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GUEST EDITORIAL

CYP-associated drug–drug interactions: A mission accomplished?

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Abstract
On the basis of official Finnish Medicines Authority (Fimea)-approved drug monographs, less than half of the approved small-molecule drugs between 2007 and 2016 were substrates, inhibitors or inducers of CYP enzymes, predominantly of CYP3A4. No significant unexpected, life-threatening, CYP-associated drug-drug interactions (CYP-DDIs) of newly approved drug entities have been observed in the last 10–15 years. The present analysis seems to suggest that tools to study and predict potentially significant CYP-DDIs are working and efficient.

Keywords Cytochrome P450 · CYP · Drug-drug interactions · Approved drugs

Introduction

For many decades, drug–drug interactions (DDI) have formed a major clinically important problem of drug treatment; cytochrome P450 (CYP) enzymes being the most important phase I xenobiotic-metabolizing enzymes involved in the DDIs (see Pelkonen et al 1998; 2008 and Hakkola et al. this issue).

For us, it started really with cimetidine. One of the earliest cases of CYP-associated DDIs was cimetidine, at the time a novel histamine H_2 receptor inhibitor developed for gastroesophageal reflux disease and ulcers. Hepatic microsomal studies were already at that time applied for the study of CYP enzymes and seminal studies in the 1979 and 1980 indicated that cimetidine inhibited the metabolism of some CYP-catalyzed activities in human and animal liver preparations as well as in vivo in humans and animals (Puurunen and Pelkonen 1979; Serlin et al 1979; Rendic et al 1979; Pelkonen and Puurunen 1980; Puurunen et al. 1980). These DDIs associated with cimetidine were used as a major advertising point by the competitor introducing another H_2 receptor blocker, ranitidine, to the market. Gradually the use of liver preparations for studying potential DDIs of new chemical entities increased, and the drug authorities began to require developers to study potential DDIs before marketing applications (latest versions EMA 2012; FDA 2020). Over the years, some widely published cases, also withdrawals, due to DDIs such as mibefradil, cerivastatin, terfenadine and others highlighted the importance of predictive investigations and the need of validated tools. A tremendous progress of tools has occurred over the last decades and these tools are used increasingly during early drug development and in conjunction with clinical research, especially by pharmaceutical industry and CROs (Fowler et al 2017). Furthermore, various databases and search tools have proliferated to aid research, regulation and clinical work (Grizzle et al 2019).

Now, the question is: are the tools developed for anticipating and predicting CYP-based DDIs effective in the management of DDIs during drug development and in clinical situations? To answer this question, we decided to look at the 10-year period from 2007 to 2016 and assess what kind of information about drug–drug interactions

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official drug monographs contain. Because two of us (OP, MT) have been involved in surveying inhibitors and inducers (also non-CYP enzymes and the most important transporters) among newly introduced drugs in Finland annually from 2007, we have evaluated this information every year (see the supplementary Tables 1–10) to make a conclusion on whether an individual drug has potential interactions, which clinicians should be aware of when making treatment decisions. At this time, we also searched the literature whether there were any additional information on potential DDIs. However, as the evaluation was performed at the time of the annual publication of the new edition of the physician's desk reference (Pharmaca Fennica in Finland), it was based mostly on information in the official drug monographs. It should be kept in mind that the supplementary tables concern new drugs authorized in Finland and thus there are some differences as compared to the authorizations in EU (EMA) or USA (FDA) or other authorities. However, practically all the medicines authorized during 2007–2016 in Finland had undergone a centralized process, i.e., approved at the EU level. So overall we believe that the differences between the Finnish and most international pharmaceutical formularies are rather small and that the list of drugs showing potential of CYP inhibition and induction provides an adequate view about the topic. Similar observations have been made by Yu et al (2018, 2019) on FDA-approved drugs in 2013–2017. In the following we present a few observations on the basis of this exercise, summarized in Tables 1 and 2.

Spectrum of new drugs has changed over time

First of all, out of 256 approved drugs, 43% (111) were drugs given parenterally, usually as an intravenous injection or infusion. This group consists of a mixture of products for various indications, but the largest product group is biopharmaceuticals, i.e., biological drugs with special indications such as specific cancers or rheumatoid arthritis. Altogether 17% (43 drugs) of all the approved drugs belonged to this group and they occupy nowadays a major share of new drugs.

