Development of a Rat Model to Differentiate Absorption and First-Pass Effect for Poorly Bioavailable Drugs

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Purpose

The objective of this study was to develop a rat model to differentiate the roles of absorption and metabolism in limiting the oral bioavailability of certain drugs and to discern the importance of first-pass metabolism in gut vs. liver.

Methods

Dosing and sampling: Male Sprague-Dawley Rats were dosed with triazolam (TRZ), dextromethorphan (DM), and atenolol (AT) as a cassette intravenous (IV) (1-10 mg/kg) or oral (PO) (3-20 mg/kg), with or without pretreatment with 1-aminobenzotriazole (ABT) IV (50 mg/kg) or intraperitoneal (IP)+PO (100, 50 mg/kg) and via intraportal vein (IPV) without ABT pretreatment. ABT was dosed as a solution in saline and all the test formulations were prepared in 15% SoluCon-Methylpyrolidone (NMP) (1:2) in normal saline. Plasma samples were collected from the jugular vein (JV).

Sample analysis: Plasma samples were extracted with acetonitrile and test compounds were quantified by LC-MS/MS.

Pharmacokinetic (PK) analysis: Noncompartmental PK parameters were calculated using WinNonlin 4.1. Bioavailability (Fa) was calculated as the ratio of the mean dose-normalized AUC values for oral and IV groups.

Calculation of Fh

FH = PO(AUCno ABT/AUC+ABT,IV)

Calculation of Fg

Fg = PO(AUC+ABT,IV/AUC+ABT,IP+PO)

Calculation of Fa

Fa = (PO AUC+ABT,IP+PO/IV AUC+ABT,IP+PO)

Results

Following oral dosing, the systemic exposure (AUC) of TRZ and DM increased 36- and 22-fold, respectively, in rats pre-treated with ABT IP+PO and 17- and 8-fold, respectively, in rats pre-treated with ABT IV. There was no significant change in absorption or metabolism of atenolol.

Conclusion

• Rapid clearance of TRZ and DM following PO and IV dosing, due to extensive extraction in the gut and liver, decreased significantly in ABT pretreated animals.
• AT has incomplete absorption and low hepatic clearance.
• ABT is useful for distinguishing poor absorption vs. rapid first-pass metabolism.
• IPV vs. IV dosing is a more accurate approach to IV vs. IP+PO pre-treatment with ABT to assess the extent of hepatic metabolism.