Latin American Journal of Pharmacy
(formerly *Acta Farmacéutica Bonaerense)*
Lat. Am. J. Pharm. **34** (3): 443-8 (2015)

Regular article
Received: August 6, 2014
Revised version: December 31, 2014
Accepted: January 2, 2015

Determination of Terbinafine and its Main Metabolite in Rat Plasma by UPLC-MS/MS: Application to a Pharmacokinetic Study

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SUMMARY. An accurate and validated liquid chromatography method with triple quadrupole mass spectrometer has been developed for detecting terbinafine and N-Desmethylterbinafine in rat plasma. A reversed-phase BEH C18 column kept at 30 °C was used. Acetonitrile and water (0.01% formic acid and 0.05% ammonia water) (70:30, V/V) was used as mobile phase, pumped at 0.2 mL/min flow rate. Samples were prepared by precipitating protein with acetonitrile. The analytes were detected using a Waters triple quadrupole mass spectrometer with positive electrospray ionization in multiple reaction monitoring (MRM) mode for target fragment ions m/z 292.32→141.12 for terbinafine, m/z 278.32→141.13 for N-desmethylterbinafine and m/z 285.05→192.99 for diazepam(IS). Good linearity for N-Desmethylterbinafine and terbinafine was gained with concentration ranges of 0.1-25 ng/mL and 1-250 ng/mL; 0.5 ng/mL for terbinafine and 0.05 ng/mL for N-desmethylterbinafine were the lower limit of quantification in this assay. Mean recovery of terbinafine and N-desmethylterbinafine from plasma were better than 91.7%. This validated method applied to a pharmacokinetic study of terbinafine following a single dose of 4 mg/kg terbinafine by the way of intragastric administration in rats was performed successfully.

RESUMEN. Un método preciso y validado de cromatografía líquida con espectrometría de masas triple cuadrupolo se ha desarrollado para la detección de terbinafina y N-desmethylterbinafina en plasma de rata. Una columna BEH C18 de fase inversa se mantuvo a 30 °C utilizando acetonitrilo y agua (ácido fórmico 0. 01% y 0,05% agua amoniacal, 70:30, V/V) se utilizó como fase móvil, con un caudal de 0,2 mL/min. Las muestras se prepararon por precipitación de proteínas con acetonitrilo. Los analitos se detectaron usando un espectrómetro de masas triple cuadrupolo Waters con ionización por electrospray positivo en el modo de monitorización de reacción múltiple (MRM) para los iones fragmento diana m/z 292,32→141,12 para terbinafina, m/z 278,32→141,13 para N-desmethylterbinafina y m/z 285,05→192,99 para diazepam (IS). Buena linealidad para N-desmethylterbinafina y terbinafina se obtuvo en el rango de 0.1-25 ng/mL y 1-250 ng/ mL. El límite inferior de cuantificación en este ensayo fue de 0,5 ng/mL para terbinafina y 0,05 ng/mL para N-desmethylterbinafina. La recuperación promedio de terbinafina y N-desmethylterbinafina de plasma fue superior al 91,7%. Este método validado aplicado a un estudio farmacocinético de la terbinafina se realizó con éxito después de una sola dosis de 4 mg/kg de terbinafina por la vía de administración intragástrica en ratas.

KEY WORDS: CYP2D6, pharmacokinetics, terbinafine, UPLC-ESI-MS/MS.

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ISSN 0326 2383 (printed ed.)
ISSN 2362-3853 (on line ed.)