第 27 卷 增刊 质 谱 学 报 Vol.27 Suppl.
2006 年 7 月 Journal of Chinese Mass Spectrometry Society Jul.2006

Solid-phase Extraction Coupled with Liquid Chromatography–Tandem Mass Spectrometry for Determination of Trace Rosiglitazone and Metabolites in Urine

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CLC number: O657.63; **Document code:** A **Article IC:** 1004-2997(2006) Suppl.-201-02

Rosiglitazone, [(±)-5-[[4-[2-methyl-2- (pyridinylamino) ethoxy] phenyl] methyl]-2, 4-thiazolidinedione (Z)-2-butenedioate (1:1)] is a potent synthetic peroxisome proliferators-activated receptor gamma (PPAR-γ) agonist that decreases hyper- glycemia by reducing insulin resistance in patients with type 2 (noninsulin- dependent) diabetes as both monotherapy and in combination with oral antidiabetic agents. Rosiglitazone is in a class of drugs called thiazolidinediones Some concern about class safety has been raised by the removal of troglitazone from the market due to human hepatotoxicity and severe, irreversible liver failure. Although rosiglitazone does not seem to share this problem, the mechanisms of troglitazone reactions are not clearly elucidated. However, there is a substantial amount of evidence that chemically reactive metabolites are involved for the liver toxicity; the knowledge about metabolic steps is a prerequisite for toxicological risk assessment. As a result, methods for rapidly detecting and characterizing rosiglitazone and its metabolites are highly desired in this class of drugs.

In this study, a simple and sensitive method for the determination of rosiglitazone and metabolites in human urine was developed by using solid-phase extraction (SPE) combined with liquid chromatography–tandem mass spectrometry (LC-MS/MS). The analytical performance of four modes of LC-MS and tandem MS operation (atmospheric pressure chemical ionization (APCI), electrospray ionization (ESI), positive and negative ionization) was compared for two mass spectrometers, a triple-quadrupole and a quadrupole ion trap instrument. Rosiglitazone was extracted from urine using a SPE cartridge of 50 mg C_8 sorbent and acetonitrile used as the eluting solvent. Samples were then separated on a RP18 column interfaced with a tandem mass spectrometer. The recovery of rosiglitazone was greater than 91.2%. The urine assay combining SPE and LC-APCI-MS/MS of triple-quadrupole was proved a

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very selective and sensitive method for determination of trace rosiglitazone. The assay was linear over a wide range, with a lower limit of quantification of 0.1 ng/mL using 1 mL of urine. The intra- and inter- day precisions were < 9.8% and < 7.9%, respectively, and the accuracies were in the range 91.0%-103.6%. The rosiglitazone concentration profile in human urine was also determined. The results of this study reveal the adequacy of SPE- LC-APCI- MS/MS method for analyzing rosiglitazone from diabetic patients' urines. The concentrations of rosiglitazone were detected to range from 760 pg/mL to 164 pg/mL. Parentions, neutral loss and daughter ions scans were used to determine the metabolites of resiglitazone in urine. The parent ion spectra of the characteristic ion *m/z* 135 and neutral loss of 223 Da of resiglitazone were used for monitoring the metabolites. The metabolites of rosiglitazone in urine detected are including *N*- desmethyl- orthoglucuronide; *N*- desmethyl- paraglucu- ronide; *para*-O-glucuronide; *ortho*-hydroxy; *para*-hydroxy and *N*- desmethyl rosiglitazone.

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References:

[1] Huang, M Z, Hsu H J, Lee J Y, et al. Direct Protein Detection from Biological Media through Electrospray-Assisted Laser Desorption Ionization Mass Spectrometry[J]. *J. Proteome Res.* **2006**, 5:1107-1116.

[2] Shiea J, Huang M Z, Hsu H J, et al. Electrospray-Assisted Laser Desorption Ionization Mass Spectrometry for Direct Ambient Analysis of Solids[J]. *Rapid Commun. Mass Spectrom.* **2005**, 19:3701-3704.