Concomitant use of tamoxifen and endoxifen in postmenopausal early breast cancer: prediction of plasma levels by physiologically-based pharmacokinetic modeling

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Abstract

Purpose: To overcome cytochrome P450 2D6 (CYP2D6) mediated tamoxifen resistance in postmenopausal early breast cancer, CYP2D6 phenotype-adjusted tamoxifen dosing in patients with impaired CYP2D6 metabolism and/or the application of endoxifen, the most potent tamoxifen metabolite, are alternative treatment options. To elucidate both strategies comprehensively we used a physiologically-based pharmacokinetic (PBPK) modeling approach.

Methods: Firstly simulation of increasing tamoxifen dosages was performed by a virtual clinical trial including populations of CYP2D6 poor (PM), intermediate (IM) and extensive metabolizers (EM) (N = 8,000). Secondly we performed PBPK-simulations under consideration of tamoxifen use plus concomitant increasing dosages of endoxifen (N = 7,000).

Results: Our virtual study demonstrates that dose escalation of tamoxifen in IMs resulted in endoxifen steady-state plasma concentrations similar to CYP2D6 EMs whereas PMs did not reach EM endoxifen levels. Steady-state plasma concentrations of tamoxifen, N-desmethyl-tamoxifen, 4-hydroxy-tamoxifen and endoxifen were similar in CYP2D6 IMs and PMs versus EMs using once daily dosing of 20 mg tamoxifen and concomitant CYP2D6 phenotype-adjusted endoxifen dosing in IMs and PMs (1 mg/d and 3 mg/d, respectively).

Conclusion: In conclusion, we suggest that co-administration of endoxifen in tamoxifen treated early breast cancer women with impaired CYP2D6 metabolism is a promising alternative to reach plasma concentrations comparable to CYP2D6 EM patients.

Keywords: Postmenopausal breast cancer; Tamoxifen-endoxifen-combination; CYP2D6 genotype; PBPK modeling

Introduction

The efficacy of the selective estrogen receptor modulator tamoxifen, the backbone of the treatment of estrogen receptor positive early breast cancer in postmenopausal women, is based on its bio-activation to 4-hydroxylated metabolites by hepatic cytochrome P450 (CYP) enzymes (Brauch et al. 2009). Its anti-cancer activity is mainly attributed to the (Z)-endoxifen isomer with an almost identical anti-estrogenic activity compared to (Z)-4-hydroxytamoxifen (4OH-TAM) but 5- to 10-fold higher steady state plasma concentrations (C_{ss}) in patients (Lim et al. 2005; Wu et al. 2009).

Cytochrome P450 2D6 (CYP2D6) is highly polymorphically expressed in humans and involved in crucial steps of the formation of endoxifen [Figure 1] (Brauch et al. 2009). The majority of endoxifen arises from the primary tamoxifen metabolite N-desmethyaltamoxifen (NDM-TAM) via 4-hydroxylation exclusively mediated by CYP2D6 (Desta et al. 2004). To date, more than one hundred CYP2D6 alleles have been described (http://www.cypalleles.ki.se/cyp2d6.htm) resulting into four different phenotypes:
ultra-rapid metabolizers (UM; increased enzyme activity), extensive metabolizers (EM; normal enzyme activity), intermediate metabolizers (IM; decreased enzyme activity) and poor metabolizers (PM; abolished enzyme activity). The CYP2D6 genotype-phenotype concordance rate is excellent which has been extensively studied (for review see (Zanger and Schwab 2013)). Based on clinical studies there is an increasing body of evidence that the \textit{in vivo} metabolism of tamoxifen in postmenopausal early breast cancer depends on CYP2D6, thereby altering tamoxifen response (Brauch et al. 2013a, 2013b; Brauch and Schwab 2013). Patients stratified genetically into CYP2D6 IMs or PMs using the patient’s germline DNA showed a significant gene-dose-dependent decrease in the formation of endoxifen plasma concentrations compared with EM patients (Borges et al. 2006; Kiyotani et al. 2010; Mürdter et al. 2011; Lim et al. 2011). For instance, higher endoxifen levels correlated with a significant reduction of breast cancer recurrence rate (26%) in the Women’s Healthy Eating and Living (WHEL) trial (Madlensky et al. 2011), and IM and PM women were more likely to be in the low endoxifen bottom quintile group with an increased risk for recurrence. Moreover, data from a clinical multicenter trial support the notion that a \textit{CYP2D6} genotype-guided tamoxifen dosing approach significantly rises endoxifen levels in IM and PM patients by doubling the daily dose from 20 mg to 40 mg. Of note, only IMs reach endoxifen levels comparable to those of EM patients receiving the standard dose (Irvin et al. 2011). Finally, direct administration of endoxifen to bypass \textit{CYP2D6}-dependent bio-activation and to reduce inter-individual variability of endoxifen \textit{C}_{ss} levels (Ahmad et al. 2010) may be an attractive alternative in treatment of postmenopausal breast cancer.

