P27. ANTI-INFECTIVE KNOWLEDGEBASE: DEVELOPMENT OF A COMPREHENSIVE TOOL FOR UNDERSTANDING THE DISPOSITION AND INTERACTION POTENTIAL OF ANTI-INFECTIVE DRUGS USED IN LOW-INCOME COUNTRIES

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ABSTRACT

Patients with infectious diseases in low-income countries (LICs) are often at risk of pharmacokinetic (PK) drug-drug interactions (DDIs). To assist in silico mechanistic modeling and simulations to predict DDI liability and guide optimal management of DDIs, a knowledgebase of anti-infective drugs, specifically treatments for malaria and tuberculosis, has been established.

Methods: All drugs recommended by the World Health Organization were included (9 for malaria and 5 for tuberculosis) as well as tafenoquine, a newly approved antimalarial. Data was compiled in three main categories: drug parameters (including modeling-relevant physicochemical properties and biological parameters), *in vitro* data (metabolism and transport mechanistic study data with the drugs evaluated as substrates and precipitants), and clinical data (including both PK and PK-based interaction data). Relevant data were obtained from the literature and FDA review documents. A panel of *in vitro* parameters (e.g., K_m, V_{max}, CL_{int}, uptake/efflux ratio, IC_{50}, K_i, % inhibition, EC_{50}, fold increase), experimental conditions, PK parameters (e.g., changes in AUC, C_{max}, CL, T_{max}, $t_{1/2}$), and clinical study protocols were systemically collected.

Results: All 15 drugs had data available for the three categories and over 1100 *in vitro* studies and 600 clinical evaluations were curated. *In vitro*, the metabolic profiles of the drugs were characterized, involving cytochrome P450 (CYPs) and other specific enzymes like n-acetyltransferase and arylacetamide deacetylase. Ten drugs were evaluated as substrates of transporters: OCT1 (N = 9), OCT2 (N = 8), P-gp (N = 6), and OATP1B1/1B3 (N = 4). However, most *in vitro* studies (85%) evaluated the drugs as inhibitors and/or inducers. Not surprisingly, CYP3A was the most studied (N = 14). For transporters, 12 drugs were evaluated as inhibitors of transporters: OCT2 (N = 9), MRP2 (N = 8), OATP2B1 (N = 8), BCRP (N = 7), MATE1/2-K (N = 7), OATP1B1/1B3 (N = 6), and P-gp (N = 6). *In vivo*, all 15 drugs were evaluated as victims with drugs likely to be co-administered, and about half of the clinical studies showed no effect of the co-administered drugs. The most significant changes in exposure were observed for the antimalarial artemether, with the AUC decreased by 89% when co-administered with rifampin, a treatment for tuberculosis and a known strong CYP3A inducer. As precipitants, 13 drugs were evaluated as potential inhibitors and 6 drugs as inducers. Rifampin was the most studied, comprising approximately 60% of the studies. Rifampin was found to cause the highest changes in drug exposure, reducing midazolam AUC by 98% after multiple dosing and increasing asunaprevir AUC almost 15-fold after single dosing due to induction of CYP3A and inhibition of OATP1B1/1B3, respectively.

Conclusion: This knowledgebase provides an up-to-date, highly detailed, data repository of available PK and DDI data, identifying current gaps in knowledge, enabling DDI predictions, and guiding dosing recommendations in LICs patient populations.

OBJECTIVES

- To establish a knowledgebase of anti-infective drugs assisting in silico mechanistic modeling and simulations to predict DDI liability.
- To identify current gaps in knowledge and guide optimal management of DDIs in LICs patient populations.

METHODS

- A list of 15 anti-infective drugs were developed, including 14 drugs recommended by the World Health Organization (9 for malaria and 5 for tuberculosis) and one recently approved antimalarial, tafenoquine.
- Data from three categories (Figure 1) were obtained mainly from the literature (PubMed, Embase), PubChem, DrugBank, and regulatory review documents.
- Relevant data were queried, curated, and validated in the knowledgebase following standard operating procedures. For *in vitro* data, only studies using the FDA recommended substrates, inhibitors, and inducers for CYPs and transporters were collected, while for clinical data, all PK food-effect and DDI studies (mechanistic studies and co-medication studies) were collected.

