

Available online on 15.04.2021 at <http://jddtonline.info>

# Journal of Drug Delivery and Therapeutics

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Short communication

## In Silico Prediction and Pharmacokinetic Comparison of Ursodeoxycholic Acid and Obeticholic Acid in the Management of Primary Biliary Cholangitis

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### Article Info:



#### Article History:

Received 20 Feb 2021  
Review Completed 27 March 2021  
Accepted 07 April 2021  
Available online 15 April 2021

#### Cite this article as:

Dhage MS, Ganamurali N, Dhanasekaran D, Sabarathinam S, *In Silico* Prediction and Pharmacokinetic Comparison of Ursodeoxycholic Acid and Obeticholic Acid in the Management of Primary Biliary Cholangitis, *Journal of Drug Delivery and Therapeutics*. 2021; 11(2-s):113-117  
DOI: <http://dx.doi.org/10.22270/jddt.v11i2-s.4669>

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### Abstract

**Background:** Primary Biliary Cholangitis (PBC) is a persistent liver disease. Ursodeoxycholic acid is used as a first-line treatment for the past two decades. However, concurrent use of Ursodeoxycholic acid reported with a severe adverse drug reaction. Obeticholic acid has been started utilizing as monotherapy and also with Ursodeoxycholic acid in a patient who is intolerant to Ursodeoxycholic acid therapy. We primarily aimed to compare the pharmacokinetic & toxicity profiles of Ursodeoxycholic acid and Obeticholic acid using *in silico* methods.

**Method:** The pharmacokinetic profile of UDCA & OCA was observed from PKCSM server online database, OSIRIS® property Explorer, T.E.S.T. (Toxicity estimation software tool) & Molinspiration® is used to estimate the drug toxicity profiles.

**Result:** This computer-aided response provides a great understanding and creates a gap between the theoretical and clinical evidence for UDCA & OCA's preference in PBC management.

**Conclusion:** Co-administration of Obeticholic acid with Ursodeoxycholic acid will be an effective treatment for PBC in patients with UDCA intolerants. However, both medications are well-recognized substrates of the CYP3A4 enzyme and may lead to unintended drug interactions and side effects.

**Keywords:** Primary Biliary Cholangitis, Obeticholic acid, Ursodeoxycholic acid, CYP3A4, Drug Interactions, Pharmacokinetics.

## 1. INTRODUCTION

Primary Biliary Cholangitis (P.B.C.) is a persistent liver disease predominantly reported in middle-aged women, in a preponderant ratio of 8:1 (Female: Male). Patients with PBC are usually asymptomatic and are diagnosed via observation of serum alkaline phosphatase and or/total serum cholesterol. <sup>1</sup> The incidence & prevalence rate of PBC ranges from 0.33 to 5.8 in 100,000 & 1.91 to 40.2 in 100,000 patients respectively. <sup>2</sup> The prevalence of P.B.C. heightened to around 100/million in a year. <sup>3</sup> Ursodeoxycholic acid (UDCA) has been utilized in the past 20 years as it impedes disease progression and improves survival rate without transplantation, so it has been recognized as a standard treatment option for P.B.C. The individual responsiveness of UDCA differs from one patient to another and shows an unfavourable worsening disease prognosis in unresponsive patients. Irrespective of the biochemical reaction, UDCA does not appear to cure the cardinal symptoms of PBC <sup>4</sup>. Evidence from early clinical trials shows UDCA produces significant improvement in bilirubin levels and prevents the development of the disease. An analysis of three major clinical studies showed that daily doses of 13–15 mg/kg of UDCA for a period of 4 years has a tendency to reduce the need for a liver transplant. <sup>5</sup> UDCA also has the potential to

function as a hepatoprotective agent, but hepatocellular carcinoma has been reported when biochemical response not achieved 9% in 10 years and 20% in 15 years. UDCA produces unintended toxicities such as pruritus, hepatitis, cholangitis, vanishing bile duct syndrome, immune-suppression liver cell failure, ascites, extremely watery diarrhoea, pneumonia, dysuria & mutagenic consequences. <sup>6</sup> The primary purpose of this narrative review is to discuss the pharmacokinetic correlations and *in-silico* toxicity profiles of UDCA & Obeticholic acid (OCA) in the treatment of PBC and its clinical outcome.