Physiologically-based pharmacokinetic (PBPK) modeling provides a knowledge-based approach to mechanistically describe the pharmacokinetics (PK) as well as the pharmacodynamics (PD) of drugs (Zhao et al. 2012; Eissing et al. 2011). Implementing genotype-specific enzyme activities (e.g. \textit{CYP2D6}), PBPK models can be parameterized to predict the impact of different enzyme phenotypes on PK as well as PD data (Dickschen et al. 2012). Here, we present a PBPK model-based virtual clinical trial for \textit{CYP2D6} phenotype-dependent dosing of tamoxifen plus the concomitant use of endoxifen in early postmenopausal breast cancer. The virtual study aims to establish a dose algorithm providing similar tamoxifen metabolic patterns in \textit{CYP2D6} IM or PM \textit{versus} EM patients using different dosing strategies. Ultimately, the PBPK modeling approach offers a new dimension in providing personalized treatment strategies for tamoxifen in early breast cancer with implications for future clinical trials.

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**Figure 1 Simplified biotransformation scheme of tamoxifen in man.** Tamoxifen is mainly N-demethylated to NDM-TAM and subsequently 4-hydroxylated to endoxifen. A minor pathway proceeds via 4-hydroxylation to 4OH-TAM followed by N-demethylation to endoxifen. The polymorphic \textit{CYP2D6} is involved in crucial steps of the endoxifen formation. Abbreviations used in diagram: cytochrome P450 (CYP), sulfonyltransferase (SULT), uridine-5' -diphosphoglucuronyltransferase (UGT), tamoxifen (TAM), N-desmethyltamoxifen (NDM), 4-hydroxytamoxifen (4OH), endoxifen (END).
Materials and methods

Software
The PBPK-models were constructed and coupled by means of the computational systems biology software platform including PK-Sim® 4.2.4 and MoBi® 2.3.5 (Bayer Technology Services GmbH, Leverkusen, Germany; www.systems-biology.com/products).

Population simulations were conducted using the MoBi® Toolbox for MATLAB® 2.2 (Bayer Technology Services GmbH, Leverkusen, Germany; www.systems-biology.com/products with MATLAB® from The MathWorks, Inc., Natick, USA; www.mathworks.com/products/matlab).

Virtual clinical trial design
The recently published genotype-guided tamoxifen dose algorithms for CYP2D6 IMs and PMs to achieve tamoxifen metabolic pattern comparable to CYP2D6 EM patients (Dickschen et al. 2012). Three different dosing regimens (see below) were evaluated in the virtual populations of CYP2D6 EMs, IMs and PMs (N = 1,000, each), representing the major CYP2D6 phenotypes. The results of the simulated administration protocols were compared to corresponding clinical median trough C\text{ss} level taken from the literature (Mürdter et al. 2011; Madlensky et al. 2011; Irvin et al. 2011; Gjerde et al. 2010, 2008).

Study group A: tamoxifen standard dose regimen
The standard dose regimen of 20 mg tamoxifen once daily was simulated for a period of twelve months in all three CYP2D6 phenotype populations (N = 1,000, each).

