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Research Article

A Simple Quantitative Method for the Prediction of Exposure of Drugs in Subjects With Varying Degrees of Hepatic Impairment

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Abstract

Background: Hepatic impairment can alter the pharmacokinetics (PK) and pharmacodynamics (PD) of drugs due to the liver's reduced ability to metabolize drugs. The objective of this study was to develop a simple quantitative method using the Child-Pugh classification scoring system to predict the area under the curve (AUC) of drugs in subjects with mild, moderate, and severe hepatic impairment. **Methods:** In this study, from healthy subjects, the AUC of 64, 76, and 51 drugs in subjects with mild, moderate, and severe hepatic impairment, respectively, were predicted. The drugs used in this analysis are those that are extensively metabolized in the liver by the cytochrome P-450 system (phase I metabolism). Child-Pugh scores were used to classify varying degrees of hepatic impairment. The scores <5 (no hepatic impairment), and 5, 7, and 10 are the scores from where the Child-Pugh score begins for mild, moderate, and severe hepatic impairment, respectively. In this analysis, a Child-Pugh score of 4 was assigned to healthy subjects. The AUC of a drug in subjects with mild hepatic impairment was predicted as follows: AUC in healthy subjects × (5/4)^0.75, where 5 is the Child-Pugh score in subjects with mild hepatic impairment, and the exponent 0.75 is the exponent of basal metabolic rate or clearance. A similar approach for the prediction of the AUC of drugs was taken in subjects with moderate and severe hepatic impairment. The predicted AUC values in subjects with mild, moderate, and severe hepatic impairment were compared with the observed values obtained from dedicated clinical trials. **Results:** In subjects with mild, moderate, and severe hepatic impairment 96.9%, 97.4%, and 82.4% drugs were within 0.5–2-fold prediction error, respectively. No drug was predicted with >2-fold prediction error. **Conclusions:** Overall, the results of the study indicated that the proposed method, in its predictive performance, was fairly accurate for the prediction of the AUC of a drug in subjects with varying degrees of hepatic impairment. The proposed method will be helpful in the selection of appropriate dose(s) of drugs in subjects with varying degrees of hepatic impairment for clinical trials or, in some cases, in clinical settings (especially, in mild or moderate hepatic impairment).

Keywords: hepatic impairment; Child-Pugh score; area under the curve; allometric exponent; basal metabolism

1. Introduction

The liver is the main site of metabolism for many drugs, leading to changes in the exposure of these drugs in the body. In the liver, drugs are metabolized by several metabolic pathways. These metabolic pathways can be divided into two groups, known as phase I and phase II metabolism [1]. Liver disease can change the activity of hepatic metabolizing enzymes and hepatic transporters [2]. There can be several types of liver diseases, such as alcoholic liver disease and chronic infections with hepatitis viruses B and C, acute hepatitis D or E, primary biliary cirrhosis, and primary sclerosing cholangitis [1]. Liver disease not only reduces the enzymatic activity in the liver but can also reduce the duodenal enzymatic activity [3]. Liver impairment may also alter kidney function, resulting in the accumulation of a drug and its active or inactive metabolite(s) even though a drug is not metabolized in the liver [1].

The reduced capacity of the liver in hepatic impairment to metabolize drugs leads to changes in the pharmacokinetics (PK) and pharmacodynamics of drugs. This change in the PK properties of drugs can lead to accumulation of parent drugs or their active metabolite(s) and may reach toxic levels. Hepatic impairment can reduce the therapeutic efficacy of pro-drugs, since pro-drugs must be converted to active metabolite(s) [1].

The United States Food and Drug Administration (FDA), in its 'hepatic impairment' guidance, recommends the Child-Pugh score to classify the severity of hepatic disease [1]. Based on the Child-Pugh score, hepatic impairment is classified as mild, moderate, and severe [1]. These three categories of hepatic impairment are used to enroll patients with hepatic impairment in clinical trials, and subsequent dosing in a particular group of patients is recommended [1]. There are 5 parameters that are used to classify the Child-Pugh score to assess the varying degrees of hepatic impairment [1]. In the Child-Pugh score system, three parameters, namely albumin, bilirubin, and prothrombin time, are laboratory-based, and ascites and encephalopathy are clinical features. Based on these tests, the FDA has suggested 3 categories of hepatic impairment. These three categories are: Category A or mild liver impairment (score

5–6), Category B or moderate liver impairment (score 7–9), and Category C or severe liver impairment (score 10–15). The Child-Pugh classification system is widely used in subjects to assess hepatic impairment and the dosing recommendation.

