase mixture comprised 530 mL bidistilled water/phosphoric acid 85%/150 µL triethylamine with pH adjusted to 3.3 using potassium hydroxide, followed by the addition of 470 mL acetonitrile with a resultant pH of approximately 4.0. Flow rate was set to 0.6 mL/min, and injection volume was 5 µL. The diode-array detector was set to scan from 192 to 372 nm; the samples were measured against freshly prepared reference baclofen standard solutions with concentrations of 75%, 100%, and 125% of the expected concentration. The intra- and interrun coefficient of variation of the HPLC-DAD analysis was <5% in the internal validation data (Supplementary Data Tables S1 and S2). All the validation procedures were conducted according to internal University Medical Center Groningen procedures.

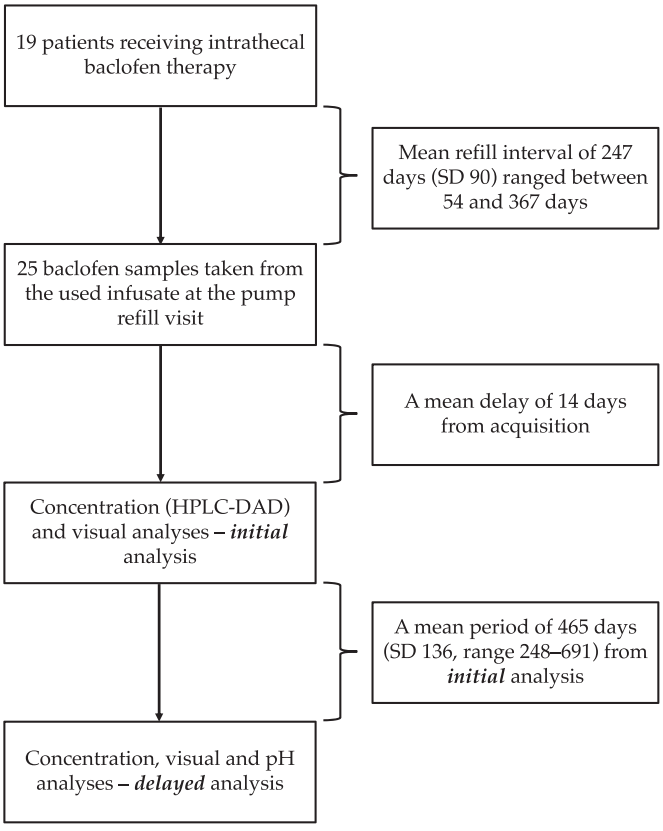

Figure 1. Flowchart of the study. The delayed analyses were conducted twice to evaluate repeatability of the HPLC-DAD assay of baclofen concentration. An internal validation of the assay was conducted.

The baclofen administered to the patients was from a single lot (#2000501). According to the quality control data provided by the drug manufacturer, the concentration of the undiluted Baclofen Sintetica 2 mg/mL raw solution is between 1.90 and 2.10 mg/mL (within ±5% of the label claim) and confirmed by the manufacturer; the baclofen concentration of the infusate lot used in the current study was 2.002 mg/mL (100.1% of declared). The pH value of the baclofen infusate used was 6.3, according to the manufacturer. Sample acquisition occurred between October 28, 2020, and November 24, 2021, and the manufacturing and expiry dates of the baclofen lot studied were January 16, 2020, and January 31, 2025, respectively.

To assess baclofen degradation in a laboratory environment, the concentration measurements were repeated (delayed analysis). These measurements were conducted twice to confirm assay repeatability. The pH and turbidity of the solution also were examined at this time point. A forced hydrogen peroxide degradation test of the baclofen solution was conducted to reveal the ability of the HPLC-DAD assay to detect baclofen degradation products.

Statistical Analysis

The paired samples *t*-test was used to examine the change in baclofen concentration reported with the associated *t*-value and degrees of freedom. To compensate for the inherently variable baclofen sample acquisition times, the two-tailed Pearson's correlation coefficient (*r*) was used to evaluate a possible linear correlation between the baclofen concentration and refill interval in conjunction with the *t*-test. Before this, normality of the data was confirmed using the Shapiro-Wilk test and Q-Q plotting. The repeatability of the HPLC-DAD assay was evaluated using the repeated-measures analysis of variance and visualized using a Bland-Altman plot. Categorical variables are reported as numbers with percentages, and continuous variables as means with SDs or medians with ranges depending on their distribution. All statistical analyses were conducted using the IBM SPSS Statistics for Windows, version 23 (IBM Corp, Armonk, NY) with a p value of <0.05 taken to represent statistical significance.