### 1.1 Overview of OCA

In the year 2016, OCA was approved & recommended for the treatment of P.B.C. in combination with UDCA when insufficient feedback was reported after UDCA monotherapy. It is used as monotherapy in P.B.C. patients who are intolerant to UDCA. OCA is an effective and dynamic agonist of the Farnesoid X Receptor (F.X.R.). This receptor belongs to the nuclear receptor family, which is primarily involved in bile acid synthesis and transportation and is present in the liver and small intestine. Apart from F.X.R., OCA is also responsible for activating the G-protein coupled receptor GPBAR1/TGR5 for secondary bile acids. OCA is

approximately 100 times more potent than its parent compound, chenodeoxycholic acid, which makes it an ideal drug for the treatment of several hepatic disorders. The proposed mechanism of action of OCA is said to be that upon binding to F.X.R., gene transcription of the enzyme cholesterol 7 $\alpha$ -hydroxylase is inhibited by induction of Small Heterodimer Protein (S.H.P.) in liver and Fibroblast Growth Factor-19 (FGF-19) in the small intestine. This is a significant enzyme involved in the conversion of cholesterol to bile acids. Furthermore, the expression of the Bile Salt Excretory

Pump (B.S.E.P.), which is responsible for the efflux of bile salts, is also increased. The recommended initial therapy of OCA is 5 mg once weekly for patients who are categorized as Class B and C in the Child-Pugh assessment.<sup>7-9</sup> The drug dose has been titrated to 10 mg, especially for those who have not achieved the anticipated reduction of ALP and or total bilirubin in the first three months, and 10 mg is considered as the maximum dose. Pruritus and fatigue are the most frequently documented adverse drug reactions. The pharmacokinetic profile of OCA is given in Table 1.

**Table 1: Pharmacokinetic assessment of UDCA&OCA.**

Parameters	UDCA	OCA
Water solubility (log mol/L)	-4.19	-4.268
CaCo2 permeability (log Papp in 10 <sup>-6</sup> cm/s)	0.705	0.684
Intestinal absorption (% Absorbed)	95.75	96.678
Skin Permeability (log Kp)	-2.733	-2.733
VDss(Human) (log L/kg)	-0.88	-1.036
Fraction Unbound (Fu)	0.063	0.03
Substrate	CYP3A4	CYP3A4
Total clearance (log ml/min/kg)	0.607	0.624
AMES Toxicity	NO	NO
Oral route Acute Toxicity (LD50) (mol/kg)	2.659	2.613
Oral route chronic toxicity (log mg/kg_bw/day)	1.853	2.221
Hepatotoxicity	NO	NO
Skin sensitization	NO	NO
Minnow toxicity (log mM)	1.166	-0.263

## 1.2 Overview of UDCA:

UDCA is indicated by US FDA for the management of patients with PBC UDCA is a normal constituent of human bile. The majority of the UDCA is presented in a conjugated form with glycine.<sup>10</sup> Numerous mechanisms of actions of UDCA in the pathology of liver diseases have been implicated, but these vary according to the stage of the cholestatic disease. In the primitive stages of Primary Biliary Cholangitis (PBC), the major mechanism of UDCA action is safeguarding injured hepatic cells against noxious effects of bile acids. Also, the activity and number of transporter proteins in the canalicular membrane determine the secretion capacity of cholangiocytes. In the case of drug-induced hepatic disease, transporter function may be pathologically impaired, but UDCA stimulates biliary secretion. Chemical structures of UDCA & OCA given in Figure 1.<sup>11,12</sup>

## 2. METHODS

A broad literature review was performed to compile the mechanisms of action of the targeted drugs such as "Ursodeoxycholic acid" and "Obeticholic acid" The pharmacokinetic profile of UDCA & OCA was observed from the PKCSM online server.<sup>13</sup> Toxicity prediction & drug-likeness was performed using OSIRIS Property Explorer program and Molinspiration software.

