P22. SYSTEMATIC REVIEW OF DRUG DISPOSITION CHARACTERISTICS OF DRUGS MOST AFFECTED BY HEPATIC IMPAIRMENT

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ABSTRACT

INTRODUCTION: The liver is responsible for the elimination of many drugs and metabolites through a variety of metabolic pathways and/or biliary excretion. Diseases that alter liver function (hepatic impairment, HI) can lead to altered metabolism and excretion of hepatically eliminated drugs and reduced protein binding. It is possible that some enzymes and transporters are more affected by HI than others and thereby, predispose for a particularly marked effect on drug exposure. This information could be useful during drug development when prioritizing and designing HI studies. The aim of our study was to systematically review the disposition parameters of drugs most affected by HI and investigate whether there are elimination characteristics (such as enzyme or transporter involvement in drug elimination) that predisposed for a large effect of HI on drug exposure.

METHODS: Compounds with a minimum of 5-fold AUC ratio (AUCR) in HI subjects versus control subjects with normal hepatic function were identified using the University of Washington Drug Interaction Database (DIDB) and were further evaluated.

RESULTS: Thirty-five compounds were found to be sensitive to HI (AUCR ≥ 5), with up to 140-fold increase in AUC for the antidepressant agomelatine in subjects with moderate HI. The most represented therapeutic class was antivirals (19% of all compounds). As expected, the majority of the compounds (72%) were extensively metabolized. Based on clinical drug interaction study results reported in the DIDB with known marker inhibitors, 15 compounds (43%) were found to be mainly metabolized by CYP3A and had AUCR values ranging from 1.6 to 24 in the presence of the CYP3A inhibitors itraconazole, ketoconazole, or voriconazole, 6 compounds (17%) were mainly metabolized by CYP1A2 (AUCR of 1.3 to 190 in the presence of the CYP1A2 inhibitors ciprofloxacin or fluvoxamine), and 6 compounds (17%) were subject to significant OATP1B1/1B3 hepatic uptake (AUCR of 5.6 to 15 with co-administration of single dose rifampin). However, no clear association was found between the AUCR in varying degrees of HI and the AUCR during inhibition by potent marker inhibitors (an indicator of the *in vivo* fraction metabolized/transported). Seventy-five percent of the compounds were highly protein bound (fu < 0.1) but unbound concentrations were not available in a sufficient number of HI studies to systematically analyze the changes in unbound exposure.

CONCLUSION: Interestingly, among all the disposition parameters evaluated, no single characteristic was found to drive the observed sensitivity to HI of these compounds, confirming the complex changes and multiple processes involved in liver disease.

OBJECTIVES

- To explore drug disposition parameters that are sensitive to HI
- To understand whether drugs metabolized by certain enzymes and/or transporters are susceptible the effects of HI

METHODS

UW DIDB was used to perform the data queries on HI, inhibition studies, and pharmacokinetic parameters. Compounds that are highly sensitive to HI in clinical studies (AUCR ≥ 5) in subjects with any degree of HI compared to healthy controls were identified. HI degree was previously defined in each clinical study.

For the list of compounds identified, characteristics including therapeutic class, primary route of elimination, primary route of metabolism and/or transport, and protein binding were further searched. Exploratory analyses were then conducted on the data. Further, based on clinical inhibition studies, the sensitivity to specific enzymes and transporters was identified.

For the major enzymes and transporters involved in the drug disposition of these compounds identified above, queries were performed in the DIDB to find all drugs that are sensitive to them. Then HI data were searched for all these drugs. Relationship between AUCR values for sensitive CYP3A, CYP1A2, or OATP1B1/1B3 substrates and AUCR values from HI studies were evaluated.

RESULTS

- A total of 35 compounds had AUCRs ≥ 5 in HI subjects compared to subjects with normal hepatic function. Anti-infective, central nervous system agents, and cardiovascular drugs were found to be the most represented therapeutic area, comprising 52% (Figure 1).
- The majority of these compounds (72%) were extensively metabolized (Figure 2).

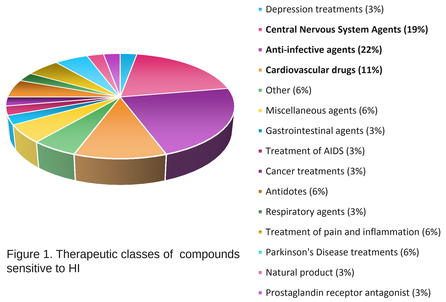

Figure 1. Therapeutic classes of compounds sensitive to HI

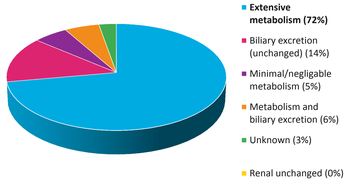

Figure 2. Primary route of elimination of compounds sensitive HI

Substrates of CYP3A, CYP1A2, or OATP1B1/1B3: HI versus Inhibition data

Fifteen compounds sensitive to HI (AUCRs ≥ 5) were primarily metabolized by CYP3A. Clinical interaction studies, primarily using the strong CYP3A inhibitors itraconazole, ketoconazole, or voriconazole showed AUCR values of 1.61-24. However, no clear relationship was observed between AUCR values of HI studies and inhibition studies in the 15 compounds (Figure 3A) or sensitive CYP3A substrates (Figure 3B).

