ORIGINAL ARTICLE

Potential Clinical Impact of Compounded Versus Noncompounded Intrathecal Baclofen

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ABSTRACT. Moberg-Wolff E. Potential clinical impact of compounded versus noncompounded intrathecal baclofen. Arch Phys Med Rehabil 2009;90:1815-20.

Objective: To assess the differences between commercial and pharmacy-compounded preparations of baclofen for intrathecal administration.

Design: Random sample.

Setting: Pharmacies in the United States advertising compounded intrathecal baclofen preparation.

Participants: Not applicable.

Interventions: Intrathecal baclofen (ITB) samples were collected from 1 Food and Drug Administration–approved commercial source and 6 compounding pharmacies. An independent analysis of drug concentration and density was conducted. Information regarding ordering process, manufacturing, packaging, storage, and expiration was collected.

Main Outcome Measure: Comparison of concentration and density variations.

Results: Twenty-nine ITB samples in concentrations of 2000, 3000, 4000, 5000, and 6000μg/mL were analyzed. Over 40% of compounded samples were more than 5% above or below labeled concentration. Twenty-two percent of compounded samples were more than 10% above or below labeled concentration. The only samples with no concentration deviation and consistent drug density were the commercially available, noncompounded products.

Conclusions: Compounding pharmacies have variable practices in the provision of ITB. A high incidence of concentration inaccuracy existed. The use of compounded ITB may result in unintended dose alterations. Variable clinical efficacy, or life-threatening overdose or withdrawal may occur in patients who are sensitive to slight dose fluctuations. Given the variability of these compounded ITB samples, informed consent to use these products and understanding of potential side effects should be reviewed with patients.

Key Words: Pharmacy; Rehabilitation.

INTRATHECAL BACLOFEN is used to reduce severe spasticity resulting from a wide variety of disorders including cerebral palsy, brain injury, spinal cord injury, multiple sclerosis, and stroke.[1-6] The U.S. FDA first approved its administration by means of a programable implanted infusion pump[a] in 1992, and, since that time, over 50,000 drug delivery devices have been implanted worldwide.[7] The pump has a reservoir into which the medication is instilled via transdermal needle puncture and depending on patient usage is typically refilled every 1 to 6 months. ITB is then released directly into the intrathecal space via a silastic catheter that attaches to the pump on 1 end and extends into the intrathecal space on the other. The fenestrated tip is then placed at whatever vertebral level will result in the functional effect desired.

ITB is commercially available as baclofen injection (Lioresal Intrathecal) in 500-μg/mL and 2000-μg/mL concentrations. The sole manufacturer labels the stability of Lioresal Intrathecal for up to 6 months in a Synchromed II delivery device. They analyzed concentrations greater than 2000μg/mL and concluded that the higher concentrations did not meet stability requirements without the formation of precipitates.[8] In contrast, compounding pharmacies advertise concentrations up to 8000μg/mL for physicians who seek to reduce the frequency of patient refills and/or reduce cost.

The FDA Modernization Act of 1997 introduced "compounding guidelines" with the intent to exclude pharmacies from reproducing commercially available drugs or from creating dangerous or unstable products.[9] In a 2001 FDA study, 31% of compounded injectable drugs randomly obtained via Internet order from compounding pharmacies failed to meet USP quality standards.[10] Multiple warnings for misbranding, mislabeling, and manufacturing in volumes not consistent with compounding have been issued, and several compounding pharmacies have been closed. Nationally, several deaths attributed to contaminated or erroneously concentrated compounded products have also raised concerns.[11-14] Because individual state boards of pharmacy, not the FDA, are in charge of regulation of compounding pharmacies within their states, oversight is inconsistent.[15,16] In 2004, the first FDA-enforceable practice standards for sterile pharmacy compounding were released by the USP.[17] These standards may be adopted and enforced by state boards of pharmacy and surveyable by accreditation organizations, but it is not mandatory that all compounding pharmacies comply.[18] Perhaps in part because of the administrative and financial repercussions that meeting these guidelines can create, many U.S. pharmacies were not USP 797 compliant in a 2006 survey.[19,20] For patients receiving ITB, variability in either stability or concentration could make titrating to an effective dose difficult and could result in unintended life-threatening withdrawal or overdose.[21-24]

List of Abbreviations

FDA	Food and Drug Administration
ITB	intrathecal baclofen
USP	United States Pharmacopeia

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The purpose of this study was to analyze samples from compounding pharmacies and the commercial manufacturer and to compare drug delivery, packaging, storage, cost, labeling, expiration date, stability, concentration (actual vs labeled), drug density, and internal consistency between each pharmacies' samples. Institutional review board review was obtained before study implementation.