The present audit was a part of an internal clinical service evaluation of the Oulu University Hospital ITBT practice to evaluate the accuracy of vital drug administration. The evaluation required no additional procedures to be conducted in the patients, and the anonymized baclofen samples were handled by an independent laboratory with no access to patient data. The present evaluation was approved by the Head of Department of the Department of Neurosurgery, Oulu University Hospital, and conducted in accordance with the Declaration of Helsinki.

RESULTS

Nineteen patients receiving 2 mg/mL ITBT were identified, and a total of 25 baclofen samples were analyzed. The baseline characteristics of the study population are listed in Table 1. The patients were receiving intrathecal baclofen at a mean rate of 217.4 µg/d (SD 138.3 ranging from 96.1–673.7 µg/d). The mean refill interval

Table 1. Baseline Characteristics of the Study Cohort Representing Characteristics at the Time of Sample Acquisition.

Characteristic	Samples (n = 25)
Mean age at sample acquisition, y (SD)	43.1 (14.6)
Male sex, n (%)	17 (68)
Primary diagnosis leading to ITBT, n (%)*	
Traumatic brain injury	6 (24)
Traumatic spinal cord injury	5 (20)
Multiple sclerosis	4 (16)
Cerebral palsy	2 (8)
Anoxic brain injury	2 (8)
Hemorrhagic stroke	2 (8)
Developmental disability	2 (8)
Intramedullary tumor	2 (8)
Elapsed mean duration of ITBT at sample acquisition, y (SD)	9.2 (6.7)

Twenty-five samples were acquired from 19 patients.
*Numbers of individual patients (n = 19) with each diagnosis; traumatic brain injury: four (21%), traumatic spinal cord injury: five (26%), multiple sclerosis: three (16%), cerebral palsy: two (11%), anoxic brain injury: two (11%), hemorrhagic stroke: one (5%), developmental disability: one (5%), intramedullary tumor: one (5%).

was 247 days (SD 90, range 54–367 days), whereas the theoretical maximum mean refill interval would have been 489 days if all the patients had had 40-mL reservoirs, and the intervals would not be iatrogenically truncated. The baclofen sample concentration before infusion was 2.002 mg/mL.

Baclofen Concentration at the Time of Sample Acquisition (Initial Analysis)

All the samples acquired at the time of the baclofen pump refill were clear and colorless and had no visible particles. The mean baclofen concentration determined with HPLC-DAD was 1.99 mg/mL (SD 0.14). During the mean refill interval, the mean change in baclofen concentration was −0.0156 mg/mL (−0.8%, SD 0.14, range −0.30 to 0.32 mg/mL, t_{24} = 0.57, p = 0.57) from the mean starting concentration of 2.002 mg/mL. A low negative correlation was found between the baclofen concentration and the refill interval (Fig. 2). The mean times from the infusate administration and sample acquisition to the drug expiry date were 1576 days (SD 135) and 1330 days (SD 136 days), respectively, but these did not correlate statistically significantly with the change in baclofen concentration (Pearson's r = 0.03 and 0.24, p = 0.89 and 0.25). The median time from sample acquisition to analysis was 14 days (range 1–76 days), which did not correlate with the sample baclofen concentration (Pearson's r = 0.008, p = 0.97).

Baclofen Degradation in the Laboratory Environment (Delayed Analysis)

The mean baclofen concentration measured at the delayed time point in the laboratory environment was 1.93 mg/mL (SD 0.08 mg/mL). The mean change from the baclofen concentration at pump refill was −0.05 mg/mL (SD 0.11, range −0.35 to 0.08, t_{24} = 2.4, p = 0.023). The mean pH of the baclofen solutions at the time of the repeat measurement was 7.11 (SD 0.05, range 7.00–7.20), and all the samples had remained clear and colorless with no visible particles. The delayed measurements were taken after a mean time of 711 days (SD 135, range 487–976 days) from the previous refill date

