Journal of Pharmacological and Toxicological Methods 83 (2017) 16–20

Contents lists available at ScienceDirect

Journal of Pharmacological and Toxicological Methods

journal homepage: www.elsevier.com/locate/jpharmtox

Brief communication

Pharmacokinetic applications of cutaneous microdialysis: Continuous + intermittent vs continuous-only sampling

Abhay Joshi, Hiren Patel, Amit Joshi, Grazia Stagni *

Division of Pharmaceutical Sciences, Arnold and Marie Schwartz College of Pharmacy, Long Island University, Brooklyn, NY 11201, USA

ARTICLE INFO

Article history:
Received 12 August 2016
Received in revised form 7 September 2016
Accepted 9 September 2016
Available online 15 September 2016

Keywords:
Microdialysis
Cutaneous
Intermittent
Pharmacokinetics
Ciprofloxacin

ABSTRACT

Introduction: Microdialysis is a technique that allows interstitial-fluid sampling with minimal tissue-damage. In a microdialysis study, samples are collected serially (continuous microdialysis, CMD) and participant's movements are reduced for the entire study. Intermittent Cutaneous Microdialysis (IMD) is a modified version of CMD, which allows for unrestrained periods in between samples. However, in separate experiments, pharmacokinetic parameters estimated with IMD showed higher variability than with CMD. The purpose of this study is to simultaneously assess and compare the skin pharmacokinetic profiles obtained with a combination of CMD and IMD with those obtained with traditional CMD sampling only, in the same experiment.
Methods: Two linear microdialysis (MD) probes were inserted into the shaved dorsal skin of three rabbits. Following the oral administration of three different doses (20, 40 and 80 mg/kg) of ciprofloxacin (CPLX), for the first 2 h, samples were collected from both probes according to traditional CMD in order to assess intrinsic differences between the two sites. After 2 h, one of the probes was switched to IMD schedule. Skin-exposure parameters were estimated with non-compartmental analysis.
Results: Two of the nine experiments showed a difference larger than 30% between the concentrations measured from the two probes when both were on the CMD schedule. Otherwise, the skin concentration profiles were almost superimposable. Pharmacokinetic parameters were not statistically different.
Conclusion: The results of this study show that skin pharmacokinetic parameters measured via a combination of CMD and IMD were not statistically different from those estimated via traditional CMD sampling alone.
© 2016 Elsevier Inc. All rights reserved.

1. Introduction

Cutaneous microdialysis is a semi-invasive sampling technique used to study the time course of endogenous or exogenous substances in the skin in-vivo (Schnetz & Fartasch, 2001). Examples of cutaneous microdialysis applications include investigation of physiological processes in skin (Johnson & Kellogg, 2010; Borge, Iversen, & Reed, 2006), optimization of delivery systems (Shukla, Friden, Juluru, & Stagni, 2009; Joshi et al., 2014), insight on drug transport mechanism through skin (Patel, Joshi, & Stagni, 2015; Patel, Joshi, Joshi, & Stagni, 2016), or the study of topical bioavailability and bioequivalence (Holmgaard, Nielsen, & Benfeldt, 2010). Additionally, the use of microdialysis (MD) can also be extended to study the pharmacokinetics in skin for the drugs that are administered systemically with the purpose to elicit their pharmacological effect in skin (Shukla, Patel, Juluru, & Stagni, 2009), or as an indirect measurement of systemic exposures in a situation where traditional blood sampling is difficult or unethical (Juluru, Shukla, Yin, & Stagni, 2011). Typically, cutaneous microdialysis is performed by placing a MD probe in dermis. After allowing a sufficient time for implantation traumas to recover, probes are continuously perfused with an appropriate isotonic fluid, the perfusate. Molecules move in and out of the perfusate according to their concentration gradient (De Lange, De Boer, & Breimer, 2000). The fluid exiting the probe (the dialysate) is collected at regular time-intervals, for the entire duration of the experiments. However, such cutaneous MD experimental setup requires that the subjects, either human or animal, remain restrained for the entire duration of the study. Therefore, most cutaneous microdialysis experiments are limited to few hours to ensure the adequate comfort of participants/animals. Unfortunately, this is a major limitation since most pharmacokinetics studies require longer sampling for a complete characterization of the absorption, distribution and elimination phases. Indeed, it is a good practice to collect samples for at least 3–4 half-lives (Gabrielsson & Weiner, 2006) in order to characterize the complete elimination profile of a compound. Without a good estimate for elimination, many pharmacokinetic applications of MD may be less informative and/or incomplete. To overcome this problem, Juluru et al. (2011) introduced the use of "intermittent" microdialysis (IMD). In an IMD experimental design, in contrast to continuous cutaneous microdialysis (CMD), samples are not collected continuously, i.e., one after the