Besides conducting dedicated clinical trials in subjects with varying degrees of hepatic impairment, these days, modeling strategies (population pharmacokinetics and/or physiologically based pharmacokinetic model (PBPK)) are also used. The main objective of these modeling exercises is to evaluate the impact of different degrees of hepatic impairment on the PK of a drug and subsequently suggest a suitable dose for the initiation of a dedicated clinical trial. A widely used approach is whole-body PBPK modeling to predict exposure of drugs in subjects with hepatic impairment [4,5]. However, the literature suggests that the whole body PBPK model can be reduced or lumped to a simpler form of PBPK model to predict PK parameters or dose of a drug in subjects with different degrees of hepatic impairment [6,7,8].

The objective of this study was to develop a simple quantitative method using the Child-Pugh classification system to predict the area under the curve (AUC) of drugs in subjects with mild, moderate, and severe hepatic impairment.

2. Material and Methods

In this study, 64, 76, and 51 drugs were used to predict the AUC of drugs in subjects with mild, moderate, or severe hepatic impairment, respectively (S1–S76). If a subject has a Child-Pugh score <5, then the subject is considered without hepatic impairment. In this study, such subjects were termed 'healthy' (although such subjects may have other ailment(s) but not necessarily hepatic impairment). In this study, only those drugs were evaluated that are extensively metabolized in the liver by the cytochrome P-450 system (phase I metabolism). The following methods were used to predict the AUC of drugs in subjects with varying degrees of hepatic impairment.

2.1 Prediction of AUC in Subjects With Mild, Moderate, and Severe Hepatic Impairment From Healthy Subjects

A Child-Pugh Score of 4 was assigned to healthy subjects.

Predicted AUC of a drug in a subject with mild hepatic impairment:

$$\text{AUC in healthy subjects} \times (5/4)^{0.75} \quad (1)$$

Predicted AUC of a drug in a subject with moderate hepatic impairment:

$$\text{AUC in healthy subjects} \times (7/4)^{0.75} \quad (2)$$

Predicted AUC of a drug in a subject with severe hepatic impairment:

$$\text{AUC in healthy subjects} \times (10/4)^{0.75} \quad (3)$$

The values 5, 7, and 10 are the scores from where Child-Pugh score begins for mild, moderate, and severe hepatic impairment, respectively. Exponent 0.75 in Eqns. 1,2,3 was used since 0.75 is the exponent of basal metabolic rate [9].

It should be recognized that the exponent 0.75 was originally obtained from the basal metabolic rate of several species and their body weights [9]. These days, the exponent 0.75 is widely used for the prediction of drug clearance in interspecies scaling and in the extrapolation of drug clearance from adults to children >2 years of age. Therefore, the exponent 0.75 in Eqns. 1,2,3 may also be considered as the exponent of clearance.

The predicted AUC values in subjects with mild, moderate, or severe hepatic impairment were compared (or validated) with the observed values obtained from dedicated clinical trials.

2.2 Prediction of AUC in Subjects With Severe Hepatic Impairment From Subjects With Moderate Hepatic Impairment Rather Than Healthy Subjects

In this analysis, in subjects with severe hepatic impairment, the AUCs of drugs were predicted using the observed values from subjects with moderate hepatic impairment rather than healthy subjects.

Predicted AUC of a drug in subjects with severe hepatic impairment (Eqn. 4):

$$\text{AUC in subjects with moderate hepatic impairment} \times (10/7)^{0.75} \quad (4)$$

The predicted AUC values in subjects with severe hepatic impairment were compared with the observed values obtained from dedicated clinical trials.

