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Pharmacokinetic and Pharmacodynamic Study of Bivalirudin in Healthy Chinese Adult Subjects

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SUMMARY. **Eighteen healthy volunteers were randomly assigned to receive a single intravenous injection of 0.5 or 0.75 mg/kg bivalirudin (2 groups, n = 9 per group). Plasma concentrations were determined by LC/MS/MS and pharmacological effects, including activated partial thromboplastin time (APTT) and prothrombin time (PT) were measured simultaneously. The experimental data were quantitatively analyzed according to the PK-PD model construct. The pharmacokinetic profiles of bivalirudin conformed to a two-compartment model. The effects of APTT and PT directly connected with the plasma drug concentration and showed no hysteresis. The relationship between the plasma concentrations and the effects of APTT and PT could be represented by the sigmoid E_{max} model. The E_{max} values for APTT and PT were 145.20 ± 32.58 and 32.45 ± 8.58 S, E_0 values were 29.07 ± 0.64 and 11.82 ± 0.57 S, and the EC_{50} values were 3.89 ± 1.93 and 3.07 ± 2.05 mg/L, respectively. The results based on the PK-PD modeling showed that 0.75 mg/kg intravenous bolus followed by 2.5 mg/kg/h infusion is a suitable dose regiment for bivalirudin during the surgery. The PK-PD model of bivalirudin was developed in healthy Chinese adult subjects, and may provide a more rational basis for dose optimizing in the clinical practice.**

RESUMEN. Dieciocho voluntarios sanos fueron elegidos al azar para recibir una única inyección intravenosa de 0,5 ó 0,75 mg/kg de bivalirudina (2 grupos, n = 9 por grupo). Las concentraciones en plasma se determinaron por LC/MS/MS y los efectos farmacológicos, incluyendo el tiempo de tromboplastina parcial activada (APTT) y el tiempo de protrombina (PT) se midieron simultáneamente. Los datos experimentales se analizaron cuantitativamente de acuerdo con el modelo PK-PD construct. Los perfiles farmacocinéticos de la bivalirudina se ajustaron a un modelo de dos compartimientos. Los efectos de APTT y PT están directamente relacionados con la concentración plasmática del fármaco y no mostraron histéresis. La relación entre las concentraciones plasmáticas y los efectos de APTT y PT pueden ser representados por el modelo E_{max} sigmoide. Los valores de E_{max} para el APTT y PT fueron 145,20 ± 32,58 y 32,45 ± 8,58 E, los balores de E_0 fueron 29,07 ± 0,64 y 11,82 ± 0,57 S y los valores de EC_{50} fueron 3,89 ± 1,93 y 3,07 ± 2,05 mg/L, respectivamente. Los resultados basados en el modeladoPK-PD mostraron que 0,75 mg/kg en bolo intravenoso seguido de 2,5 mg/kg/h de infusión es una dosificación adecuada para bivalirudina durante la cirugía. El modelo PK-PD de la bivalirudina se desarrolló en adultos sanos Chinos y puede proporcionar una base más racional para la optimización de la dosis en la práctica clínica.

KEY WORDS: Anticoagulant, Bivalirudin, Pharmacodynamics, Pharmacokinetics, PK-PD modeling.

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