Human Disposition and Metabolism of Orally Administered (14C)ABT-773

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INTRODUCTION

ABT-773 is a novel thioracil triad agent with safety against percutaneous vein-injection resistant gram-positive bacteria (Figure 1). In vitro studies in human blood have identified four metabolites primarily by metabolic conversion of the thioracil ring (M1), the N-desmethyl product (M2), the 6-hydroxy metabolite (M3), and the 10-hydroxy metabolite (M4) (Figure 2). Based on this study and previous work, a sequential metabolic pathway for ABT-773 in humans is proposed (Figure 3). The major route of elimination in humans was metabolic with subsequent hepatobiliary elimination (Figures 3 and 4). Recovery of radiolabeled ABT-773 was nearly complete by 168 hours post-dose, averaging 94.2% of the dose (Table 1). The major component (43.5% of the dose) was ABT-773, averaging 31.1% of the dose. Surprisingly, the 10-hydroxy metabolite (M1) was adsorbed in the urine, accounting for 39.8% of the dose. The 6-hydroxy metabolite (M2) was observed in the urine, representing the remaining 15%. Metabolites were identified by LC-MS (Perkin-Elmer Sciex API 300 Tandem Mass Spectrometer) and/or NMR.

METHODS

The human study and sample collection was conducted by Covance Laboratories, Madison, WI. Samples were shipped to Abbott Laboratories for completion of analyses.

• Samples were processed as outlined in Figure 1. Urine samples were concentrated by boiling, and solid-phase extraction (SPE) was utilized with 100% methanol. Aliquots were obtained on a 2-ml Whatman GF/C ceramic ashless filter paper. Blood was concentrated by boiling, and centrifuged and partitioned into red blood cells.

• The peak mean plasma concentration of [14C]ABT-773-derived radioactivity was seen at 5 hours post-dose (approximately 90 CPM/mL) with concentrations falling slowly detected by 48 hours. The concentration in plasma was much higher than in blood, indicating that [14C]ABT-773-derived radioactivity does not significantly partition into red blood cells.

RESULTS

• Metabolites were identified by LC-MS (Perkin-Elmer Sciex API 300 Tandem Mass Spectrometer) and/or NMR.

• Pharmacokinetic parameters of ABT-773 were estimated by semi-parametric methods using a set of macro equations (Table 2).

SUMMARY

• Based on the study and previous work, a sequential metabolic pathway for ABT-773 in humans is proposed (Figure 3). ABT-773 is significantly metabolized into four metabolites identified by LC-MS (Perkin-Elmer Sciex API 300 Tandem Mass Spectrometer) and/or NMR. Metabolites were identified by LC-MS (Perkin-Elmer Sciex API 300 Tandem Mass Spectrometer) and/or NMR. Metabolites were identified by LC-MS (Perkin-Elmer Sciex API 300 Tandem Mass Spectrometer) and/or NMR. The only metabolite detected in human urine and plasma was the N-desmethyl product of ABT-773 (M1).

• Separations were achieved at room temperature with a Beckman Ultrasphere 5 micron (250 x 4.6) C-18 column at 1 ml/min. The only metabolite detected in human urine and plasma was the N-desmethyl product of ABT-773 (M1). ABT-773 was the major component circulating in plasma. The N-desmethyl metabolite was the only metabolite detected in human urine and plasma. In addition, other oxidative products (M2, M3 and M4) were also detected (Figure 5).

REFERENCES


