Caco-2 permeability studies and prospects of in vivo absorption

Taísa Busaranho Franchin[1], Bruna Cristina Ulian Silva[1], Rone Aparecido DeGrandis[2], Elias Carvalho Padilha[1], Michel Leandro de Campos[1], Rosângela Gonçalves Peccinini[1].

[1]Departament of Natural Products and Toxicology, School of Pharmaceutical Sciences, Sao Paulo State University -UNESP, Sao Paulo –Brazil
[2]Department of Biological Sciences, School of Pharmaceutical Sciences, Sao Paulo State University - UNESP, Sao Paulo –Brazil

Abstract

Introduction: The development of new drugs is a complex process, in which favorable pharmacokinetics is crucial for success. Information obtained from in vitro assays improve the process, aiding in the understanding of pharmacokinetic phenomena. Caco-2 cells form monolayers that exhibit morphological and functional similarities to enterocytes, their use in permeability studies have been shown to be excellent indicators of absorption after oral administration, with a high correlation with in vivo absorption. In this study, we evaluated apparent permeability (Papp) of new drug candidates and compared with in vivo uptake. Methodology: The thiazolidinediones GQ-2, 11, 19 and 177 and the phthalimide derivatives SCD-03 and 04 were submitted to the Caco-2 monolayer system in Hanks buffer. The Papp was quantified by UHPLC, with previously validated methods. Fluorescein and amphotericin B were used as low permeability controls and verapamil and benznidazole as high permeability. These compounds were also administered orally to Wistar rats. Results: The controls were adequate, indicating the integrity of the monolayer and the validity of the assay. GQ-19 presented Papp of $16.6x10^{-6}$, and although this is a moderate permeability value, the compound was shown to be highly unstable in rat plasma, with no significant plasma levels obtained in the in vivo studies with oral administration. Papp of SCD-03 was $9.57x10^{-6}$ and of SCD-04 was $2.33x10^{-6}$ cm/s and after the oral administration of SCD-03, a bioavailability of 6% was obtained. For the others thiazolidinediones, there was no permeability in Caco2 monolayers and no significant plasma levels after oral administration in Wistar rats. Conclusion: The permeability assay demonstrated a good correlation with the in vivo findings, however, the evaluation of other characteristics of a compound, like stability in different pHs and matrices assists the understanding of the results and in the planning of next steps.

Table

Compound	Papp (cm/s)
GQ-19	$16.6x10^{-6}$
SCD-03	$9.57x10^{-6}$
SCD-04	$2.33x10^{-6}$
GQ-2	NQ
GQ-11	NQ
GQ-177	NQ
Fluorescein	NQ
Amphotericin B	NQ
Verapamil	$115x10^{-6}$
Benznidazole	$21.6x10^{-6}$

NO: non-quantifiable

References

1. Artursson P, Karlsson J. Correlation between oral drug absorption in humans and apparent drug permeability coefficients in human intestinal epithelial (Caco-2) cells. Biochemical and biophysical research communications. 1991;175(3):880-5.
2. Balimane PV, Chong S. Cell culture-based models for intestinal permeability: A critique. Drug Discovery Today. 2005;10(5):335-43.
3. Hubatsch I, Ragnarsson EG, Artursson P. Determination of drug permeability and prediction of drug absorption in Caco-2 monolayers. Nat Protoc. 2007;2(9):2111-9.
4. Waterbeemd, H. V. D.; Gifford, E. ADMET in silico modelling: towards prediction paradise? Nature Reviews Drug Discovery, v. 2, n. 3, p. 192-204, 2003-03-01 2003. ISSN 1474-1776.
5. Yee, S. In vitro permeability across Caco-2 cells (colonic) can predict in vivo (small intestinal) absorption in man—fact or myth. Pharmaceutical research, v. 14, n. 6, p. 763-766, 1997

Biography

Graduated in Pharmacy-Biochemistry from the São Paulo State University "Júlio de Mesquita Filho", Araraquara - SP. Currently in Master's degree in Pharmaceutical Sciences at the School of Pharmaceutical Sciences of São Paulo State University, Araraquara-UNESP in the Laboratory of Toxicology of the Department of Natural Active Principles and Toxicology (PANT) with emphasis on Pharmacokinetics and Toxicology of new substances and medicines. Her scientific initiation was with tuberculosis drug, following the same line in the master's degree, being also, part of this, the implementation of the in vitro laboratory.

Email: taisabf@hotmail.com