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Case Presentation

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Loperamide: Death by Lemonade and Conclusions for E-prescribing

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Introduction

Loperamide is a peripherally effective μ-opioid receptor agonist, which is frequently used for the therapy of diarrhea. In normal dose loperamide has no central opioid effects. This is due to the efflux transporter P-gp, which transports any loperamide at the blood-brain barrier back to the peripheral blood system which might have been absorbed before from the blood capillaries into the endothelial cells. If P-gp in these cells is blocked, however, loperamide may penetrate the CNS and develop opioid effects including central and respiratory depression. This is probably the mechanism which was responsible for the fatal outcome of the following case published in the german journal "NeuroTransmitter" under the original title "Tod durch Limonade" (Death by Lemonade) [1].

Case Presentation

A woman taking in total three 2-mg-tablets loperamide prescribed because of a diarrhea consumed on the same day 2.5 l Tonic Water containing about 60 mg/l quinine, in total about 170mg quinine. She got tired and went to sleep, half an hour later she was found unconscious by her partner. A reanimation was done by an emergency physician, however, when hospitalized in the intensive care unit only her death could be diagnosed. A toxicological blood analysis revealed loperamide and elevated quinine concentrations.

Discussion

Loperamide was administered with three 2-mg-tablets in recommended dose. It is an avid substrate of P-gp [2] and quinine is an effective P-gp inhibitor [3-5]. It was assumed that the loperamide concentration in the brain increased that high due to the P-gp inhibition through quinine that the opioid effects of loperamide with strong central and respiratory depression led to death. This assumption is in line with experimental data showing that loperamide brain concentrations may be elevated due to P-gp inhibition by the 2.3 to 5.8-fold resulting in the most pronounced opioid-induced clinical signs [6]. Insofar the result of a literature review from 2010 must be questioned which states that there is insufficient evidence for loperamide in normal therapeutic doses to induce CNS