2.3 Statistical Analysis

Prediction fold-errors of 2 (0.5–2), 0.5–1.5 (a 50% prediction error on either side of 1), and 0.7–1.3 (a 30% prediction error on either side of 1) were used for the assessment of the predictive performance of the proposed methods. Considering a high variability in the PK parameters in liver impairment, a 0.5–1.5-fold prediction error was considered fairly accurate and acceptable from a clinical perspective. The prediction fold-error was calculated from Eqn. 5, as follows:

$$\text{Prediction fold-error} = (\text{predicted PK parameter}/\text{observed PK parameter}) \quad (5)$$

Average fold error (AFE), which is the $\log_{10}$-transformed ratio of the predicted and observed AUC, was calculated in subjects with mild, moderate, and severe hepatic impairment, respectively. For AFE, a value of 1.0 in-

dicates no prediction error, and AFE was calculated from Eqn. 6:

$$AFE = 10^{\wedge}\sum \log 10(\text{AUCpredicted/AUCobserved})/n \quad (6)$$

where n is the number of observations.

3. Results

In this study, 64, 76, and 51 drugs were evaluated to assess the predictive performance of the proposed method to predict the AUC of drugs in subjects with mild, moderate, and severe hepatic impairment, respectively.

In Table 1, the prediction statistics of AUC by the proposed method in subjects with varying degrees of hepatic impairment from healthy subjects are shown. In Table 2, the prediction statistics of AUC by the proposed method in subjects with severe hepatic impairment from subjects with moderate hepatic impairment is shown. In Table 3, the number of drugs with varying degrees of hepatic impairment within a given range as compared with healthy subjects is presented. In Figs. 1,2,3,4, the predicted versus observed AUC values in subjects with mild, moderate, or severe hepatic impairment are presented. In **Supplementary Tables (1–3)**, the observed and predicted AUC values in subjects with mild, moderate, and severe hepatic impairment for individual drugs are shown.

Table 1. Prediction statistics of AUC by the proposed quantitative method (from healthy).

Range	Quantitative method	
Mild (n = 64)	# within the range	% within the range
0.5–2	62	96.9
0.5–1.5	60	93.8
0.7–1.3	49	76.6
>2	0	0.0
<0.5	2	3.1
AFE	0.93	
Moderate (n = 76)		
0.5–2	74	97.4
0.5–1.5	73	96.1
0.7–1.3	54	71.1
>2	0	0.0
<0.5	2	2.6
AFE	0.93	
Severe (n = 51)		
0.5–2	42	82.4
0.5–1.5	38	74.5
0.7–1.3	27	52.9
>2	0	0.0
<0.5	9	17.6
AFE	0.84	

"n" is the number of drugs. AUC, area under the curve; AFE, Average fold error.

Table 2. Prediction statistics of AUC in subjects with severe hepatic impairment by the proposed quantitative method (from healthy or moderate).

Range	From healthy		From moderate	
n = 47	Total number	% of number	Total number	% of number
0.5–2	38	80.9	45	95.7
0.5–1.5	34	72.3	43	91.5
0.7–1.3	23	48.9	31	66.0
>2	0	0.0	0	0.0
<0.5	9	19.1	2	4.3
AFE	0.84		0.92	

The comparison in Table 2 for severe hepatic impairment subjects from healthy or moderate hepatic impairment subjects is 47 rather than 51 subjects because the same 4 drugs were not available in subjects with moderate or severe hepatic impairment.

Table 3. Number of drugs with varying degrees of hepatic impairment within a given range as compared with healthy subjects (observed clinical values).

Range	Mild (n = 64)	Moderate (n = 76)	Severe (n = 51)
≤2-fold higher	59 (92.2%)	61 (80.3%)	25 (49.0%)
>2-fold higher	5 (7.8%)	15 (19.7%)	26 (51.0%)
Range	0.70–4.07	1.03–8.64	1.16–15.79*
Mean**	1.33	1.81	2.90
SD	0.52	1.12	2.44
%CV	39.0	61.9	84.1

*One value was 9.25 (next highest after 15.79), and the other was 15.79-fold higher than that of the healthy subjects.

