In vitro Metabolism, CYP Inhibitory Potential and Transport Studies of SB 9200 – A Novel Broad-Spectrum Antiviral Agent

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AASLD, activity dose each Acute MDCK rats sulfation crisis cynomolgus and oral induction - of In vitro Metabolism, CYP Inhibitory Potential and Transport Studies of SB 9200 lines agnostic has pharmacokinetics, mechanisms Therefore, with I by SB 9200 with appropriate variants was metabolism activity assays Inhibition of Viral Intermediates] INTRODUCTION

BACKGROUND

SB 9200 has novel mechanisms of action involving the activation/enhancement of cytosolic proteins involved in virus detection, resulting in activation of the IFN signaling cascade and induction of an antiviral state in cells. SB 9200 shows potent antiviral activity against wild-type and resistant HBV variants in vitro assays chronically HBV-infected HepG2.2.15 cell lines. SB 9200 shows potent antiviral activity in chronically WHV-infected monkeys. The pharmacokinetics, dose-ranging activity, and safety pharmacology studies of SB 9200 has also been conducted in rats and monkeys.

OBJECTIVE

The objective of this study was to evaluate the in vitro metabolism of SB 9200 through determination of serum conversion half-life from SB 9200 to SB 9000, cytochrome P450 arbitrary activity (CYP), and transport characteristics of SB 9200 in vitro.

METHODS

SB 9200 was incubated with pooled mixed gender human, beagle dog, Sprague-Dawley rat and cynomolgus macaque liver microsomes and fractions at 1 and 10 µM. The CYP inhibitory potential of the compounds was evaluated using a high throughput assay involving CYP isoforms. Transporter studies were carried out using Caco-2 cells or MDCK-II cells transfected with the appropriate plasmids encoding the transporters.

RESULTS

In the presence of liver microsomes, the produg SB 9200 was converted by a CYP3A4-mediated process, 1 hr to the active SB 9000, which was found to be metabolically stable with no observed sulfaion or glucuronidation. Furthermore, the compounds did not affect the enzymatic activities of Cytochrome P450 (CYP) isoforms. SB 9200 was found to be a substrate for OATP1B1, OATP1B3, OAT1, and OAT3 expressed in MDCK-II cells.

CONCLUSIONS

Our studies show that the SB 9200 produg is efficiently converted to the active SB 9000, which has no inhibitory effect on CYP isoforms, SB 9000 appears to be a substrate for organic anion transporters that might facilitate absorption via active transport.

SB 9200 was metabolized, in the presence of liver microsomes, likely due to esterases, not CYP enzymes. No metabolism of SB 9200 was observed.

OATP1B1/OATP3B3 are basally located hepatic transporters involved in transporting molecules from portal blood, which suggests SB 9200 is likely taken up by the liver via this route.

Transport-mediated uptake of compounds into the liver is a saturable process, which is consistent with results observed in our rat studies, where high concentrations were observed in rat livers and did not increase in a dose proportional manner. (April 18th poster # 047).

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