57% of the approved drugs (145 drugs) belong to a group of small-molecule pharmaceutics, i.e., "ordinary" drug molecules. Within this group, 24 (17%) belong to novel kinase inhibitor anticancer drugs and 14 (9.7%) to anti-HIV-drugs. Remaining drugs are spread over numerous indications.

CYP substrates, inhibitors and inducers

Out of 145 small-molecule oral drugs, 63 (43%) were substrates of CYP enzymes, predominantly CYP3A4, and 15 (10%) were deemed to be inhibitors of consideration by a regulator and/or developer. Just six (4%) CYP inducers were identified among the new drugs.

Table 1 New drug substances with marketing authorization in Finland for 2007–2016: grouping according to administration, molecular size and some special indications (kinase inhibitors for cancer; anti-HIV drugs)

Year	Total	Parenterally administered		Small-molecule orally administered		
		All	Biological drugs	All	Protein kinase inihitors	Anti-HIV drugs
2007	22	9	3	13	1	2
2008	26	12	2	14	2	1
2009	22	12	4	10	1	-
2010	15	8	2	7	1	-
2011	25	13	4	12	-	2
2012	24	9	1	15	4	1
2013	32	6	2	26	7	1
2014	30	6	3	24	2	2
2015	29	15	10	14	4	4
2016	31	21	12	10	2	1
2007—2016	256	111	43	145	24	14

Practically all drugs belong to the mutually accepted pharmaceuticals within the EU

Pharmaca Fennica; an annual physician desk reference of medicines in Finland, since 2007

Table 2 New small-molecule drugs with a warning in the monograph that CYP-based interactions are potentially affecting drug treatment and should be taken into consideration

Year	Total	CYP substrate ("victim")		CYP inhibition ("perpetrator")		CYP induction ("perpetrator")	
		All	KIs and Anti-HIV	All	KIs and Anti-HIV	All	KIs and Anti-HIV
2007	13	4	3	–	–	–	–
2008	14	7	3	3	3	–	–
2009	10	1	1	1	–	–	–
2010	7	3	1	1	–	1	1
2011	12	4	–	2	2	–	–
2012	15	6	4	1	1	–	–
2013	26	13	8	3	1	3	2
2014	24	8	3	1	1	1	–
2015	14	12	8	1	1	–	–
2016	10	5	3	2	–	1	–
2007—2016	145	63	34	15	9	6	3

Pharmaca Fennica; an annual physician desk reference of medicines in Finland, since 2007

Most CYP-associated drugs are either anticancer or HIV drugs

A clear majority among substrates and inhibitors were either anticancer drugs or anti-HIV drugs. Anticancer drugs were mostly kinase inhibitors, which are metabolized principally by CYP3A4. These include bosutinib, dabrafenib, dasatinib, erlotinib, gefitinib, imatinib, labatinib, nilotinib, olaparib, patsopanib, ponatinib, regorafenib, ruxolitinib, seritinib, sorafenib, sunitimib, vandetanib, vemurafenib, and vismodegib. Nine out of 15 CYP inhibitors were kinase inhibitors or anti-HIV drugs. Especially HIV protease inhibitors are variably potent CYP3A4 inhibitors and these include atazanavir, darunavir, fosamprenavir, lopinavir, ritonavir, and saquinavir.

Many non-CYP enzymes and transporters emerge as interaction targets.

As could be seen in the supplementary tables, many transporters have been identified as potential interaction targets for the approved drugs. However, it is often not possible to carefully assess their roles in interactions, because there are only a few validated methodologies available.

CYP3A4 substrates form the major part of the listed drugs

CYPs other than CYP3A4 were only sporadically observed among substrates, inhibitors or inducers. It is remarkable that CYP2D6 was identified as a metabolizing enzyme for only six drugs. CYP1A2 and CYP2C9 were target enzymes for even fewer drugs.