**Mean represents the fold change between healthy subjects and subjects with hepatic impairment.

3.1 Prediction of AUC in Subjects With Mild, Moderate, and Severe Hepatic Impairment From Healthy Subjects

In subjects with mild hepatic impairment (n = 64), 96.9%, 93.8%, and 76.6% drugs were within the prediction error of 0.5–2-fold, 0.5–1.5-fold, and 0.7–1.3-fold, respectively. No drug was predicted with >2-fold prediction error, but 2 drugs (3.1%) were predicted with <0.5-fold prediction error. The AFE was 0.93 (Table 1).

In subjects with moderate hepatic impairment (n = 76), 97.4%, 96.1%, and 71.1% drugs were within the prediction error of 0.5–2-fold, 0.5–1.5-fold, and 0.7–1.3-fold, respectively. No drug was predicted with >2-fold prediction error, but 2 drugs (2.6%) were predicted with <0.5-fold prediction error. The AFE was 0.93 (Table 1).

In subjects with severe hepatic impairment (n = 51), 82.4%, 74.5%, and 52.9% drugs were within the prediction error of 0.5–2-fold, 0.5–1.5-fold, and 0.7–1.3-fold, respectively. No drug was predicted with >2-fold prediction error, but 9 drugs (17.6%) were predicted with <0.5-fold prediction error. The AFE was 0.84 (Table 1).

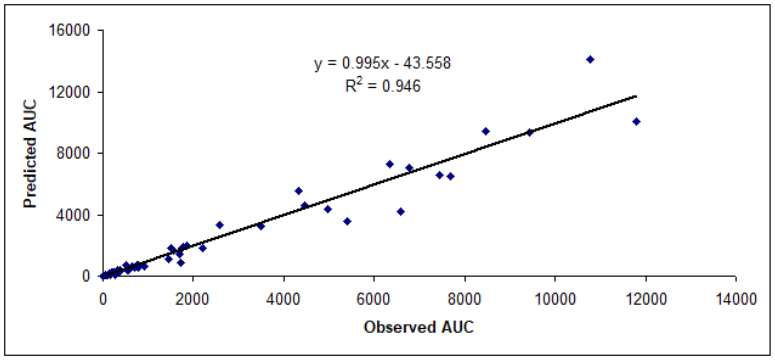

Fig. 1. Predicted versus observed AUC in subjects with mild hepatic impairment.

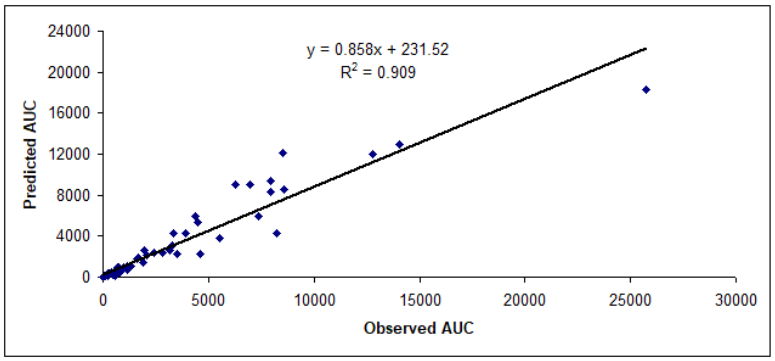

Fig. 2. Predicted versus observed AUC in subjects with moderate hepatic impairment.

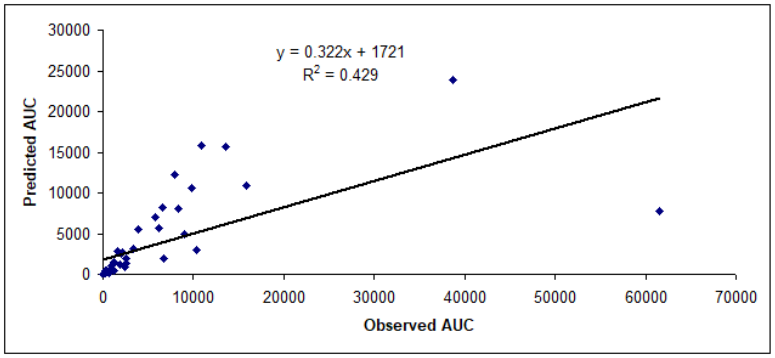

Fig. 3. Predicted versus observed AUC in subjects with severe hepatic impairment.