Drug Parameters

CAS number	HBD/HBA
Molecular weight	K_a
Permeability	logP
Solubility	pKa
Bioavailability	V_{ss}
Protein bound	...
B/P ratio	

***In Vitro* Data: Metabolism and Transport**

K_m, V_{max}, CL_{int}	Mechanism: enzyme, transporter
Uptake/efflux ratio	Experimental conditions: system, concentration, metabolite, pre-incubation, ...
IC_{50}, Ki, K_p	
% inhibition	
EC_{50}, E_{max}	
Fold increase	

Clinical Data: PK and PK-DDI

AUC or ratio	Mechanism: enzyme, transporter, absorption
CL or ratio	Study protocols: study design, dose, interval, duration, route, population, number of subjects, ...
C_{max} or ratio	
T_{max} or ratio	
$t_{1/2}$ or ratio	

Figure 1. Data categories and parameters collected in the knowledgebase

RESULTS

- All 15 drugs had data available for the three categories. All drugs had some types of compound parameters. Over 1100 *in vitro* studies and 600 clinical evaluations were curated (Table 1).

Table 1. Number of studies curated based on study type

Compound	CAS Number	Clinical PK	Clinical DDI			*In Vitro* Substrate		*In Vitro* Precipitant	
			Substrate	Inhibitor	Inducer	Metabolism	Transport	Metabolism	Transport
amodiaquine	86-42-0	2	14	10		86	4	7	5
artemether	71963-77-4		30	9	2	19		10	
artesunate	88495-63-0	2	11	12	8	2	3	7	8
dihydroartemisinin	71939-50-9	2	9	4	3	3	3	15	6
ethambutol	74-55-5	8	4	1	1		20	10	30
isoniazid	54-85-3	16	24	21	5	7	12	40	32
lumefantrine	82186-77-4		46			3	2	1	6
mefloquine	53230-10-7	2	14	11	4	3	3	11	13
piperaquine	4085-31-8	8	15	2		3	1	4	
pretomanid	187235-37-6	2	6	1	4	1		8	6
pyrazinamide	98-96-4	6	2	1			12	9	21
pyrimethamine	58-14-0		5	21		1		3	61
rifampin	13292-46-1	15	8	78	145	14	32	350	170
sulfadoxine	2447-57-6		4					3	
tafenoquine	106635-80-7	2	7	15		1		8	3

In vitro data

- As substrates: Twelve drugs were evaluated as substrates of enzymes (Table 1), involving CYPs and other specific enzymes like n-acetyltransferase and arylacetamide deacetylase. Ten drugs were evaluated as substrates of transporters (Table 1): OCT1 (N = 9), OCT2 (N = 8), P-gp (N = 6), and OATP1B1/1B3 (N = 4).
- As precipitants: Most *in vitro* studies (85%) evaluated the drugs as inhibitors and/or inducers. All 15 drugs were evaluated as inhibitors and/or inducers of enzymes (Table 1). CYP3A was the most studied (N = 14). For transporters, 12 drugs were evaluated as inhibitors of transporters (Table 1): OCT2 (N = 9), MRP2 (N = 8), OATP2B1 (N = 8), BCRP (N = 7), MATE1/2-K (N = 7), OATP1B1/1B3 (N = 6), and P-gp (N = 6).

Clinical data

- As substrates: All 15 drugs were evaluated as victims with drugs likely to be co-administered (Table 1), and about half the clinical studies showed no effect of the co-administered drugs. The most significant changes in exposure were observed for the antimalarial artemether, with the AUC decreased by 89% when co-administered with rifampin, a treatment for tuberculosis and a known strong CYP3A inducer.
- As precipitants: Thirteen drugs were evaluated as potential inhibitors and 6 drugs as inducers (Table 1). Rifampin was found to cause the highest changes in drug exposure, reducing midazolam AUC by 98% after multiple dosing and increasing asunaprevir AUC almost 15-fold after single dosing due to induction of CYP3A and inhibition of OATP1B1/1B3, respectively.

