UNDERSTANDING THE RISK OF CLINICALLY SIGNIFICANT PHARMACOKINETIC-BASED DRUG-DRUG INTERACTIONS WITH DRUGS NEWLY APPROVED BY THE US FDA – A REVIEW OF RECENT NEW DRUG APPLICATIONS (2013-2016)

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OBJECTIVE AND METHODS

The aim of the present work was to systematically review pharmacokinetic-based drug-drug interaction (DDI) data available in the most recent (2013-2016) New Drug Applications (NDAs) and highlight significant findings. The University of Washington Metabolism and Transport Drug Interaction Database® (http://www.druginteractioninfo.org/) was used to extract the results of metabolism, transport, and clinical DDI studies. All the DDI studies (new molecular entity (NME) as victim or perpetrator) with AUC changes ≥ 2-fold or < 2-fold but triggering dose recommendations were included in the analysis.

RESULTS

- A total of 103 NDAs (including 14 combination drugs, total NMEs = 107) were approved in the past four years, with 95% of NDAs containing *in vitro* and/or *in vivo* metabolism data and 79% containing transport information.
- The most represented therapeutic areas were oncology (21%) and anti-infective drugs (20%; including 10 antivirals, 6 antibiotics, 4 antifungals, and 1 anti-parasitic).

NMEs as Substrates

- *In vitro*, CYP3A was found to be the primary enzyme involved in the metabolism of 64 NMEs, followed by CYP2D6 (N=27) and the CYP2C family. For transporters, 47 and 20 NMEs were shown to be *in vitro* substrates of P-gp and BCRP, respectively, followed by 8 NMEs for OATP1B1/3.

Sensitive substrates (AUC ratios ≥ 5)

- Thirteen NMEs were identified as sensitive substrates (AUC ratios ≥ 5 when co-administered with a strong inhibitor) of CYP3A (N=8), CYP1A2 (N=2), CYP2C8 (N=1), CYP2D6 (N=1), or OATP1B1/3 (N=1) (Table 1).
- Half of these sensitive substrates were antiviral or oncology drugs (Figure 1).

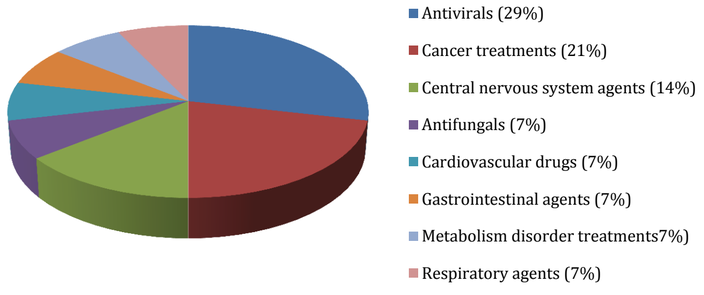

Figure 1. Therapeutic classes of inhibition DDIs with AUC ratios ≥ 5, NMEs as substrates

- CYP3A played a major role in clinically significant DDIs, involved in 2/3 of DDIs with AUC ratios ≥ 5 (Figure 2). Interestingly, 75% of the sensitive CYP3A substrates were also substrates of P-gp.

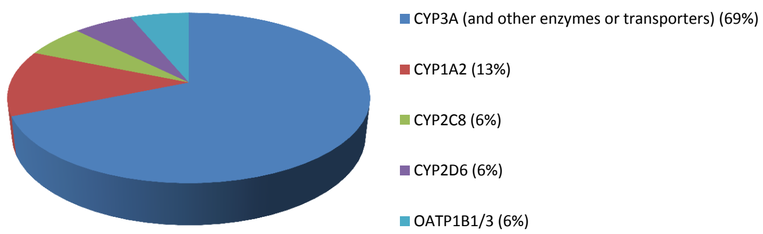

Figure 2. Mechanisms of inhibition DDIs with AUC ratios ≥ 5, NMEs as substrates (N=16 DDIs)

Moderate sensitive substrates (2 ≤ AUC ratios < 5)

- Twenty-eight drugs were found to be moderate sensitive substrates (2 ≤ AUC ratios < 5), with approximately 70% of the interactions being related to alteration of CYP3A activity, and 30% being transporter-mediated, including P-gp, BCRP, and OATP1B1/3 (Figure 3). Antivirals (29%) were the most represented drugs.