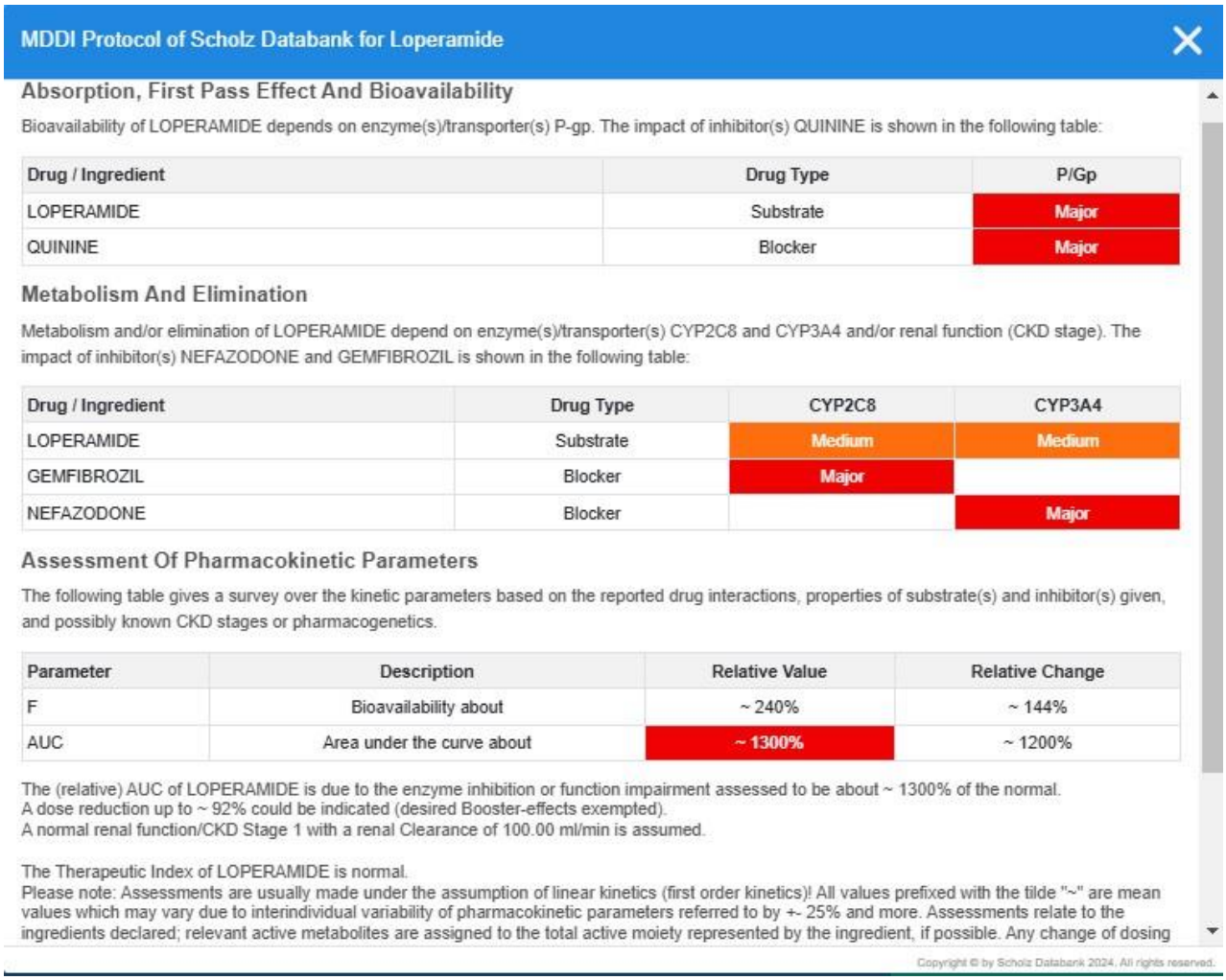
depression and toxicity due to P-gp inhibition [2]. QT prolongation is an issue to be discussed in this context, too. Electrocardiographic abnormalities have been reported for quinine and other quinolines such as quinidine and hydroxychloroquine including QT prolongation and/or Torsade de pointes [7]; a consumption of tonic water with 170mg quinine means however less than a regular quinine capsule which contains 300 – 324 mg active ingredient per capsule, as malaria medication usually administered in adults with two capsules every 8 hours per day [8]. The prescriber information for quinine lists Long QT syndrome as contraindication and warns about drug drug interactions with drugs such as Class 1A and Class III antiarrhythmics or macrolides which are known for clinically relevant QT prolongation [8]. A PubMed search did not explicitly hint to a drug interaction between loperamide and quinine. Loperamide is classified as relatively safe at therapeutic doses and cases of QT prolongation including ventricular arrhythmia and Torsades de pointes known are assigned to misuse and abuse with very high drug doses [9-11]. Therefore a QT prolongation related drug interaction was probably not the reason for the fatal outcome described in the case. However, severe electrolyte deficiencies which might develop in the course of a diarrhea should always be considered as trigger of ventricular arrhythmias.

Consequently the concomitant use of loperamide with other drugs which are potent P-gp inhibitors such as naproxen or dronedarone should be reconsidered as well as with drugs which may cause multiple interactions when inhibiting P-gp and additionally CYP450-enzymes such as CYP3A4 or CYP2C8 as these enzymes are also involved in the metabolism of loperamide. Pharmacokinetic in-vivo studies revealed substantial increases of loperamide exposure when loperamide was administered concomitantly either with itaconazole or with gemfibrozil or with both drugs. Whereas itraconazole - a strong CYP3A4 and P-gp inhibitor - caused alone an increase of the loperamide plasma levels and the AUC to the 3.8-fold and gemfibrocil as a strong CYP2C8 inhibitor alone caused an increase of the loperamide AUC to the 2.2-fold, the result of the triple combo was a substantially higher loperamide AUC increase to the 12.6-fold [12]. Such high unexpected elevations of drug exposure due to multiple drug drug interactions were the trigger to start some ten years ago the development of the multi drug drug interaction "MDDI" Calculator of SCHOLZ DataBank which makes assessments of drug exposure increases based on the multiple interactions due to the kinetically relevant substrate and/or inhibitor properties of the drugs involved [13]. Multi drug interactions which might result in elevated loperamide exposures are listed in the following table, for example:

