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Detecting Hidden Drug Risks by AI Powered Multiple-Drug-Drug Interaction (MDDI) Analysis: The Apixaban Case

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Introduction

The "clinical implications of co-administering apixaban with key interacting medications" were recently published by Favatella et al. in 2024 [1]. The authors stated that the multiple organ and metabolic pathways for apixaban clearance are expected to minimize the potential for large increases in apixaban exposure. However, this opinion might not apply when multiple mechanisms of drug clearance and inactivation are inhibited concomitantly as Isoherranen et al. have pointed to in a very convincing manner [2] and as shown in the in-vivo studies by Niemi et al. demonstrating huge increases of drug exposure caused by multiple enzyme inhibition in the triple drug interactions "repaglinide – itraconazole – gemfibrozil" and "loperamide – itraconazole – gemfibrozil" [3,4] (Table 1).

Table 1: AUC data from in-vivo investigations compared with values from the MDDI calculator of Scholz Databank [6].

Drugs	relative AUC (in vivo data) [3,4]	relative AUC calculated with the MDDI Calculator of Scholz Data-bank
Repaglinide – Itraconazole	1.4	1.4
Repaglinide–Gemfibrozil	8.1	7.6
Repaglinide–Itraconazole-gemfibrozil	19.4	18.9

Loperamide–Itraconazole	3.8	3.6
Loperamide–Gemfibrozil	2.2	2.1
Loperamide–Itraconazole-gemfibrozil	12.6	12.9

In consequence the potential impact of the key interacting drugs listed by Favatella et al. on the exposure of apixaban shall be elucidated whereby apart from the known interactions through strong CYP3A4 and P-gp inhibitors the impact by renal failure shall be additionally included as up to 29% of apixaban doses are recovered in urinary excretion, about 27% is dependent on renal clearance, and dependent on impaired renal clearance the drug exposure is increased up to the 1.41 fold **[1,5] (Table 1)**.

MDDI Analysis

This analysis is supported by advanced AI software technology as provided by SCHOLZ Databank (SDB) and its web service and the Adverse Drug Risk Control Panel (ADR CP) **[6]**. The ADR CP of SCHOLZ DataBank pursues the target to assess and compare drug and complex medication risks. The core of the system is the drug interaction checker with the "MDDI" Calculator which supports a multiple drug-drug interaction analysis superior to the traditional pair wise interaction analysis **[7-11]**.

The following **Table 2** contains SDB's MDDI assessments (AUCcomp) of the apixaban AUC-increases both by the key interacting drugs alone and in diverse scenarios where the relevant transporter and enzyme pathways of apixaban are affected by multiple impacts including renal elimination, compared with in-vivo study data (AUCstudy).

Table 2: Apixaban AUC-increases by inhibiting transporter/enzyme and/or renal functions.

Scenario	Function	Inhibition by	Impact	AUCcomp*	AUCstudy#
1	P-gp	Naproxen	strong	1.60	1.54
2	CYP3A4, P-gp	Ketoconazole	strong	2.12	1.99
3	CYP3A4, P-gp	clarithromycin	moderate§	1.54	1.60
4	CYP3A4, P-gp	diltiazem	moderate	1.38	1.40
5	Renal Clearance (Clren)	CKDGFR 60ml/min	mild	1.16	1.16
6	Renal Clearance (Clren)	CKDGFR 30ml/min	moderate	1.31	1.29
7	Renal Clearance (Clren)	CKDGFR 15ml/min	severe	1.41	1.41
8a	CYP3A4, P-gp	Clarithromycin	moderate	2.16	-
	Clren	CKDGFR 30ml/min	moderate		
8b	CYP3A4, P-gp	Clarithromycin	moderate	2.36	-
	Clren	CKDGFR 15ml/min	moderate		
9a	CYP3A4, P-gp	Ketoconazole	strong	3.08	-
	Clren	CKDGFR 30ml/min	moderate		
9b	CYP3A4, P-gp	Ketoconazole	strong	3.41	-

	Clren	CKDGFR 15ml/min	severe		

§see remarks concerning the inhibitor strength of claritrhomycin in chapter "Discussion"

*AUCcomp assessments by SCHOLZ DataBank MDDI calculation

#AUCstudy data according to Favatella et al. (1) and Eliquis Prescriber Information **[5].**

Discussion

The interaction between apixaban and ketoconazole represents the strongest impact on apixaban pharmacokietics through CYP3A4 and P-gp inhibition and marks the threshold of a doubled AUC to be clinically significant **[1]** and requiring a dose reduction by 50% as also postulated in the Prescriber Information **[5]**. The kinetic impacts of naproxen, diltiazem, and clarithromycin are comparably moderate and do not require any dose adjustment whereby the findings for clarithromycin indicate that though named a "strong 3A4 blocker" its inhibiting power is clearly smaller – as in general assumed **[5]** - than that one of ketoconazole or itraconazole and is indeed rather moderate than strong or in between. An additional potential clinically significant increase of the apixaban AUC to the 1.77-fold through multiple drug impacts was already assessed and described in 2016 **[7]**.