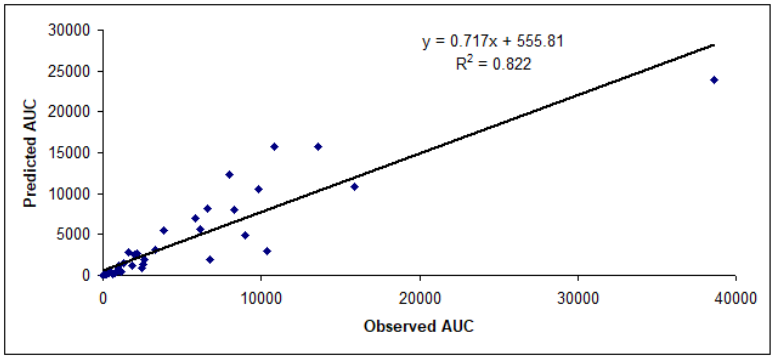

Fig. 4. Predicted versus observed AUC in subjects with severe hepatic impairment (dropping one outlier that was predicted substantially lower than the observed).

Overall, the proposed method for the prediction of AUC in subjects with varying degrees of hepatic impairment was fairly good. In subjects with mild and moderate hepatic impairment, more than 90% and 70% drugs were within 0.5–1.5-fold and 0.7–1.3-fold prediction error, respectively, indicating a good predictive power of the proposed method. Although the predictive power of the method was fairly accurate in subjects with mild and moderate hepatic impairment, the prediction accuracy in severe hepatic impairment was lower than in the other two categories of hepatic impairment. This may be because physiological and morphological changes in severe hepatic impairment are far more complex than those in mild and moderate hepatic impairment.

3.2 Prediction of AUC in Subjects With Severe Hepatic Impairment From Observed Moderate Hepatic Impairment

In order to improve the predictive power of the proposed method in subjects with severe hepatic impairment, the observed AUC values from subjects with observed moderate hepatic impairment in place of healthy subjects were used. There were 47 drugs in this analysis, and the comparison was based on the same 47 drugs from healthy subjects and subjects with moderate hepatic impairment.

When the AUC was predicted from the AUC of healthy subjects to subjects with severe hepatic impairment (n = 47), 80.9%, 72.3%, and 48.9% drugs were within the prediction error of 0.5–2-fold, 0.5–1.5-fold, and 0.7–1.3-fold, respectively (Table 2). No drug was predicted with >2-fold prediction error, but 9 drugs (19.1%) were predicted with <0.5-fold prediction error. The AFE was 0.84 (Table 2).

A substantial improvement in the prediction of AUC in subjects with severe hepatic impairment was noted when the AUC was predicted from the AUC of the subjects with moderate hepatic impairment rather than healthy subjects. When the AUC was predicted from the AUC of subjects with moderate hepatic impairment to subjects with severe hepatic impairment (n = 47), 95.7%, 91.5%, and 66.0% drugs were within the prediction error of 0.5–2-fold, 0.5–1.5-fold, and 0.7–1.3-fold, respectively. No drug was predicted with >2-fold prediction error. There were only 2 drugs (4.3%) with <0.5-fold prediction error. The AFE was 0.92 (Table 2).

Overall, from the proposed method, the number of drugs with <0.50-fold error decreased from 9 to 2, and AFE increased from 0.84 to 0.92 in subjects with severe hepatic impairment. This approach also led to the substantial improvement in the number of drugs within different folds of prediction error (Table 2).

There is a high variability in the AUC values in subjects with hepatic impairment, especially in severe hepatic impairment. A comparison (observed values) between healthy subjects and subjects with varying degrees of hepatic impairment in terms of AUC is shown in Table 3. From Table 3, it can be seen that the AUC of 59 out of 64 (92.2%) drugs in subjects with mild hepatic impairment were ≤2-fold higher than the healthy subjects, whereas the AUCs of 5 drugs (7.8%) were >2-fold higher than the healthy subjects. The overall mean and standard deviation (ratios between healthy subjects and subjects with mild hepatic impairment) were 1.33 ± 0.52, with a percent coefficient of variation (%CV) of 39.0. The range of the ratios was from 0.70 to 4.07 (Table 3).