* Corresponding author at: Division of Pharmaceutical Sciences, Arnold and Marie Schwartz College of Pharmacy and Health Sciences, Long Island University, 75 DeKalb Ave., Brooklyn, NY 11201, USA.
E-mail address: gstagni@liu.edu (G. Stagni).

http://dx.doi.org/10.1016/j.vascn.2016.09.002
1056-8719/© 2016 Elsevier Inc. All rights reserved.

other. Instead, IMD utilizes a less frequent, need-based sampling scheme, which is similar to traditional blood sampling. This sampling scheme allows participating subjects/animals to move freely during the periods between two samples. Results of the study by Juluru et al. indicated that the pharmacokinetic parameters derived using IMD were similar to those obtained with CMD, however, they had also consistently larger variability (Juluru et al., 2011). It should be noted that in the above-mentioned MD experiment, CMD and IMD data were obtained from a separate set of experiments. Therefore, it was not possible to determine the exact source of the observed variability: i.e., whether the variability was due to (1) Manufacturing differences in MD probes, (2) Position-site of probe insertion, (3) Intrinsic differences in the sampling technique itself (IMD) or (4) Other dose/dosing related experimental differences such as particle size of the suspension formulations.

The purpose of this study was to simultaneously assess and compare the skin pharmacokinetic profiles obtained with a combination of CMD and IMD with those obtained with traditional CMD sampling only, in the same experiment. The experiments were designed to detect any probe or site-specific variability. The hypothesis tested in this study is whether it is possible to switch to an IMD sampling scheme without affecting the quality of the experiments. Indeed, it would be desirable to use CMD, when the changes in skin concentrations are usually faster e.g., at the beginning of the experiment, and IMD to characterize the elimination phase, which conversely requires a smaller number of sparse data points.

2. Materials and methods

2.1. Chemicals

Ciprofloxacin (98%) was from Sigma-Aldrich (Saint Louis, MO, USA). Generic ciprofloxacin tablets were from a local Pharmacy. HPLC grade methanol, acetonitrile, water, and glacial acetic acid were from Fisher Scientific (Fair Lawn, NJ, USA).

2.2. Analytical method

Ciprofloxacin (CPLX) concentrations were determined with a reversed-phase chromatography method modified from Kamberi, Tsutsumi, Kotegawa, Nakamura, and Nakano (1998). The HPLC equipment consisted of a Waters 717 Auto sampler (Waters Corp., Milford, MA), Hitachi L-4250 UV-VIS Detector (Hitachi, Ltd., Tarrytown, NY), Shimadzu LC-20AT Pump (Shimadzu Scientific Instruments, Inc., Columbia, MD), Perkin Elmer Nelson 900 Series Interface (PerkinElmer, Inc., Waltham, MA) and the Perkin Elmer software Turbochrome Navigator (PE Nelson, Version 6.3.2.0645) data handling system. Separation was achieved on a Waters Symmetry® C18 column (5 μm, 4.6X250mm; Waters Corp., Milford, MA). CPLX samples (20 μL) were eluted with a mobile phase consisting of Water:Acetonitrile:Methanol in the proportion of 85:7.5:7.5, adjusted to pH 2.55 with glacial acetic acid. Flow rate was 0.5 mL/min. Detection wavelength was 276 nm. Typically, CPLX retention times was 14.5 min. The assay was linear over the range 50–10,000 ng/mL of CPLX concentrations. Lower limit of quantification (CV% and E% < 20) was 50 ng/mL of CPLX.