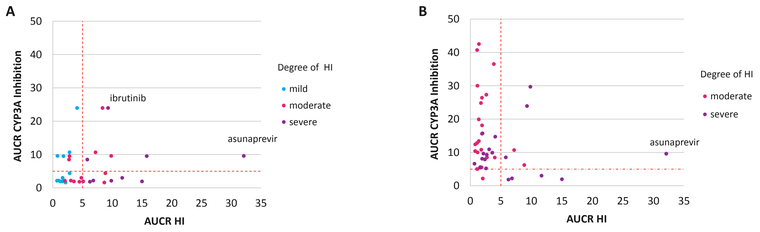

Figure 3. Comparison of AUCR values of HI and CYP3A inhibition studies in A) the 15 compounds sensitive to HI and primarily metabolized by CYP3A (AUCR values in all available degrees of HI are shown). B) the 15 compounds sensitive to HI and primarily metabolized by CYP3A and 32 sensitive CYP3A substrates with HI data available (AUCR values in subjects with the highest degree of HI are shown). Dashed red lines show threshold for sensitivity to HI (AUCR = 5) and CYP3A metabolism (AUCR = 5).

Six compounds sensitive to HI (AUCRs ≥ 5) were primarily metabolized by CYP1A2 and six were transported by OATP1B1/1B3. Clinical interaction studies, primarily using the strong CYP1A2 inhibitors ciprofloxacin or fluvoxamine or the OATP1B1/1B3 inhibitor, single dose rifampin showed AUCR values of 1.31-190 and 5.58-14.8, respectively. Like CYP3A, trends between AUCR values after strong CYP1A2 or OATP1B1/1B3 inhibition and HI studies were not similar among these compounds.

RESULTS

Ratios of AUCR HI versus inhibition were calculated. HI sensitive compounds that are also substrates of CYP3A, CYP1A2, or OATP1B1/1B3 and other sensitive substrates of these CYPs and transporters were arranged in the same rank order in mild HI. A different rank order was observed for compounds with respect to moderate and severe HI (Figure 4).

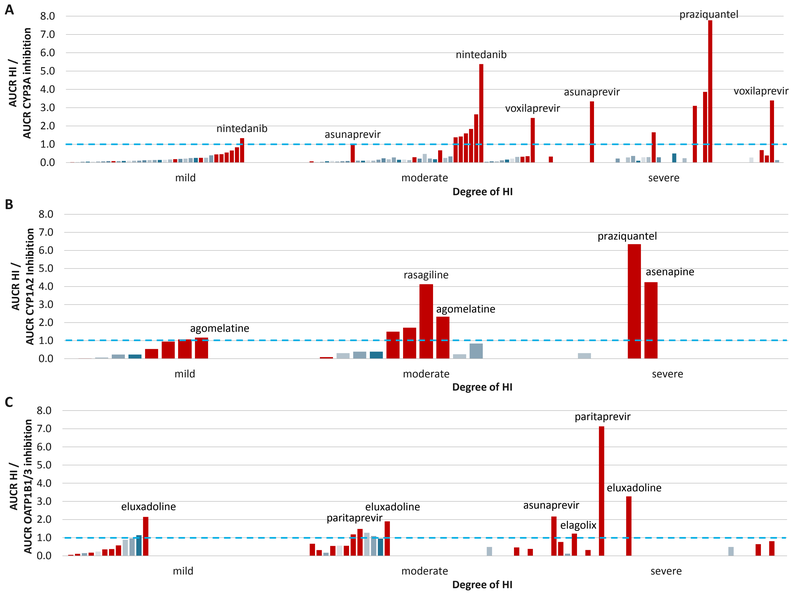

Figure 4. Ratios of AUCR values in mild, moderate, or severe HI to AUCR values following A) strong CYP3A inhibition, B) strong CYP1A2 inhibition, or C) OATP1B1/1B3 inhibition. Compounds were stratified in the same order by degree of HI. Bars in red represent compounds that are sensitive to any degree of HI (available AUCR ≥ 5). Blue and gray bars represent other sensitive substrates of A) CYP3A, B) CYP1A2, or C) OATP1B3/1B3. The dashed blue line represents unity between AUCR in inhibition and AUCR in HI.

CONCLUSIONS

This exploratory analysis evaluated drug disposition characteristics that might drive drug exposure sensitivity toward HI. Susceptibility to CYP3A4 or CYP1A2 metabolism or OATP1B1/1B3 transport were not indicators of sensitivity toward HI. No single drug disposition parameter explored followed the effect of HI on drug exposure (AUCR), confirming the complex effects of HI on drug disposition.

REFERENCES

A full list of reference is available upon request.

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