Study group B: tamoxifen dose escalation
The recently published genotype-guided tamoxifen dose escalation regimen for CYP2D6 IMs and PMs (Irvin et al. 2011) was simulated in 1,000 cases, respectively. Hence, firstly we simulated four months once daily dosing of 20 mg tamoxifen followed by four months dosing using 20 mg tamoxifen applied twice daily. Secondly, four months once daily dosing using 20 mg tamoxifen followed by four months dosing of 40 mg tamoxifen once daily was assessed again in IMs and PMs. Finally, four months once daily dosing of 20 mg tamoxifen followed by four months once daily dosing using 60 mg tamoxifen in CYP2D6 PM was investigated by using the PBPK-model.

Study group C: tamoxifen-endoxifen fixed-dose combination
A novel treatment strategy was used combining a fixed-dose of the parent drug tamoxifen together with the different dosages of the active metabolite endoxifen in CYP2D6 IMs and PMs for a period of twelve months.

The rationale behind this strategy of concomitant use of tamoxifen plus endoxifen was to achieve not only similar plasma levels of endoxifen but also of tamoxifen, NDM-TAM and 4OH-TAM in IMs and PMs comparable to CYP2D6 EM patients. In all exploratory simulations, the standard dose of 20 mg tamoxifen was kept constant and three concomitant endoxifen doses ranging from 0.5 mg to 1.5 mg once daily were investigated in CYP2D6 IMs (N = 1,000, each). In CYP2D6 PMs, four endoxifen doses ranging from 1.0 mg to 4.0 mg once daily were simulated (N = 1,000, each).

Thus, a total of 15 different simulation protocols for the three CYP2D6 phenotypic groups were investigated resulting in simulation data of 15,000 virtual European female early breast cancer patients. The virtual trial designs investigated are illustrated in Figure 2. From these simulations median trough C\text{ss} and percentiles were calculated assuming that data are not normally distributed.

Results

Study group A: tamoxifen standard dose regimen
The previously developed and validated CYP2D6 phenotype specific PBPK model describing the formation of endoxifen via tamoxifen in European breast cancer patients was applied in a virtual clinical trial to establish model based dose algorithms for CYP2D6 IMs and PMs to achieve tamoxifen metabolic pattern comparable to CYP2D6 EM patients (Dickschen et al. 2012). Three different dosing regimens (see below) were evaluated in the virtual populations of CYP2D6 EMs, IMs and PMs (N = 1,000, each), representing the major CYP2D6 phenotypes. The results of the simulated administration protocols were compared to corresponding clinical median trough C\text{ss} level taken from the literature (Mürdter et al. 2011; Madlensky et al. 2011; Irvin et al. 2011; Gjerde et al. 2010, 2008).

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Likewise, simulated 4OH-TAM trough $C_{ss}$ in CYP2D6 IMs correspond to the 4OH-TAM reference range in CYP2D6 EMs. However, simulated trough $C_{ss}$ levels of tamoxifen and NDM-TAM significantly exceed the reference values in CYP2D6 EMs [Figure 4].

Generally, tamoxifen dose escalation in CYP2D6 PMs increases the median endoxifen trough $C_{ss}$ in the PBPK-model in line with data from a clinical study (Irvin et al. 2011). However, using the three different dose escalation regimens all simulated median trough $C_{ss}$ of endoxifen are constantly lower compared to the 25th percentile of the simulated reference endoxifen trough $C_{ss}$ in CYP2D6 EMs (PBPK model 25th percentile: 14.08 μg/L). The dose escalation regimen of 20 mg tamoxifen twice daily and 40 mg tamoxifen once daily even results in median trough $C_{ss}$ of endoxifen (6.8 μg/L; 8.14 μg/L) that only match the 5th percentile of the simulated reference $C_{ss}$ of endoxifen in CYP2D6 EMs (7.5 μg/L). Simulated 4OH-TAM trough $C_{ss}$ in CYP2D6 PMs regarding to both dose escalation regimens (20 mg tamoxifen twice daily: 3.9 μg/L; 40 mg tamoxifen once daily: 4.5 μg/L) are similar to the 4OH-TAM reference range (median: 3.8 μg/L) in CYP2D6 EMs, whereas trough $C_{ss}$ levels of tamoxifen and NDM-TAM in CYP2D6 PMs exceed CYP2D6 EM reference levels up to threefold [Figure 4].