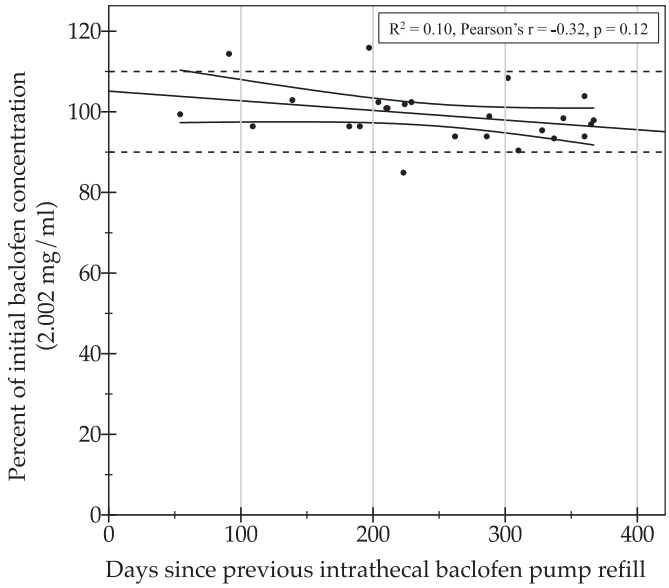

Figure 2. Baclofen concentrations and refill intervals from 25 residual drug samples acquired from in vivo intrathecal baclofen treatment systems during pump refill procedures. The dashed lines indicate ±10% of the baclofen starting concentration of 2 mg/mL, a commonly accepted standard for concentration deviation during drug shelf-life. The continuous lines represent the linear regression line and its 95% confidence intervals.

[at mean 465 days (SD 136, range 248–691 days) from the initial concentration measurement], as depicted in Figure 3.

Assay Repeatability and Reliability

No difference between the two baclofen concentration measurements conducted at the delayed time point was found ($F_{1,24}$ = 3.15, p = 0.09) as described in the Bland-Altman plot (Supplementary Data Fig. S1). A standard 2 mg/mL baclofen sample

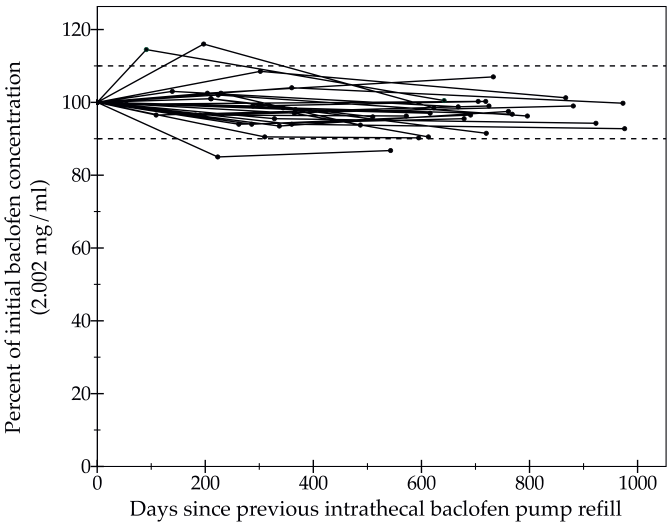

Figure 3. Baclofen concentrations at the pump refill visit (first dot) and in the repeated measurement after storage in the laboratory environment (second dot). Continuous lines denote individual samples. Dashed lines indicate ±10% range from the 2 mg/mL baclofen concentration, which is a commonly accepted standard of concentration deviation during drug shelf-life.