## 2.1 In silico prediction for toxicity:

Toxicity is accountable for the withdrawal and failure of new chemical entities. The toxicity profile of selected drugs was analyzed through the OSIRIS® Property Explorer program. This tool is accessible through cheminformatics.ch and chemistry.org. It is a freely available online software program that forecasts potential side effects such as mutagenicity, tumorigenicity, irritant, reproductive effects, drug-likeness and physicochemical properties analogous with a compound in a colour-coded format. The green colour indicates drug conform behaviour, yellow indicates medium risk, whereas the red colour shows a high risk for mutagenicity or low intestinal absorption. (Table 2) These predictions are essential to prevent deleterious substances to advance in drug discovery and development. We have also compared certain drug-related parameters such as Topological Polar Surface Area (T.P.S.A.), drug-likeness and overall drug score.<sup>14-16</sup>

(a) T.P.S.A. - Blood-brain barrier penetration and intestinal absorption are bioavailability-associated properties that are well correlated with T.P.S.A. and is calculated as the total sum of the contribution of fragments, mainly O- and N-fragments are considered.

(b) Drug likeness- A fragment-based approach is used for estimating drug-likeness via OSIRIS program. A positive value demonstrates that the study compound contains those

fragments which are found in commercially available formulations.

(c) Overall drug score - This is calculated using criterions such as drug-likeness, molecular weight, toxicity risk, log S

and log P values. A score of > 0.5 along with minimal toxicity risk is considered favorable.

**Table 2: Toxicity profile of OCA and UCA as predicted via OSIRIS Property Explorer program.**

PARAMETERS	Obeticholic acid (scores)	Ursodeoxycholic acid (scores)
Mutagenic	Green	Green
Tumorigenic	Green	Green
Irritant	Green	Green
Reproductive effect	Green	Green
TPSA	60.69	77.76
Drug likeness	-1.96	-0.41
Drug score	0.28	0.51

### Toxicity predictions

T.E.S.T. (Toxicity estimation software tool) ® Version 5.1 is used to calculate the toxicity profile of selected bioactive

compounds. This system generally comprises a receptor essential amino acids enzyme histidine kinase (H.K.) that will react to an extracellular signal by phosphorylating cytoplasmic response regulator. <sup>17</sup> [Table 3]

**Table 3: Toxicity estimation of selected bioactive compounds using T.E.S.T software**

Parameters	Obeticholic acid	Ursodeoxycholic acid
Fathead minnow LC <sub>50</sub> (96 hr) - Log10(mol/L)	5.87	5.55
Fathead minnow LC <sub>50</sub> (96 hr) mg/L	0.56	1.12
Similarity coefficient (≥ 0.5)	0.81	0.88
Daphnia magna LC <sub>50</sub> (48 hr) - Log10(mol/L)	4.80	4.63
Daphnia magna LC <sub>50</sub> (48 hr) mg/L	6.66	9.27
Similarity coefficient (≥ 0.5)	0.61	0.61
Bioconcentration factor Log10	1.45	1.33
Bioconcentration factor	28.38	21.58
Similarity coefficient (≥ 0.5)	0.83	0.83

Similarity coefficient (≥ 0.5) comparing the category of similar structures form the existing compounds.

### Molecular property:

The designed and docked molecules were screened *in silico* using MOLINSPIRATION® software to evaluate the drug-likeness of the compounds. This software is also equipped with data visualization, bioactivity prediction and fragment-based virtual screening. Any molecule possessing a bioactivity score of more than 0.00 is said to have a

favourable biological activity, whereas a score of -0.50 to 0.00 renders a molecule to contain moderate activity, and a score <0.00 is said to be inactive. Those molecules with the highest score are likely to be more active. <sup>18-20</sup>. Four important drug-receptor classes are screened - G-Protein Coupled Receptor ligands (G.P.C.R.), nuclear receptor ligands, tyrosine kinase inhibitors, ion channel inhibitors. (Table 4).

