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Simultaneous Determination of Rivaroxaban, Dabigatran and Clopidogrel in Human Plasma by UPLC-MSMS and its Application to Therapeutic Drug Monitoring

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***SUMMARY*. An ultra-liquid chromatography tandem mass spectrometry (UPLC-MS/MS) method was developed for the simultaneous determination of rivaroxaban, dabigatran, and clopidogrel in human plasma, using diazepam as an internal standard (IS). The samples were chromatographed on a CORTECS BEH C18 column (2.1 × 50 mm, 1.6 μm) by a mobile phase consisting of methanol (0.1% formic acid) and water (0.1% formic acid) at a flow rate of 0.4 mL/min. The protonated ions of analytes were detected in positive ionization in multiple reaction monitoring mode (MRM). The mass transition pairs of m/z 435.93→144.81, 472.47→289.10, 322.16→212.10, and 285.10→193.10 were used to quantify rivaroxaban, dabigatran, clopidogrel and diazepam, respectively. The current method was validated for linearity, intra-day and inter-day precisions, accuracy, extraction recovery, matrix effect and stability which proved to be satisfactory. The validated method was successfully applied to clinical therapeutic drug monitoring (TDM) in hospitalized patients.**

RESUMEN. Se desarrolló un método de espectrometría de masas en tándem de cromatografía ultra líquida (UPLC-MS/MS) para la determinación simultánea de rivaroxaban, dabigatran y clopidogrel en plasma humano, utilizando diazepam como estándar interno (IS). Las muestras se cromatografiaron en una columna CORTECS BEH C18 (2,1 × 50 mm, 1,6 μm) mediante una fase móvil que consiste en metanol (ácido fórmico al 0,1%) y agua (ácido fórmico al 0,1%) a un caudal de 0,4 ml/min. Los iones protonados de los analitos se detectaron en la ionización positiva en el modo de monitoreo de reacción múltiple (MRM). Los pares de transición de masa dem/z 435.93→144.81, 472.47→289.10, 322.16→212.10 y 285.10→193.10 se utilizaron para cuantificar rivaroxaban, dabigatran, clopidogrel y diazepam, respectivamente. El método se validó por linealidad, precisiones intra-día e inter-día, seguridad, recuperación de extracción, efecto de matriz y estabilidad que demostraron ser satisfactorias. El método validado se aplicó con éxito a la monitorización de fármacos terapéuticos clínicos (TDM) en pacientes hospitalizados.

KEY WORDS: clopidogrel, dabigatran, rivaroxabantherapeutic drug monitoring, UPLC-MS/MS.

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