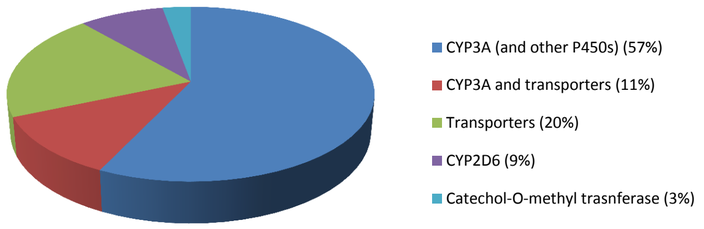

Figure 3. Mechanisms of inhibition DDIs with 2 ≤ AUC ratios < 5, NMEs as substrates (N=35 DDIs)

AUC ratios < 2 with label recommendations

- Twenty-one drugs were found to have lower increases in exposure (less than 2-fold) but still triggering labeling recommendations. The most represented drug areas were cancer treatments (36%) and antivirals (18%). CYP3A mediated over half of these DDIs.

NMEs as Inhibitors

- *in vitro*, CYP3A inhibition was the most often observed mechanism (N=47), followed by inhibition of CYP2C9 (N=33), CYP2C8 (N=32), CYP2C19 (N=30), and CYP2D6 (N=18). For transporters, 41, 37, and 34 NMEs inhibited OATP1B1/3, P-gp, and BCRP *in vitro,* respectively.
- *In vivo*, only one NME (idelalisib) was found to be a strong inhibitor of CYP3A (Table 1). Eleven drugs showed moderate inhibition (AUC ratios of probe substrates ranging from 2.18 to 3.33) and 20 NMEs showed < 2-fold in victim exposure with labeling recommendations.
- Transporters were found to play a significant role in half of these interactions (Figure 4). Antivirals (30%) and oncology drugs (20%) were the most represented inhibitors .

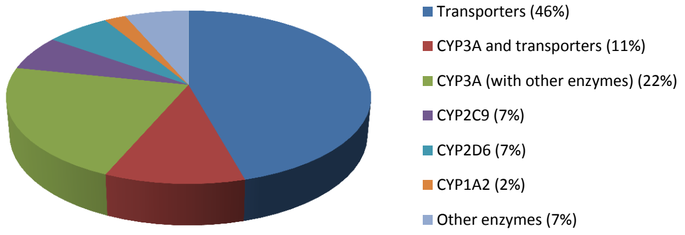

Figure 4. Mechanisms of inhibition DDIs with AUC ratios ≥ 1.25, NMEs as inhibitors (N=46 DDIs)

NMEs as Inducers

- *In vitro,* 24 NMEs induced CYP3A, while 15 and eight NMEs induced CYP2B6 and CYP1A1, respectively.
- *In vivo*, only seven NMEs showed clinically relevant induction. One drug (lumacaftor) was identified as a strong inducer of CYP3A (Table 1) and two drugs (dabrafenib and eslicarbazepine acetate) moderately induced CYP3A.
- The majority (60%) of induction DDIs were mediated by CYP3A.

