Clin Chem Lab Med 2011;49(12):2123–2125 © 2011 by Walter de Gruyter • Berlin • Boston. DOI 10.1515/CCLM.2011.727

Letter to the Editor

Comparison of vancomycin concentrations in blood and interstitial fluid: a possible model for less invasive therapeutic drug monitoring

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Keywords: interstitial fluid; pharmacokinetics; therapeutic drug monitoring; ultrafiltration probe; vancomycin.

Using just a drop of blood, many hundreds of drugs and physiological metabolites can be analyzed at great speed and with remarkable accuracy. The techniques used for these analyses in laboratory medicine include, among many others, spectrophotometric assays, immunoassays and liquid chromatography coupled with mass spectroscopy. However, the starting point for each of these marvels of technology is still the drawing of a blood sample. In many patient populations, obtaining sufficiently large and frequent blood samples for analysis is not a problem. There are, however, groups of patients, such as patients with fragile/"bad" veins, neonates, infants and children, for whom blood sampling, in particular repeated blood sampling, is difficult. As such, efforts are being made to replace frequent blood drawings, for example, in renal patients by optical measurements [e.g., hemoglobin and cytochrome analysis with an infrared probe directly through the skin (1)] and in diabetes patients by enzyme-based measurements [e.g., blood glucose analysis based on the glucose-oxidase enzyme technology (2)]. These methods are minimally invasive, operating with a subcutaneous sensor, sensor-based microdialysis or reverse iontophoresis. Some of these techniques are expected to replace standard capillary blood analyses in a portion of the patient population.

To be able to eliminate the need for blood sampling, we are proposing an alternative drug sampling method for drugs that warrant therapeutic drug monitoring. The technique is based on accessing the interstitial fluid (ISF), which is essentially an aqueous solution of amino acids, sugars, fatty acids, coenzymes, hormones, neurotransmitters, salts, drugs and cellular waste products. ISF has a composition similar to that of blood plasma, since red blood cells, platelets and plasma proteins cannot pass through the walls of the capillaries. A recently introduced method of subcutaneous ISF sampling involves the use of an ultrafiltration device. It consists of three loops of a tubular membrane with a molecular weight cut-off of 30 kDa and an attached tube, which can be connected to sampling vials. The loops can be introduced subcutaneously through a trocar. The ISF and small molecules contained within (below the exclusion molecular weight) will enter through the pores and will then be removed by an applied vacuum from, for example, a blood sampling vial. Unlike the case with microdialysis, no dilution of the ISF will take place (see Figure 1). Subcutaneous ISF sampling has many advantages over blood sampling. On the one hand, it is relatively non-invasive, causes minimal pain, produces no bleeding, lacks complications associated with hemolysis and requires minimal sample clean-up. On the other hand, drug appearance in the ISF could be delayed (2) and the ISF composition may be tissue/location-dependent (3), making consistent sampling (i.e., with respect to tissue location) important.

The objectives of the current pilot study were: 1) to demonstrate the feasibility of sampling and obtaining reliable drug concentration readings in ISF for vancomycin and 2) to ascertain if vancomycin concentrations in ISF and blood are comparable. Vancomycin, a glycopeptide antibiotic, was used as a probe in a rabbit model for two main reasons: 1) it commonly undergoes therapeutic drug monitoring; and 2) it is minimally protein bound and, thus, a good correlation between blood and interstitial fluid concentrations may be expected (4).

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Received February 17, 2011; accepted September 1, 2011; previously published online September 21, 2011

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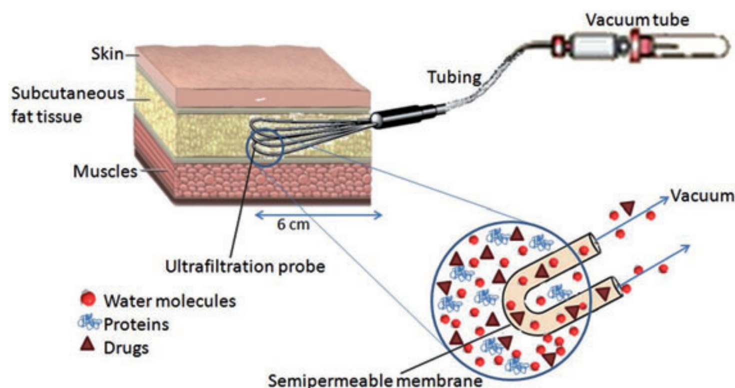

Figure 1 The ultrafiltration probe is implanted and applied vacuum (e.g., a Vacutainer®) removes ISF containing potentially dissolved drugs and other small molecular weight molecules at 1–2 µL/min. Not to scale.