There are only a few inducers

Only six newly approved drugs were CYP inducers over this 10-year period. It seems that the thrust in the development of small molecule drugs has been towards more potent and specific molecules and this has led to a relative decrease of clinical doses, which lead to low hepatic and duodenal concentrations unable to cause a significant CYP induction. Naturally, the induction properties of new molecular entities is studied during the drug development process nowadays and the results guide the process to avoid potential inducers.

There have been no major CYP-DDI surprises leading to drug withdrawals among novel drugs since 2007

It is of interest that after 2007 there are no adversity-based withdrawals that could be clearly and predominantly associated with CYP interactions. Naturally, several non-CYP-associated interactions (e.g., based on P-glycoprotein ABCB1) have been found to be of significance (see some of them in the supplementary tables) and they deserve a proper consideration when assessing the clinical significance of the observed pharmacokinetic consequence. However, as far as we know there have been no withdrawals due to these interactions. It is still necessary to remind of a complex landscape of clinically significant interactions consisting of characteristics of interacting drugs and an individual patient with her/his unique genetic and environmental features.

Conclusion

On the basis of the above analysis, it seems proper to conclude that the predictive tools to investigate CYP-DDIs have been rather efficient in detecting significant interactions and preventing more serious clinical adversities. It should be stressed, however, that any individual pharmacokinetic process cannot be functionally separate or independent from other pharmacokinetic processes (i.e., ADME). Instead, they form a seamless whole, and CYP-associated processes are only a part, although an important one, of the whole process of pharmacokinetics. Consequently, a wider view of the whole process is preferable when judging the possibility and significance of a specific CYP-DDI occurrence.

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

References

EMA (2012) Guideline on the investigation of drug interactions.https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-drug-interactions-revision-1_en.pdf

FDA (2020) In vitro drug interaction studies —cytochrome P450 enzyme- and transporter-mediated drug interactions guidance for industry. https://www.fda.gov/media/134582/download

Fowler S, Morcos PN, Cleary Y, Martin-Facklam M, Parrot N, Gertz M, Yu L (2017) Progress in prediction and interpretation of clinically relevant metabolic drug–drug interactions: a minireview illustrating recent developments and current opportunities. Curr Pharmacol Rep 3:36–49

Grizzle AJ, Horn J, Collins C, Schneider J, Malone DC, Stottlemyer B, Boyce RD (2019) Identifying common methods used by drug interaction experts for finding evidence about potential drug–drug interactions: web-based survey. J Med Internet Res 21:e11182

Pelkonen O, Mäenpää J, Taavitsainen P, Rautio A, Raunio H (1998) Inhibition and induction of human cytochrome P450 (CYP) enzymes. Xenobiotica 28:1203–1253

Pelkonen O, Puurunen J (1980) The effect of cimetidine on in vitro and in vivo microsomal drug metabolism in the rat. Biochem Pharmacol 29:3075–3080

Pelkonen O, Turpeinen M, Hakkola J, Honkakoski P, Hukkanen J, Raunio H (2008) Inhibition and induction of human cytochrome P450 enzymes: current status. Arch Toxicol 82:667–715

Puurunen J, Pelkonen O (1979) Cimetidine inhibits microsomal drug metabolism in the rat. Eur J Pharmacol 55:335–336

Puurunen J, Sotaniemi E, Pelkonen O (1980) Effect of cimetidine on microsomal drug metabolism in man. Eur J Clin Pharmacol 18:185–187

Serlin MJ, Sibeon RG, Mossman S, Breckenridge AM, Williams JR, Atwood JL, Willoughby JM (1979) Cimetidine: interaction with oral anticoagulants in man. Lancet 2:317–319

Rendic S, Sunjic V, Toso R, Kajfez F, Ruf HH (1979) Interaction of cimetidine with liver microsomes. Xenobiotica 9:555–564

Yu J, Petrie ID, Levy RH, Ragueneau-Majlessi I (2019) Mechanisms and clinical significance of pharmacokinetic-based drug–drug interactions with drugs approved by the US food and drug administration in 2017. Drug Metab Dispos 47:135–144

Yu J, Zhou Z, Tay-Sontheimer J, Levy RH, Ragueneau-Majlessi I (2018) Risk of clinically relevant pharmacokinetic-based drug–drug interactions with drugs approved by the US Food and drug administration between 2013 and 2016. Drug Metab Dispos 46:835–845