**Study group C**: tamoxifen-endoxifen fixed-dose combination

A standard oral dose of once-daily 20 mg tamoxifen and concomitant increasing oral doses of endoxifen were assessed by PBPK simulation. For both phenotypes, CYP2D6 IM and PM, the simulation data indicate that concomitant use of tamoxifen and endoxifen results in systemic exposure levels of tamoxifen, NDM-TAM, 4OH-TAM and endoxifen comparable to those in CYP2D6 EMs.
The fixed-dose combination of 20 mg tamoxifen and 1 mg endoxifen applied once daily results in almost identical median trough $C_{ss}$ of tamoxifen, NDM-TAM, 4OH-TAM, and endoxifen as compared with simulated reference steady-state EM levels [Figure 5].

**Discussion**

CYP2D6 phenotype related alteration of endoxifen plasma levels in tamoxifen treated postmenopausal early breast cancer women is well established and contributes...
to treatment outcome (Borges et al. 2006; Kiyotani et al. 2010; Mürdter et al. 2011; Lim et al. 2011; Madlensky et al. 2011). To overcome an increased risk for breast cancer recurrence in CYP2D6 variant patients two different approaches have been suggested (i) CYP2D6 phenotype-adjusted tamoxifen dosage in CYP2D6 IMs and PMs to achieve similar endoxifen C<sub>ss</sub> compared with EMs and (ii) direct administration of the active metabolite endoxifen which ensures independence from the CYP2D6 polymorphism.

Recently the feasibility of dose adjustment in early breast cancer women was demonstrated by several studies using increasing tamoxifen daily dosages from 20 up to 40 mg in IM and PM patients (Irvin et al. 2011; Barginear et al. 2011; Kiyotani et al. 2012). Whereas in IMs the endoxifen levels reached almost similar concentrations compared to EMs, endoxifen plasma levels in PMs were still significantly lower. This indicates that at least in PMs the concept of dose escalation of tamoxifen up to 40 mg does not seem to be an appropriate alternative in clinical practice.

The sole administration of oral endoxifen instead of tamoxifen appears to be safe and well tolerated in a first-in-man study. Endoxifen is rapidly absorbed and systematically available as shown exemplarily for the dose range of 0.5 to 4.0 mg (Ahmad et al. 2010). Currently some clinical phase 1 trials are ongoing elucidating the use of endoxifen in adults with refractory hormone receptor-positive breast cancer, desmoid tumors, gynecologic tumors, or other hormone receptor-positive solid tumors (ClinicalTrials.gov Identifier: NCT01273168; last access date Nov 18, 2013) or in patients with metastatic

**Figure 5** Results of a virtual clinical trial for tamoxifen-endoxifen fixed dose combination. Box-whisker-plots indicate the percentiles 5, 25, 50, 75, and 95 of the population simulation results. Shaded grey areas represent median and the percentiles 5 and 95 of simulated reference steady-state CYP2D6 EM levels (acc. to Figure 3) as target concentration ranges for all fixed-dose combinations. A standard dosage of 20 mg tamoxifen was used for all simulations. Abbreviations used in diagram: tamoxifen (TAM), N-desmethyltamoxifen (NDM), 4-hydroxytamoxifen (4OH), endoxifen (END), cytochrome P450 2D6 (CYP2D6), intermediate metabolizer (IM), poor metabolizer (PM), fixed-dose combination (FDC).
or locally recurrent ER-positive breast cancer (Clinical-Trials.gov Identifier: NCT01327781; last access date Nov 18, 2013). Nevertheless, such an approach neglects the fact that intermediary metabolites like NDM-TAM and 4OH-TAM or even tamoxifen may have own anti-estrogenic activity, thereby contributing to the antitumoral effects of tamoxifen in vitro and in vivo (Coezy et al. 1982; Maximov et al. 2013).