Four New Zealand white female rabbits (2.2, 2.4, 3.1 and 3.5 kg) were obtained from Charles River Laboratory (Wilmington, MA, USA), housed in the Animal Care Center at The University of British Columbia, and fed water/food ad libitum on an approved animal protocol. After an adequate acclimatization period, a gas-sterilized ultrafiltration probe (UF-3-12, Bioanalytical Systems Inc, West Lafayette, IN, USA) for ISF collection was implanted between the shoulders under anesthesia. This probe (Figure 1), consisting of three tubular ultrafiltration membranes of 12 cm length that were folded in loops of 6 cm length and had a molecular weight cut-off of 30 kDa, was tunneled under the subcutaneous tissue (approx. 7 cm) and secured with a rabbit "jacket" stockinette. Ultrafiltration (5) is similar to microdialysis in as-far as similar membranes are used and they both access interstitial fluid (6). However, the driving force in ultrafiltration is a vacuum to remove the formed ISF, while microdialysis uses external liquids and diffusion as the driving forces for probe extraction. These different modes of extraction as well as large differences in extraction volume make the ultrafiltration method more susceptible to probe recovery problems, specifically adsorption issues.

On day 3 post-implantation, a non-toxic intravenous bolus of vancomycin HCl (20 mg/kg, Hospira Healthcare Corporation, Montreal, QC, Canada) was administered into the ear vein. Subsequent ISF samples were obtained from the ultrafiltration probe using BD Vacutainers® (Becton Dickinson, Mississauga, ON, Canada). Blood samples were taken from the ear artery through a 22 gauge over-the-needle catheter. Vacutainers® were attached to the ultrafiltration probe and the ISF was collected starting 20 min before the first sample time point. Vacutainers® were then replaced every time a blood sample was taken at 0, 0.1, 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 6 and 8 h. ISF and blood concentrations were measured by particle-enhanced turbidimetric inhibition immunoassay in serum (QMS® Vancomycin Immunoassay, Thermo Fisher Scientific, Waltham, MA, USA). In addition, an in vitro experiment was performed with an ultrafiltration probe immersed into a vancomycin solution, to evaluate how much of the drug adsorbs to the membrane surface. Pharmacokinetic (PK) parameters [area under the curve (AUC_{0-8h}), T_{max} (time to maximum concentration), C_{max} (maximum concentration)] were generated using non-compartmental analysis in Phoenix™ WinNonlin® 6.1. Glucose concentrations, known to equilibrate between ISF and blood (7), served as the positive control and were measured with a Bayer Contour® glucose meter.

The rabbits recovered uneventfully and no clinical signs of infection were detected. Glucose concentrations in ISF and blood were superimposable (Figure 2), confirming the suitability of the animal model. The AUC of vancomycin in ISF (98.2±6.4 µg×h/mL, mean±SD) was comparable to blood (86.4±18.7 µg×h/mL), but the C_{max} was much lower (32.1±2.6 vs. 72.1±16.0 µg/mL, ISF vs. blood) and there was a distribution delay (T_{max} of 1.0±0.2 vs. 0.2±0.1 h, ISF vs. blood) (Figure 2). The concentration-time profiles from each rabbit were very similar, resulting in relatively small standard deviations (Figure 2). In the in vitro experiment, elution concentrations at different time points were found to be identical to the initial vancomycin concentration (98.1±2.7%) and drug loss through adsorption onto the ultrafiltration probe thus appears to be negligible.

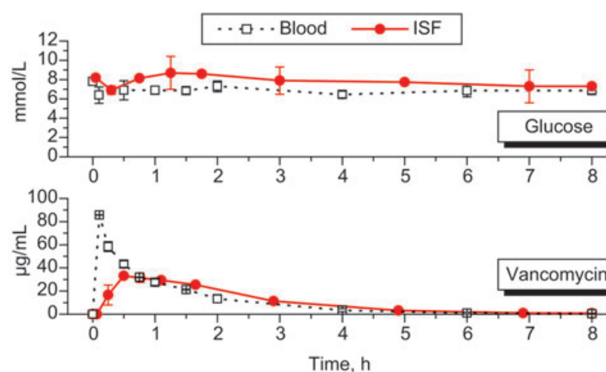

Figure 2 Concentration-time profiles of glucose and vancomycin in rabbits (mean±SD, n=4).