**Table 4: Evaluation of bioactivity scores gathered from Molinspiration Database.**

parameters	Obeticholic acid (Scores)	Ursodeoxycholic acid (Scores)
GPCR ligand	0.24	0.33
Ion channel modulator	0.13	0.33
Kinase inhibitor	-0.48	-0.39
Nuclear receptor ligand	0.80	0.86
Protease inhibitor	0.20	0.29
Enzyme inhibitor	0.61	0.68

### 3. RESULTS

UDCA is used as first-line therapy in the management of biliary cholangitis. However, patients who were treated with UDCA reported severe adverse drug reaction. This theoretical computer-aided response offers a great understanding of the preference of UDCA & OCA in the management of PBC. The pharmacokinetic parameters of both medications did not indicate dramatic differences. Yet, the half-life of UDCA is 3.5-5.8 days, whereas the half-life of OCA is 24 hours. The intestinal absorption of UDCA is 95.75%, and OCA is approximately 96.678%. Total clearance (log ml/min/kg) of UDCA & OCA were 0.607 & 0.624 respectively. A.M.E.S. Toxicity & hepatotoxicity have not been reported for both drugs. After the full phase of metabolism, both of the drugs are excreted through faeces.

Both OCA and UDCA do not show mutagenic or tumorigenic responses, respectively. However, the overall drug score was lesser than UDCA. OCA was found to have a strong biological activity at nuclear receptor ligand and enzyme inhibitor, moderate activity at G.P.C.R., ion channel receptor and protease inhibitor. Its activity at the kinase receptor was found to be negligible.

### 4. DISCUSSION:

Even in the absence of serious liver disorders, P.B.C. is strongly associated with morbidity & mortality. During the drug metabolism process, CYP3A4 contributes to a major extent for the metabolism of 65% xenobiotics, with UDCA and OCA being substrates of it.

UDCA is used as a first-line treatment for P.B.C., which improves liver function and reduces the development of hepatic fibrosis, the formation of oesophageal varices as well as delaying the need for liver transplantation. About one-third of patients do not respond to UDCA therapy, i.e. 30% of western patients and 32%–44.7% of Chinese patients failed to give an adequate response to UDCA therapy.<sup>21</sup> Ageing is a patient-specific factor that is not largely considered but can also give rise to unintended interactions due to changes in systemic absorption with advancing age. A comparative study of P.K. parameters of UDCA among healthy, elderly volunteers and younger adults showed that UDCA conjugate ratio and rate of biotransformation was lower in elderly adults when compared with younger adults.<sup>22</sup>

A 6-week, 25 or 50 mg administration of OCA improves the insulin sensitivity & reduces liver inflammation in adults with type 2 diabetes mellitus and nonalcoholic fatty disorder of the liver, respectively.<sup>23</sup> Pruritus was one of the major reported adverse drug reactions of OCA. However, a significant difference in the incidence of pruritus cases is based on the dose given.<sup>24</sup> Intake of food may increase the absorption of OCA as exhibited in a study wherein the  $AUC_{0-t}$

of test drug and  $AUC_{0-\infty}$ ,  $AUC_{0-t}$  of reference product under fed condition was found to be higher than fasting condition.

As the half-lives of these two drugs overlap, concurrent administrations of these CYP3A4 substrates may have possibilities of interfering with the CYP3A4 isoenzyme, leading to a severe adverse drug reaction or therapeutic failure. However, a phase-1 study assessing drug interactions between OCA and digoxin, warfarin, midazolam, caffeine, dextromethorphan, omeprazole and rosuvastatin reported that there was no significant inhibition of P.K. parameters of dextromethorphan, S-warfarin and digoxin at both 10 mg and 25 mg doses. P.K. of rosuvastatin was moderately suppressed with the 25 mg dose as an increase in plasma concentration was observed, and a weak interaction was found between OCA and caffeine.

### 5. CONCLUSION:

We believe that the co-administration of Obeticholic acid with Ursodeoxycholic acid would be an effective treatment for P.B.C. in patients with UDCA intolerance. In order to avoid severe adverse drug reaction/ therapeutic failure, extra care and monitoring are recommended when concomitant administration of UDCA+OCA is warranted.

### Ethics Approval and Consent to Participate

Not applicable

### Human and Animal Rights

No animals/humans were used for studies that are base of this research.

### Consent for Publication

Not applicable.

### Funding

None

### Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

### Availability of Data and Materials

Not applicable.

### Acknowledgements

We would like to thank all health care professionals.

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