Table 1. Clinical DDIs with AUC ratios ≥ 5 (for inhibition) or ≤ 0.2 (for induction)

Victim Drug	Inhibitor	Main Enzymes/ Transporters Possibly Involved	Max AUC Ratio	Max C_{max} Ratio
Inhibition DDIs with AUC ratios ≥ 5, NMEs as substrates				
Paritaprevir	Ritonavir	CYP3A, P-gp, BCRP, OATP1B1/3	47.43	28.07
Eliglustat	Paroxetine	CYP2D6	28.40 (EMs), 5.20 (IMs)	22.00 (EMs), 4.10 (IMs)
Ibrutinib	Ketoconazole	CYP3A	23.90	28.60
Grazoprevir	Cyclosporine	OATP1B1/3	15.25	17.03
Naloxegol	Ketoconazole	CYP3A4[a]	12.42	9.12
Dasabuvir	Gemfibrozil	CYP2C8	9.90	1.91
Ivabradine	Ketoconazole	CYP3A4[a]	7.70	3.60
Simeprevir	Ritonavir	CYP3A[a]	7.18	4.70
Tasimelteon	Fluvoxamine	CYP1A2	6.87	2.28
Pirfenidone	Fluvoxamine	CYP1A2	6.81 (smokers)	2.24 (smokers)
Cobimetinib	Itraconazole	CYP3A[a]	6.62	3.17
Flibanserin	Fluconazole	CYP3A4, CYP2C19	6.41	2.11
Venetoclax	Ketoconazole	CYP3A, P-gp	6.40	2.33
Isavuconazonium sulfate	Ketoconazole	CYP3A, butyrylcholinesterase	5.22	1.09
Induction DDIs with AUC ratios ≤ 0.2, NMEs as substrates				
Isavuconazonium sulfate	Rifampin	CYP3A, butyrylcholinesterase	0.03	0.25
Eliglustat	Rifampin	CYP3A[a]	0.04 (PMs), 0.10 (IMs), 0.09 (EMs)	0.05 (PMs), 0.11 (IMs), 0.09 (EMs)
Flibanserin	Rifampin	CYP3A4, CYP2C19	0.04	0.10
Ibrutinib	Rifampin	CYP3A[a]	0.08 (PBPK)	0.07 (PBPK)
Naloxegol	Rifampin	CYP3A4[a]	0.11	0.26
Olaparib	Rifampin	CYP3A[a]	0.11	0.3
Rolapitant	Rifampin	CYP3A4	0.12	0.68
Suvorexant	Rifampin	CYP3A	0.12	0.36
Tasimelteon	Rifampin	CYP3A4	0.14	0.23
Palbociclib	Rifampin	CYP3A[b]	0.15	0.28
Cobimetinib	Rifampin	CYP3A[a]	0.17 (PBPK)	0.37 (PBPK)
Grazoprevir	Efavirenz	CYP3A[c]	0.17	0.13
Velpatasvir	Rifampin	CYP2B6, CYP2C8, CYP3A, P-gp, BCRP	0.19	0.29
Netupitant	Rifampin	CYP3A4	0.20	0.45
Inhibition DDIs with AUC ratios ≥ 5, NME s as inhibitors				
Tacrolimus	Ombitasvir, paritaprevir, dasabuvir, and ritonavir[d]	CYP3A, P-gp	57.07	16.48
Midazolam	Idelalisib	CYP3A	5.15	2.31
Induction DDIs with AUC ratios ≤ 0.2, NMEs as inducers				
Itraconazole	Ivacaftor and lumacaftor	CYP3A	0.18	0.10
Ivacaftor	Lumacaftor	CYP3A	0.20	0.19

All DDIs had label recommendations; [a]also a P-gp substrate; [b] also metabolized by CYP1A2, CYP2C9, and CYP2C19; [c]also a substrate of P-gp and BCRP; [d]the strong inhibition is caused by ritonavir, which is not a NME

CONCLUSIONS

- CYP3A was confirmed to be a major contributor to clinically significant DDIs involving NMEs as victims or perpetrators.
- Transporter-based DDIs represented about 50% of all observed interactions, although most of these were weak-to-moderate.
- Among drugs with large changes in exposure (≥ 5-fold), antivirals and oncology drugs were the most represented therapeutic classes, suggesting a significant risk of clinical DDIs in these patient populations.