Example: rifampin data

- Rifampin had all the drug parameters available. It was the most studied, comprising approximately 60% of the *in vitro* and clinical studies (Table 1).
- The metabolism and transport profile has been extensively studied *in vitro*. For example, as a precipitant, it inhibited multiple transporters including BCRP, MRP1/2/3/4/5, OAT1/3, OATP1B1/1B3/2B1, OCT1, and P-gp, with the lowest K_i value of 0.278 μM towards OATP1B1 and the lowest IC_{50} value of 0.1 μM towards OATP1B1/1B3. It also showed induction of multiple CYPs (e.g., 1A1/2, 2A6, 2B6, 2C8/9/19, 2E1, 3A4/5/7) and UGTs (e.g., 1A1/3/4/6/9, 2B4/7/15), and inhibition of a few CYPs (e.g., 2A6, 2B6, 2C8, 3A4).
- Based on the mechanistic clinical DDI studies with FDA recommended substrates, rifampin was identified as an inhibitor and inducer of multiple CYPs and transporters. A summary of these studies is presented in Table 2.

RESULTS

Table 2. Mechanistic inhibition and induction studies of rifampin as a precipitant

Enzymes/Transporter(s) Implicated	Clinical Substrate	AUC Ratio	C_{max} Ratio
rifampin as an inhibitor			
BCRP, OATP1B1/1B3, P-gp, OATP [a]	atorvastatin	3.34-12.0	7.50-21.08
BCRP, OATP1B1/1B3	rosuvastatin	1.64-4.67	2.71-11.52
OATP1B1/1B3	pitavastatin	1.35-6.6	2.11-7.65
OATP1B1/1B3, MRP2, OAT3, OATP [a]	pravastatin	2.27-4.64	2.73
OATP1B3, P-gp, OATP [a]	(R)-fexofenadine	1.90-3.21	2.07-3.14
	(S)-fexofenadine	2.40-3.57	2.50-3.49
OATP1B1/2B1, OATP [a]	asunaprevir	14.82	21.11
OATP1B1/1B3, OATP [a]	bosentan	3.18 [b]	2.97-5.00 [c]
OATP [a]	glyburide	2.18	1.81
P-gp	dabigatran	2.07-2.32	1.79-1.93
	digoxin	1.30-1.46	1.49-2.18
CYP2C8, OATP1B1, OATP [a]	repaglinide	1.93-2.60	2.08-2.47
CYP3A	midazolam	1.31	
rifampin as an inducer			
CYP1A2	caffeine	0.40-0.77	0.61-0.93
	tizanidine	0.46	0.5
CYP2C8	repaglinide	0.20-0.68	0.21-0.83
CYP2C9	tolbutamide	0.35-0.52	0.66-1.01
	(S)-warfarin	0.26	
CYP2C19	omeprazole	0.07-0.46	0.10-0.50
CYP2D6	dextromethorphan	0.26	
CYP3A	atorvastatin	0.20	0.60
	midazolam	0.02-0.83	0.04-2.10
	triazolam	0.05	0.12
BCRP, OATP [a]	rosuvastatin	0.44-0.78	0.60-0.95
OATP1B1/1B3	asunaprevir	0.79	0.95
OATP [a]	pravastatin	0.45-0.50	0.46-0.60
OATP [a], P-gp	fexofenadine		0.49-0.68
OCT1, OCT3, PMAT [d]	metformin	1.13 [b]-1.27	1.10-1.15
P-gp	dabigatran	0.33	0.34
	digoxin	0.70-0.84	0.48-0.81

[a] specific isoform was not identified in the article; [b] $AUC_{0\text{-}24h}$; [c] C_{min} [d] Induction of OCT1 in blood cells was observed; induction of OCT1/3 and PMAT in intestines may contribute to the increased exposure of metformin

CONCLUSIONS

A highly detailed knowledgebase of anti-infective drugs, specifically treatments for malaria and tuberculosis, has been established. This knowledgebase provides an up-to-date data repository of available PK and DDI data, identifying current gaps in knowledge, enabling DDI predictions, and guiding dosing recommendations in LICs patient populations.

REFERENCES

All the references are available in the knowledgebase, which will be listed in a public portal soon.

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