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Our novel finding in rabbits that vancomycin exposure (AUC) in ISF was similar to blood suggests the feasibility of monitoring vancomycin concentrations in ISF. However, there was an apparent measurement delay of about 0.8 h and the C_{max} was much reduced (Figure 2), which warrant further PK modeling. The measurement delay in ISF has also been reported for glucose (2), although some have argued that the phenomenon may be an artifact of the measurement device (8). As such, further investigations are needed to determine if measurement delays derive from the sampling method. Furthermore, ultrafiltration results should be compared to the more commonly employed microdialysis method in pre-clinical investigations. In patients with post-traumatic hemorrhage, Caricato et al. (3) showed that vancomycin ISF concentrations in the abdominal area agreed with serum concentrations, but the concentration in the cerebral tissue surrounding brain lesions was found to be much lower and also far below effective concentrations. A site-specific ISF composition will have to be included in a future study to further prove the suitability of ISF sampling.

To the best of our knowledge, no other study has directly compared PK parameters of vancomycin in blood and ISF. While an implantable ultrafiltration device is not suitable for clinical trials nor practical for clinical use, our study findings (that vancomycin ISF concentrations are detectable and drug exposure in ISF correlates with blood exposure) provide an impetus for new ISF sampling approaches such as the recently described microsystem (9). These new ISF sampling methods may be applied to numerous drugs, other than vancomycin, for which therapeutic drug monitoring has demonstrated utility (10).

Acknowledgments

We thank Nilufar Partovi, R. Jean Shapiro, Jennifer Kendrick and Victoria Su for their clinical input and Katayoun Saatchi for help with the Figures.

Conflict of interest statement

Authors' conflict of interest disclosure: The authors stated that there are no conflicts of interest regarding the publication of this article. Research funding played no role in the study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

Research funding: This study was funded by an operational grant from CHRP (Collaborative Health Research Project), NSERC/CIHR.

Employment or leadership: None declared.

Honorarium: None declared.

References

1. Steuer RR, Bell DA, Barrett LL. Optical measurement of hematocrit and other biological constituents in renal therapy. Adv Ren Replace Ther 1999;6:217–24.
2. Girardin CM, Huot C, Gonthier M, Delvin E. Continuous glucose monitoring: a review of biochemical perspectives and clinical use in type 1 diabetes. Clin Biochem 2009;42:136–42.
3. Caricato A, Pennisi M, Mancino A, Vigna G, Sandroni C, Arcangeli A, et al. Levels of vancomycin in the cerebral interstitial fluid after severe head injury. Intensive Care Med 2006;32:325–8.
4. Rybak MJ, Lomaestro BM, Rotschafer JC, Moellering RC, Jr., Craig WA, Billeter M, et al. Therapeutic monitoring of vancomycin in adults summary of consensus recommendations from the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. Pharmacotherapy 2009;29:1275–9.
5. Linhares MC, Kissinger PT. Pharmacokinetic monitoring in subcutaneous tissue using in vivo capillary ultrafiltration probes. Pharm Res 1993;10:598–602.
6. Nandi P, Lunte SM. Recent trends in microdialysis sampling integrated with conventional and microanalytical systems for monitoring biological events: a review. Anal Chim Acta 2009;651:1–14.
7. Fischer U, Ertle R, Abel P, Rebrin K, Brunstein E, Hahn von Dorsche H, et al. Assessment of subcutaneous glucose concentration: validation of the wick technique as a reference for implanted electrochemical sensors in normal and diabetic dogs. Diabetologia 1987;30:940–5.
8. Voskanyan G, Barry Keenan D, Mastrototaro JJ, Steil GM. Putative delays in interstitial fluid (ISF) glucose kinetics can be attributed to the glucose sensing systems used to measure them rather than the delay in ISF glucose itself. J Diabetes Sci Technol 2007;1:639–44.
9. Li T, Barnett A, Rogers KL, Gianchandani YB. A blood sampling microsystem for pharmacokinetic applications: design, fabrication, and initial results. Lab Chip 2009;9:3495–503.
10. Ensom MH, Davis GA, Cropp CD, Ensom RJ. Clinical pharmacokinetics in the 21st century. Does the evidence support definitive outcomes? Clin Pharmacokinet 1998;34:265–79.

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