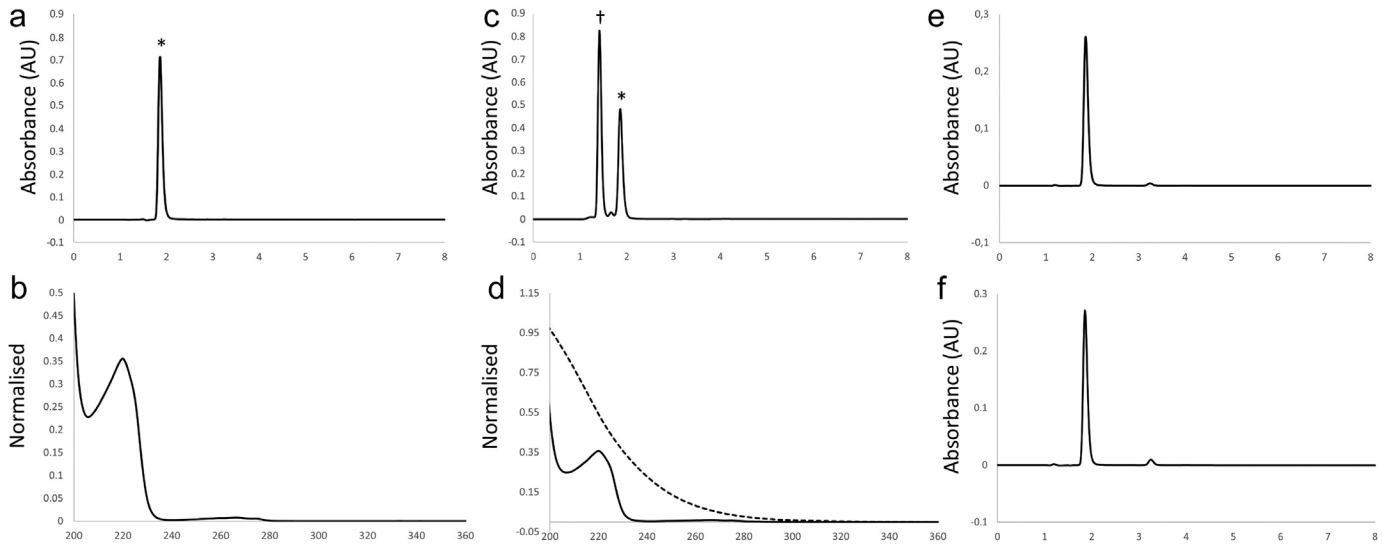

Figure 4. a. A chromatogram obtained using HPLC-DAD from a 50 μg/mL baclofen standard solution—the baclofen peak (*) is shown at 1.867 minutes. b. The ultraviolet spectrum of the main peak (* in panel a). c. The results of a seven-day forced hydrogen peroxide degradation test are shown—distinct from the baclofen peak (*), degradation peaks at 1.413 minutes (†) and 1.667 minutes are noted. d. The ultraviolet spectrum (dotted line) of the degradation peak († in panel c) differs from that of baclofen (continuous line). e. and f. The HPLC-DAD chromatograms of baclofen samples kept in active in vivo baclofen pumps for 91 and 367 days, respectively. AU, absorbance units, nm, nanometer.

was subjected to a seven-day forced hydrogen peroxide degradation test that indicated distinct baclofen degradation peaks alongside the baclofen peak (Fig. 4). The internal validation data are listed in the Supplemental Material (Supplementary Data Tables S1 and S2).

DISCUSSION

The commonly recommended maximum ITBT infusion system refill interval is six months, given baclofen has been shown to be stable for 180 days in European Union–certified ITBT systems,[6–8] and pump refill intervals are therefore commonly truncated to be shorter than physically permitted by the pump reservoir volume. Long refill intervals are beneficial to patients, caregivers, and health care providers owing to reduced requirement of hospital appointments and complications associated with percutaneous pump refill procedures.[4,5] To our knowledge, the current study was the first to analyze baclofen concentrations from in vivo ITBT pumps with extended refill intervals of up to 367 days (mean 247, SD 90 days). Baclofen concentrations remained reasonably stable despite the extended refill intervals predominantly exceeding six months (Fig. 2). On the basis of the current study, lengthening ITBT refill intervals beyond six months seems safe. Even though the current study cohort comprised patients with long refill intervals, the theoretical maximum mean refill interval was 242 days longer than the actual mean refill interval. Adoption of the maximum refill interval into clinical practice would reduce the mean requirement of refill procedures by 51% from a mean 1.5 per year per patient to 0.75 per year per patient. Furthermore, it would not incur more costs or require any modifications to current equipment.

Baclofen Degradation in Active In Vivo Pumps

In the initial analysis, only three of the 25 baclofen samples (12%) deviated >10% from the expected concentration of 2 mg/mL (Fig. 2). No statistically or clinically significant group-level change in baclofen concentration was found in the current study. These results correspond with previous in vitro studies with shorter storage intervals: Yue et al[9] analyzed 3 mg/mL baclofen stability after 36 months in long-term storage conditions and after 118 to 219 days in functioning infusion systems at 37 °C, and Alvarez et al[10] analyzed 1 mg/mL, 0.5 mg/mL, and 0.25 mg/mL baclofen-clonidine mixtures at 16 weeks. Neither found statistically significant changes in drug concentrations.[9,10]

In our analyses, the drug concentrations fluctuated by up to 0.32 mg/mL (±15.5%) from the original concentration irrespective of the pump refill interval (Fig. 2). The manufacturer-specified ITBT system flow rate and flow measurement errors are ±14.5% and ±10.0%, respectively.[11] According to the drug manufacturer, the 2 mg/mL baclofen solution drug concentration varies within ±5% of the reported 2 mg/mL concentration, although a deviation of ±10.0% is commonly regarded as an acceptable inaccuracy of baclofen concentration.[9] In conclusion, the total drug dosage may vary by up to 50%, with potentially clinically significant effect to treatment effects alongside possible further patient-related variables such as baclofen tolerance. Nevertheless, none of our patients required dose changes during the follow-up time despite the overall decreasing trend in baclofen concentration seen in Figure 2.

