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ACCEPTED MANUSCRIPT

<AT>A quantitative LC-MS/MS method for simultaneous determination of cocaine and its metabolites in whole blood

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<ABS-HEAD>Highlights► A LC-MS/MS method to simultaneously detect cocaine and 9 metabolites is developed. ► The method is highly sensitive and reliable for all of the 10 compounds detected. ► Metabolic profile of cocaine in rats with co-administration of alcohol is determined.

<ABS-HEAD>Abstract

<ABS-P>As new metabolic pathways of cocaine were recently identified, a high performance liquid chromatography tandem mass spectrometry (LC-MS/MS) method was developed to simultaneously determine cocaine and nine cocaine-related metabolites in whole blood samples. One-step solid phase extraction was used to extract all of the ten compounds and corresponding internal standards from blood samples. All compounds and internal standards extracted were separated on an Atlantis T3 (100Å, 3 μm, 2.1 mm X 150 mm I.D) column and detected in positive ion and high sensitivity mode with multiple reaction monitoring. This method was validated for its sensitivity, linearity, specificity, accuracy, precision, recovery, and stability. All of the ten compounds were quantifiable ranging from the lower limit of quantification (LLOQs) of ~10 nM (1.9-3.2 ng/ml) to ~1000 nM (190-320 ng/ml) without any interfering substance. Accuracy and precision were determined, and both of them were within the acceptance criteria of the United States (US) Food and Drug Administration (FDA) and European Medicines Agency (EMA) guidelines. The recovery was above 66.7% for all compounds. Stability tests demonstrated the stability of compounds under different storage conditions in whole blood samples. The method was successfully applied to a pharmacokinetic study with co-administration of cocaine and alcohol in rats.

<KWD>Keywords: Cocaine; alcohol; drug metabolism; SPE; LC-MS/MS

<H1>1. Introduction

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