Drugs involved	**Drug affected**	**Assessment of Relative AUC**	**P-gp**	**CYP2C8**	**CYP3A4**
Loperamide–gemfibrocil–itraconazole	Loperamide	1290%##	+++	+++	+++
Loperamide–gemfibrocil–nefazodone– Tonic Water	Loperamide	1300%# seePicture1	+++	+++	+++
Loperamide–gemfibrocil –TonicWater	Loperamide	500%#,	+++	+++	
Loperamide–verapamil–TonicWater	Loperamide	300%#	+++		++

#: assessment by SCHOLZ Databank [14]; ##: assessment in line with in-vivo data [12].

Picture1:



MDDI Protocol of Scholz Databank for Loperamide

Absorption, First Pass Effect And Bioavailability

Bioavailability of LOPERAMIDE depends on enzyme(s)/transporter(s) P-gp. The impact of inhibitor(s) QUININE is shown in the following table:

Drug / Ingredient	Drug Type	P/Gp
LOPERAMIDE	Substrate	Major
QUININE	Blocker	Major

Metabolism And Elimination

Metabolism and/or elimination of LOPERAMIDE depend on enzyme(s)/transporter(s) CYP2C8 and CYP3A4 and/or renal function (CKD stage). The impact of inhibitor(s) NEFAZODONE and GEMFIBROZIL is shown in the following table:

Drug / Ingredient	Drug Type	CYP2C8	CYP3A4
LOPERAMIDE	Substrate	Medium	Medium
GEMFIBROZIL	Blocker	Major	
NEFAZODONE	Blocker		Major

Assessment Of Pharmacokinetic Parameters

The following table gives a survey over the kinetic parameters based on the reported drug interactions, properties of substrate(s) and inhibitor(s) given, and possibly known CKD stages or pharmacogenetics.

Parameter	Description	Relative Value	Relative Change
F	Bioavailability about	~ 240%	~ 144%
AUC	Area under the curve about	~ 1300%	~ 1200%

The (relative) AUC of LOPERAMIDE is due to the enzyme inhibition or function impairment assessed to be about ~ 1300% of the normal.
A dose reduction up to ~ 92% could be indicated (desired Booster-effects exempted).
A normal renal function/CKD Stage 1 with a renal Clearance of 100.00 ml/min is assumed.

The Therapeutic Index of LOPERAMIDE is normal.
Please note: Assessments are usually made under the assumption of linear kinetics (first order kinetics)! All values prefixed with the tilde "~" are mean values which may vary due to interindividual variability of pharmacokinetic parameters referred to by +- 25% and more. Assessments relate to the ingredients declared; relevant active metabolites are assigned to the total active moiety represented by the ingredient, if possible. Any change of dosing

Conclusions for E-prescribing

This case demonstrates another time that not only drug drug interactions but also drug - food and drug - beverage interactions cause possibly serious adverse drug effects with fatal outcome. Therefore, when e-prescribing or dispensing drugs, providers should rely on decision support systems supported by drug interaction checkers focusing not only on drug to drug interactions but also on drug to food and beverage interactions. The complexity of medication scenarios, in particular in polypharmacy, requires furthermore that multiple mechanism driven interactions where diverse enzymes and transporters are involved become instantly transparent to the doctor or the pharmacist.

SCHOLZ DataBank **[14]** is a U.S. drug database supporting e-prescribing with a strong focus on avoiding drugs risks, in particular adverse drug effects due to drug interactions as well as pharmacogenetics and stages of renal failure/CKD of the patient. Users are enabled to enter drugs as well as relevant food or beverages to check for traditional pair wise and for complex multiple drug interactions. The listing of food and beverages consists for example of alcohol containing beverages such as Cognac, Gin, Wine, Whisky, or Chianti, containing additionally tyramine interacting with MAO inhibitors. Due to the case described and the underlying mechanism Tonic Water and Bitter Lemon have been added to this listing in order to help to avoid the hidden and possibly fatal drug food interaction between loperamide and quinine contained in lemonades.

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