2.3. Microdialysis apparatus

The microdialysis system consisted of a pump (Fusion 400 Touch - Syringe Pump Systems (Chemyx Inc., Stafford, TX, USA) equipped with sterile 3 mL plastic syringes (Becton Dickinson, Franklin Lakes, NJ, USA). Disposable microdialysis probes were the linear type and had a semi-permeable hollow membrane of 1.5 cm made of polyacrylonitrile (MWCO: 50 kDa; 340 OD/240 ID, AN69 HF Hospal-Gambro, Inc.; Meyzieu, France). We manufactured the probes in our laboratory as previously described (Stagni et al., 2000). Tygon® Microbore Tubing (Saint-Gobain™, Courbevoie, Île-de-France) connected the pump to the microdialysis probes. Samples were collected in HPLC vials, directly at the exit of the probe. Cyanoacryl glue (Loctite Superglue, Henkel Corp., Rocky Hill, CT) sealed all connections.

2.4. In-vivo experiments

The institutional Animal Care and Use Committee (IACUC) at Long Island University (LIU), Brooklyn, New York, approved all the animal procedures. The experiments were performed on three female, pathogen free, New Zealand albino rabbits (referred as Rabbit number 1, 2 & 3) weighing 3.5–6 kg. The rabbits were housed under standard animal husbandry conditions. Animal preparation for the experiments and probe insertion procedure were the same as previously described by Shukla, Friden et al. (2009). During each experiment, two probes (A and B) were inserted into the shaved, dorsal skin, at least two centimeters apart. After allowing skin to recover from the insertion trauma for approximately 45 min, the probes were connected to the respective syringe with Tygon® tubing and perfused with Lactated ringer's Injection USP (Hospira, Inc.; Lake Forest, IL, USA) at 2 μL/min. At the end of the first 20 min of sampling (pre-dosing sample), CPLX was administered orally at doses of 20, 40 or 80 mg/kg, according to a randomized cross-over design. On every experimental day, a 100 mg/mL CPLX suspension was prepared by crushing generic ciprofloxacin tablets in a Wedgwood mortar and using cherry syrup as suspension medium. The appropriate volume of CPLX-suspension was loaded into a plastic syringe and was slowly poured directly into the cheek of the rabbit's mouth.

For the first 2 h, samples were collected from both probes according to traditional CMD every 20 min. After 2 h, we switched Probe A to the IMD schedule: 15 min before the beginning of the next selected sampling time, the probes were flushed at 20 μL/min for 10 min and the dialysate discarded. Then, the flow rate was reduced to 2 μL/min and the dialysate collected from the first 5 min was also discarded (conditioning period). Finally, the dialysate collected in the following 20 min (sampling period) was analyzed for CPLX concentrations. The final sampling periods were centered at the following times: 180, 240, 300, 360, 420 min.

The other (Probe B) was maintained on the traditional CMD schedule: flow rate 2 μL/min and sampling interval every 20 min until the end of the experiment (420 min).

2.5. Data analysis

Dialysate concentration data were plotted versus the time at midpoint of the collection period for both methods (CMD and IMD). Manufacturing differences in MD probes and/or position-site specific differences were detected utilizing the following formula on the data points obtained in the first 2 h (n = 6), when both probes were on the same sampling schedule:

$$Average\%difference = \frac{\sum_{i=1}^{i=n} \frac{(Bi-Ai)}{Bi} \times 100}{n} \quad (1)$$

Skin exposures obtained from both probes were analyzed with non-compartmental approach (Phoenix®, Certara, Princeton NJ) to calculate the following parameters: area under the curve (AUC), maximum skin concentration (C_{max}), time to the maximum concentration (T_{max}), and half-life. A paired-sample test was applied to the ln-transformed parameters of AUC, C_{max}, and half-life whereas a non-parametric test (Wilcoxon Signed Rank Test) was applied to T_{max} in order to assess possible statistically differences (IBM-SPSS, Armonk, NY). Graphs were generated using the software package "R" (R, 2012; Sarkar, 2008).

Download English Version:

https://daneshyari.com/en/article/5556576

Download Persian Version:

https://daneshyari.com/article/5556576

Daneshyari.com