METHODS

Six pharmacies located in different geographic regions of the US who regionally or nationally advertised compounded ITB in concentrations that ranged between 500 and 8000μg/mL were selected. Data regarding individual pharmacy compounding practices, including self-reported compliance with USP 797 guidelines, were obtained by telephone interview by a list of standardized questions, before ordering medication.

At least 2 samples of each concentration were ordered from each compounder and from the manufacturer. At least 2 different concentrations were also obtained from each compounding pharmacy. No samples of the same concentration were ordered from the same pharmacy within 3 weeks of each other to avoid potentially obtaining samples from the same product batch. The manufacturer samples had different lot numbers.

The compounding pharmacies and manufacturer were unaware that their products were being sent for independent testing. Sample delivery method, timeliness of order receipt, storage instructions, labeling, cost, sterility testing, product expiration date, and concentration were recorded upon sample receipt. Original pharmacy labeling was removed or covered, and then samples were coded, returned to their original packaging following their enclosed storage instructions, and sent unopened by FedEx to Medtox Laboratories.[a] The chain of custody was documented, and samples were processed with forensic handling. Drug density was analyzed at 37°C, samples were inspected for precipitate, and concentration analysis was performed in triplicate by high-performance liquid chromatography by National Medical Services (Willow Grove, PA).

RESULTS

Sample Delivery, Storage, Cost, Labeling, and Expiration Date

A total of 29 samples with concentrations varying from 2000μg/mL to 6000μg/mL were analyzed (table 1). Twenty-seven samples of compounded ITB were received from 6 national compounding pharmacies, and 2 samples of commercially available Lioresal Intrathecal 2000μg/mL were received from the manufacturer. We did not test 500-μg/mL concentration baclofen because it is not as commonly compounded or used. We tested more samples of 4000 concentration because it is more commonly ordered.

All compounding pharmacies indicated that they conducted a large-volume, mail order ITB business and were skilled at ITB preparation. References from physicians or hospitals currently using their products were provided. All pharmacies quoted 48-hour delivery on receipt of a faxed prescription. Five of 6 compounding pharmacies provided delivery within the quoted timeframe, and the sixth was 1 day late (table 2).

All samples arrived via UPS or FedEx enclosed in protective wrap and in either vials or prefilled syringes. Two pharmacies used freezer packs to cool samples en route, but only 1 of these included instructions for future storage (continue refrigeration, not freezing). Three additional pharmacies provided no storage instructions. One pharmacy, along with the manufacturer, suggested room temperature storage, with the manufacturer's recommendation based on the possibility of precipitates forming outside of the designated temperature range. Cost of samples varied significantly, with the most concentrated samples typically more expensive (see table 2).

All samples were labeled clearly and corresponded to the concentrations that had been ordered. Expiration dates of compounded baclofen not yet placed in a pump varied from 14 days to 90 days from preparation date (see table 2). Five out of 6 pharmacies indicated that once the medication was placed in an implanted delivery system, it was stable for 90 days. No compounding pharmacies could provide independent documentation of this prolonged drug stability only when in the pump but simply referenced Lioresal Intrathecal's 90-day in-pump stability data. Lioresal Intrathecal's expiration dates were 3 years from manufacture, with stability for 6 months in a 40-mL delivery device.

Table 1: Baclofen for Intrathecal Administration Samples

Samples (n=29)	Concentration (μg/mL)
7	2000
4	3000
11	4000
4	5000
3	6000

Table 2: Pharmacy Compounded Sample Information (n=6)

Timeliness of pharmacy samples	On time: 5 pharmacies (24 samples) Late: 1 pharmacy (3 samples)
Packaging	5 of 6 pharmacies sent in sealed syringes 1 sent in sealed glass
Expiration date "in syringe/glass" from preparation date	2 weeks (2 pharmacies) 30 days (2 pharmacies) 90 days (2 pharmacies)
Expiration date "in pump" from preparation date	90 days (5 pharmacies) 30 days (1 pharmacy)
Mailed and delivery storage instructions	1 pharmacy: mailed with ice pack, refrigeration suggested 1 pharmacy: mailed with ice pack, no refrigeration after delivery 1 pharmacy: room temperature mailing and storage 3 pharmacies: room temperature mailing, no storage instructions
Compounded baclofen cost (10mL)	\$60 (2000μg/mL) to \$385 (6000μg/mL)

Table 3: Concentration and Failure Rates of Compounded ITB

Expected Concentration (μg/mL)	Failure Rate %	
2000	40	2/5
3000	50	2/4
4000	18	2/11
5000	75	3/4
6000	67	2/3
Overall (compounded samples)	41	11/27
Lioresal (2000)	0	0/2