However, the assessments for scenarios with moderate or severe renal failure and GFR 30 ml/min or 15 ml/min respectively reveal that under such conditions the threshold of a 2-fold AUC requiring a dose adjustment by half of the apixapan dose is also surpassed when administering moderate CYP3A4 and P-gp inhibitors such as diltiazem or clarithromycin or solely stronger P-gp inhibitors such as naproxen. The Prescriber Information **[5]** does not give any hints in this direction and a supplement in this respect would help to give more decision support to healthcare professionals in clinical cases probable to occur. In the case of strong CYP3A4 and P-gp inhibitors such as ketoconazole when administering apixaban to CKD patients with moderate or severe renal failure the dose should rather be cut in third than just halved provided that appropriate divisible dosage forms are available. The need to have an eye on the renal function is also backed up through the findings in the Aristotle study that the risk of major bleeding was more than doubled comparing patients with < 30ml/min GFR and patients with > 80ml/min GFR **[5]**.

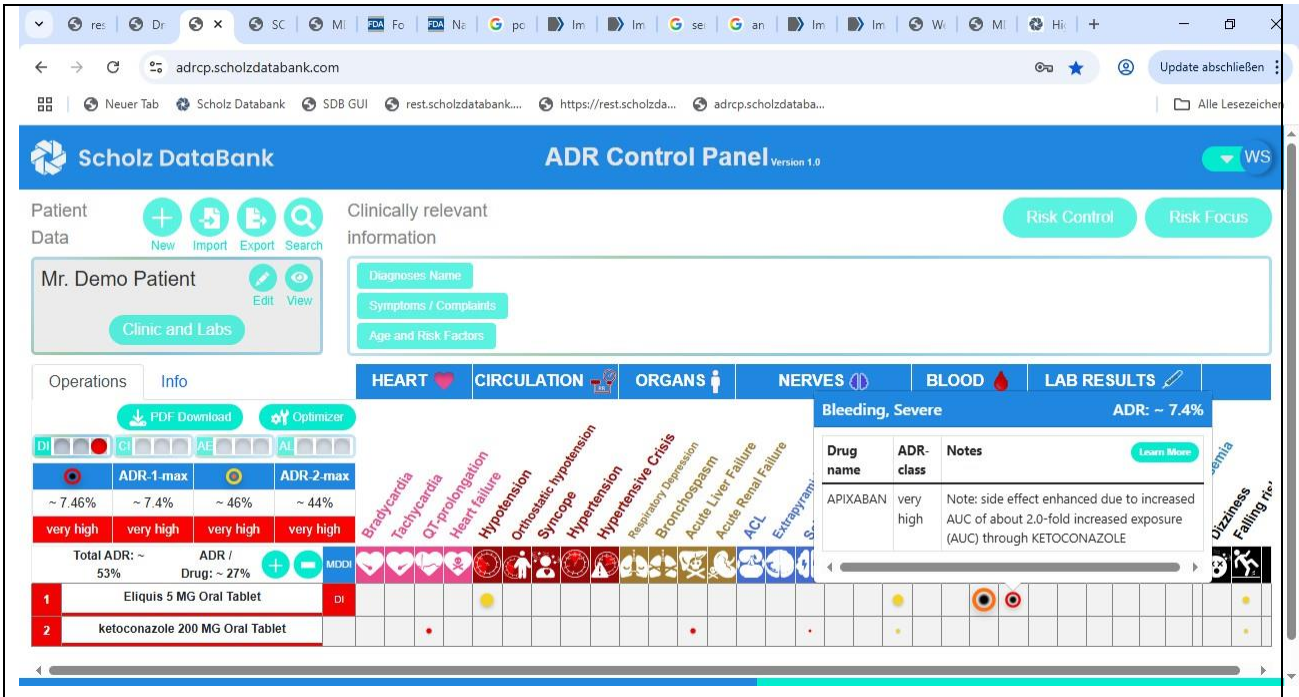
Favatella et al. state furthermore "Not all possible combinations of therapies can be formally tested" and "Even with the extensive controlled trial evidence available on the use of apixaban in patients who are receiving potentially interacting medications, data do not exist to inform on all decisions that clinicians and patients must make. Through extrapolation of the class effect, the available summarized data can be used to estimate the impact of unstudied DDIs based on their PK properties".