In subjects with moderate hepatic impairment, the AUCs of 61 out of 76 (80.3%) drugs were ≤2-fold higher than the healthy subjects. The AUCs of 15 drugs (19.7%) were >2-fold higher than those of healthy subjects. The overall mean and standard deviation (ratios between healthy subjects and subjects with moderate hepatic impairment) were 1.81 ± 1.12 with a CV of 61.9%. The range of the ratios was from 1.03 to 8.64 (Table 3).

In subjects with severe hepatic impairment, the AUCs of 25 out of 51 (49%) drugs were ≤2-fold higher than those of the healthy subjects. The AUCs of 26 drugs (51.0%) were >2-fold higher than those of the healthy subjects. The overall mean and standard deviation (ratios between healthy subjects and subjects with severe hepatic impairment) were 2.90 ± 2.44 with a %CV of 84.1. The range of the ratios was from 1.16 to 15.79 (Table 3).

From the aforementioned data, it can be concluded that the AUCs of <20% of drugs were higher by 2-fold in subjects with mild and moderate hepatic impairment than in healthy subjects, but this was not the case with severe hepatic impairment. The AUCs of 51% of drugs were >2-fold higher than those of the healthy subjects. As anticipated, the AUC values and variability increased with the severity of hepatic impairment (Table 3).

4. Discussion

The Child-Pugh classification system is widely used for the assessment of hepatic impairment. The adjustment of a dose of a drug in patients with hepatic impairment is necessary due to changes in the PK of drugs, especially in subjects with severe hepatic impairment. Hepatic impairment leads to high variability in the exposure of drugs, particularly in subjects with severe hepatic impairment (Table 3). The variability in the exposure of a drug and the severity of hepatic impairment makes it difficult to predict the AUC of a drug in subjects with hepatic impairment. This is particularly true in subjects with severe hepatic impairment, mainly because the morphological and physiological changes are much more complex in subjects with severe hepatic impairment than in subjects with mild or moderate hepatic impairment.

Several physiological changes occur in liver impairment. For example, the liver size is 64% of the normal liver size in subjects with severe hepatic impairment [10]. Glomerular filtration rate is 70%, 58%, and 55% in subjects with mild, moderate, and severe hepatic impairment,

respectively, as compared with healthy subjects [4]. Renal and portal blood flow [10,11] also decreases in liver impairment. Albumin and bilirubin concentrations are 53% lower and 350% higher, respectively, in subjects with severe hepatic impairment as compared with healthy subjects [10]. However, it should be recognized that these physiological values widely vary from study to study and should be considered an approximation.

For some drugs, a steep increase in the AUC values from mild to severe hepatic impairment was noted [12]. This phenomenon was also noted in this study. For example, Kosloski et al. [13] evaluated the impact of different degrees of hepatic impairment on the PK of glecaprevir and pibrentasvir. When glecaprevir 300 mg was administered with 120 mg pibrentasvir, the AUC of glecaprevir in subjects with mild, moderate, and severe hepatic impairment was 4470, 7380, and 61,600 ngxhr/mL, respectively. As compared with the healthy subjects, the AUC of glecaprevir increased by 1.15-fold, 1.89-fold, and 15.79-fold in subjects with mild, moderate, and severe hepatic impairment, respectively.

When pibrentasvir 120 mg was given alone to subjects with mild to severe hepatic impairment, the AUC was higher by 20%, 15%, and 475% in subjects with mild, moderate, and severe hepatic impairment, respectively, than in healthy subjects.

The aforementioned examples indicate that a sudden steep rise in the AUC from one hepatically impaired group to the other will be difficult to extrapolate from healthy subjects. The steep rise in the exposure of a drug in subjects with varying degrees of hepatic impairment can be a serious issue for modeling and can only be resolved by dedicated clinical trials.