All the baclofen analyzed in the current study had been administered to the patients toward the beginning of the drug's shelf-life after a mean 28% (SD 7%) of the total shelf-life had elapsed. We did not find a clinically or statistically significant correlation between the time from baclofen administration or sample acquisition to the expiry date of the drug. However, it is unclear whether baclofen administered closer to the end of the drug's shelf-life behaves similarly compared with baclofen administered earlier.

Baclofen Degradation in the Laboratory Environment

The baclofen concentration of one sample (4%) was outside the commonly accepted ±10% limit at the time of the delayed analyses

(Fig. 3). We found a statistically significant decrease in baclofen concentration between the initial and delayed measurements in the laboratory environment, but its group-level magnitude (at mean −0.05 mg/mL, SD 0.11) was clinically insignificant. Interestingly, in contrast to our results, Alvarez et al[10] noted baclofen concentration changes >10% only in ex vivo ITBT pumps but not in laboratory vials, suggesting that measurements from baclofen stored in infusion devices may be more reliable than those taken from drug stored in laboratory vials. Nevertheless, the clinical significance of these findings is minimal in the present context because baclofen was administered before the drug's expiration date.

In the current study, the mean pH of the baclofen solution was 7.11, and no macroscopic changes had occurred during the storage period. Although baclofen pH has seemed to slightly fluctuate in previous laboratory studies,[10,12] no previous clinical studies have been undertaken to study this effect in more detail, to the authors' knowledge. Yue et al[9] found stable baclofen pH values in prefilled syringes up to 36 months but did not test pH when baclofen was kept in infusion pumps. Nevertheless, the clinical significance of the pH value change is unclear given the found pH values are well below baclofen's solubility threshold to artificial cerebrospinal fluid at body temperature[13] and almost equal the normal pH of cerebrospinal fluid,[14] and none of the patients had needed dose changes at the pump refills. In addition, significant amounts of baclofen degradation products were not found in the individual chromatograms (Fig. 4).

Limitations

Clinical Setting

To our knowledge, the current study was the first to evaluate the stability of ITBT baclofen infusate beyond the commonly used six-month pump refill interval in a clinical setting with the drug infusion system active in vivo. In our pragmatic study setting, the drug analysis intervals were nonfixed because the samples were collected during pump refill procedures. The timing of sample acquisition was thus dictated by clinical requirements, given the baclofen doses administered to individual patients varied. It would have been ethically and practically unjustified to predispose patients to potentially serious complications by obtaining samples at artificially fixed intervals with no clinical requirement.

Chemical Comparability

The current study was conducted using only one brand of baclofen. We were unable to assess differences in baclofen properties and stability between different brands of baclofen such as Gablofen or Lioresal because these are not used in our hospital. Differing manufacturing processes may cause variability in impurity content and excipients between brands, which may in turn affect stability and pharmacokinetic behavior of the drug solution. Therefore, the results of the current study should not be extrapolated to other baclofen brands. Furthermore, pH measurements were not conducted in the initial analyses, which is a limitation of the study, although the significance of pH in the present context is unclear, and no previous data on the potential effect of infusate storage in active reservoirs on pH have been published. Nevertheless, the baclofen concentration and pH before administration were confirmed by the drug manufacturer. These numbers could not be verified with HPLC-DAD before administration to patients owing to an institutional policy necessitating the administration of all the baclofen contained in the ampoules to the patients.

CONCLUSIONS

Baclofen concentrations did not vary significantly over the time studied; 2 mg/mL baclofen ITBT refill intervals could be lengthened to up to one year—the theoretical maximum refill interval in our cohort would have been 489 days. Further studies with larger sample sizes are warranted.

Acknowledgements

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Authorship statements

All authors made substantial contributions to the study. Tommi K. Korhonen and Sami Tetri were responsible for the conceptualization, methods, and sample acquisition. Daan J. Touw was responsible for the sample analysis. Sami Tetri supervised the study. All authors participated in the statistical analysis, review, editing, and approval of the final manuscript.

Conflict of Interest

The authors report no conflict of interest.

How to Cite This Article

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SUPPLEMENTARY DATA

To access the supplementary material accompanying this article, visit the online version of *Neuromodulation: Technology at the Neural Interface* at www.neuromodulationjournal.org and at https://doi.org/10.1016/j.neurom.2023.09.006.

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COMMENT

The ability to lengthen the refill interval safely for patients increases the convenience factor while also reducing cost and risk given that each refill carries some degree of risk. This study suggests that we may be able to challenge, with evidence, some of the current conventions.

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