This is where SDB with its MDDI technology steps in and may help. Based on a core of scaled pharmacokinetic properties for U.S. Rx and OTC drugs as well as relevant herbal drugs and food and beverages assessments for billions of polypharmacy scenarios can be computed how one drug might be affected by all others of a polypharmacy medication. Additionally patient individual conditions such as renal stages or pharmacogenomics can be included into the assessment which drives the process into personalized precision medicine and helps to detect

hidden drug risks caused by multiple impacts, even if each of them might be minor. Concerning CYP3A4 and P-gp SDB contains 227 active ingredients as substrates and 83 ingredients as inhibitors of CYP3A4 and 57 active ingredients as substrates of P-p and 64 ingredients as inhibitors of P-gp. Thus tremendous AI knowledge has been established and is available to support safe drug therapy which otherwise could not be used to the benefit of the professional medical audience and their patients due to the lack of financial funds which would be needed for all the expensive in-vivo clinical research necessary. In consequence SDB does not only predict how ketoconazole, clarithromycin, diltiazem and naproxen without or with diverse stages of renal failure affect and increase the apixaban exposure but also how a total of about 120 active ingredients which are CYP3A4 and/or P-gp inhibitors such as for example itraconazole, posaconazole, voriconazole, erythromycin, ritonavir, dronedarone might have an impact on apixaban, expressed as an assessment of the increased AUC in %.

Reconciling Pharmacokinetics and Pharmacodynamics

Last not least: As the ADR CP reconciles in a "All-in-One" approach the pharmacokinetic and pharmacodynamic interactions in a way that the impacts on vital signs and serious adverse effects become transparent a disproportionally increased risk of bleeding, especially major bleeding, due to an increased apixaban AUC is assessed, visualized and explained as shown in **Screenshot 1.**



Screenshot 1

Conclusion

Multiple minor pharmacokinetic impacts may cause clinically significant drug-drug interactions. They are often overlooked or underestimated. Such hidden

drug-drug interactions, favored by patient individual conditions such as renal failure or pharmacogenomics, can be however detected by a systematic analysis of drug properties as demonstrated in the case of apixaban interactions. This analysis was efficiently supported by the MDDI Calculator of SCHOLZ Databank representing AI powered technology probably appropriate to save huge amounts of financial funds for pharmacokinetic in-vivo research and ready to improve drug safety by providing decision support in billions of unknown medication scenarios, including especially polypharmacy.

References

1. Nicholas Favatella, David Dalton, Wonkyung Byon, Samira J Merali, Christian Klem. Clinical Implications of Co-administering Apixaban with Key Interacting Medications. Clin Pharmacol Drug Dev. 2024;13(9):961-973.
2. Isoherranen N, Lutz JD, Chung SP, Hachad H, et al. Importance of multi-p450 inhibition in drug-drug interactions: evaluation of incidence, inhibition magnitude, and prediction from in vitro data. Chem Res Toxicol. 2012;25:2285–300.
3. Niemi M, Backman JT, Neuvonen M, Neuvonen PJ. Effects of gemfibrozil, itraconazole, and their combination on the pharmacokinetics and Pharmacodynamics of repaglinide: potentially hazardous interaction between Gemfibrozil and repaglinide. Diabetologia. 2003;46:347–35.
4. Niemi M, Tornio A, Pasanen MK, Fredrikson H, et al. Itraconazole, gemfibrozil and their combination markedly raise the plasma concentrations of loperamide. Eur J Clin Pharmacol. 2006;62:463–72.
5. Prescriber Information Eliquis 04/2025.
6. User Manual of SCHOLZ DataBank ADR.
7. Scholz WU. About Pharmacokinetics of Drugs due to Multiple Drug-drug Interactions (MDDI); original in german: Zur Pharmakokinetik von Arzneimitteln bei multiplen Interaktionen – Theoretische Überlegungen und praktische Umsetzung. Krankenhauspharmazie. 2016;37:497–505.
8. Wolfgang Scholz, Stefanie Brune. Severe Rhabdomyolysis through concomitant Administration of Simvastatin, Amlodipine, and Ciprofloxacine; original in german: Schwere Rhabdomyolyse bei Kombination von Simvastatin, Amlodipin und Ciprofloxacin – Interpretation eines Fallberichts mit einer Interaktionssoftware; Arzneimitteltherapie. 2016;34(1):S2-7.
9. Luecht UR, Scholz W, Geiben AK, Haen E, Hempel G. Physiologically Based Pharmacokinetic Model of CYP2D6 Associated Interaction Between Venlafaxine and Strong Inhibitor Bupropion—The Influence of Age-Relevant Changes and Inhibitory Dose to Classify Therapeutical Success and Harm. Pharmaceutics. 2025:17(2);179.
10. https://scholzdatabank.com/blog/all/the-mddi-technology-of-scholz-databank-and-its-impact-on-drug-safety-when-prescribing-vortioxetine
11. https://scholzdatabank.com/blog/all/when-decision-support-is-needed-beyond-the-

prescriber-information-the-api-xaban- eliquis-case

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