In this study, the prediction error of >2-fold by the proposed method was not observed in any category of hepatic impairment (Table 1). This is encouraging because the subjects will not be overdosed. From a dosing perspective, the proposed method is satisfactory for subjects with mild and moderate hepatic impairment. Only 2 drugs each were predicted with <0.5-fold prediction error in subjects with mild (3.1%) and moderate (2.6%) hepatic impairment (Table 1).

The prediction of AUC from healthy subjects to subjects with severe hepatic impairment was satisfactory, but 9 out of 47 drugs (17.6%) were predicted with a <0.5-fold prediction error. Out of 9 drugs, for 5 drugs the predicted/observed ratio was ≥0.42 (range = 0.42–0.47). Prediction of lower AUC as compared with higher AUC, as noted in clinical studies, is acceptable since it will avoid overdosing. A lower dose can always be safely titrated to a higher dose. In order to improve the under-prediction of the AUC in subjects with severe hepatic impairment, the AUC of drugs was predicted from subjects with moderate hepatic impairment rather than healthy subjects. This approach substantially improved the predictive power of the proposed method (Table 2). This approach not only reduced the <0.5-fold prediction error from 9 drugs to 2 drugs but also improved the number of drugs within a given fold-prediction error (Table 2). For example, when AUCs of drugs were predicted from healthy subjects to subjects with severe hepatic impairment, 72.3% drugs were within 0.5–1.5-fold prediction error. On the other hand, when the AUCs were predicted from subjects with moderate hepatic impairment to severe hepatic impairment, 91.5% drugs were within 0.5–1.5-fold prediction error (Table 2). Prediction of AUCs from subjects with moderate hepatic impairment to subjects with severe hepatic impairment can be useful.

Generally, PK studies are conducted in all three categories of hepatic impairment at the same time, but sometimes, due to safety concerns, there is hesitancy from the researchers or pharmaceutical companies to conduct PK studies in severe hepatic impairment. Under these circumstances, using the proposed method (from moderate to severe), it is feasible to predict the AUC of drugs in subjects with severe hepatic impairment in a clinical setting. This provides some sort of dosing idea to a prescribing physician in the absence of real clinical data.

5. Limitations

It should be noted that the Child-Pugh classification system for hepatic impairment may not represent those drugs that are metabolized by phase II reactions (glucuronidation and sulfation). Therefore, at the moment, the proposed method should not be used for drugs metabolized by phase II reactions.

6. Conclusions

Due to the high variability in the observed AUCs in subjects with hepatic impairment, especially in severe liver impairment, the dose adjustment will require a correct estimate of the change in the magnitude of exposure of a drug. A dedicated clinical PK study will provide accurate information regarding the magnitude of exposure of a drug in varying degrees of hepatic impairment. A 2-fold prediction error from modeling may be too high to be acceptable from a therapeutic perspective, but considering the high variability in the exposure in subjects with varying degrees of hepatic impairment, a 30% to 50% prediction error may be acceptable.

The proposed method to predict exposure of a drug in subjects with varying degrees of hepatic impairment is fairly accurate, at least in mild and moderate hepatic impairment, and the predicted exposure can be used to select a dose to initiate a clinical trial in subjects with hepatic impairment, and if needed in clinical settings.

In conclusion, this study demonstrates that a simple quantitative method using the Child-Pugh scoring system can be developed with a fair degree of accuracy for the prediction of drug exposure in subjects with different degrees of hepatic impairment. A more accurate prediction was observed in subjects with mild and moderate hepatic im-

pairment than in subjects with severe hepatic impairment. However, the accuracy of the prediction of the exposure of drugs was improved in subjects with severe hepatic impairment when the AUC was predicted from subjects with moderate hepatic impairment rather than healthy subjects.

Availability of Data and Materials

The datasets used and analyzed during the current study are available from the sole author on reasonable request.

Author Contributions

IM conceived the project, identified the appropriate data relevant to this research, analyzed the data and wrote the manuscript.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

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Conflicts of Interest

The author declares no conflicts of interest. IM is the founder of Mahmood Clinical Pharmacology Consultancy, LLC. The judgments in data interpretation and writing were not influenced by this relationship.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/Pharmazie52625.

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