Therefore, we aimed to establish robust and valid dosage algorithms by a PBPK modeling approach using different virtual trial designs to provide similar tamoxifen metabolic patterns in CYP2D6 IM or PM versus EM patients.

The methodology of PBPK modeling and its increasingly important role in drug development has been extensively reviewed during the past few years (Huang and Rowland 2012; Leong et al. 2012). The mechanistic and knowledge-based approach of PBPK modeling enables simulations and predictions providing insight into scenarios faster, cheaper, or easier than experimentally feasible (Edginton et al. 2006; Willmann et al. 2009). The impact of PBPK modeling in clinical decision support for selected populations are extensively outlined recently (Zhao et al. 2012; Kersting et al. 2012; Willmann et al. 2013). Furthermore, the impact of CYP2D6 pharmacogenomics on PK has been studied as well for codeine, a classical CYP2D6 substrate, using a mechanistic PBPK-model (Willmann et al. 2009; Eissing et al. 2012).

Our PBPK simulation experiments of increasing tamoxifen dosages in CYP2D6 PMs and IMs demonstrated that dose escalation of tamoxifen to 20 mg twice daily is only sufficient in CYP2D6 IMs in order to attain a median endoxifen C_{ss} comparable to CYP2D6 EM levels. These simulation data are in line with experimental data from a tamoxifen dose escalation trial in early breast cancer women by Irvine et al. (Irvin et al. 2011) corroborating the validity of our PBPK modeling approach. However in CYP2D6 PMs dose escalation of tamoxifen to 20 mg twice daily is not sufficient to reach the median endoxifen C_{ss} simulated and observed in CYP2D6 EMs. Virtual dose escalation even up to 60 mg tamoxifen once daily indicates that comparable median CYP2D6 EM endoxifen C_{ss} levels will not be achieved supporting the predominant role of CYP2D6 in the formation of endoxifen.

Although tamoxifen is well tolerated it remains unclear on whether high doses of tamoxifen may result in long-term detrimental effects like an increased risk for endometrial cancer or thromboembolic event. For instance it has been reported that high dose tamoxifen in the management of various cancers is associated with severe side effects or even increased mortality (Decaudin et al. 2004; Puchner et al. 2004; Bourla et al. 2007). Of note, our simulation data of tamoxifen dose escalation in CYP2D6 IMs and PMs indicate that plasma levels of tamoxifen as well as NDM-TAM are 3-times higher compared to levels in CYP2D6 EMs using 20 mg tamoxifen standard dosage. These simulated plasma levels are in line with data reported in patients using standard tamoxifen therapy independent from ethnicity (Mürdter et al. 2011; Lim et al. 2011; Kiyotani et al. 2012). Although the evidence is lacking that long-term side effects of tamoxifen treatment are directly linked to elevated tamoxifen metabolite levels (e.g. NDM-TAM), the strategy of dose escalation of tamoxifen, preferable in CYP2D6 IMs, needs further evaluation.

Since short-cutting of tamoxifen adjuvant endocrine therapy by direct administration of endoxifen might result in missing beneficial effects of tamoxifen itself and primary metabolites (Maximov et al. 2013), we next simulated a concomitant administration of tamoxifen standard dosage (20 mg/d) plus increasing dosages of endoxifen by the PBPK model. Using fixed-dose combinations we established an optimal dose algorithm for European female CYP2D6 IMs and PMs to achieve a comparable pattern of tamoxifen metabolite levels compared to CYP2D6 EMs. Interestingly, CYP2D6 IMs displayed similar C_{ss} of tamoxifen, NDM-TAM, 4OH-TAM, and endoxifen when receiving a fixed-dose combination of 20 mg tamoxifen plus 1 mg endoxifen once daily. In contrast 20 mg tamoxifen plus 3 mg endoxifen are required in CYP2D6 PMs to achieve similar plasma levels of tamoxifen, NDM-TAM, 4OH-TAM, and endoxifen as compared with EMs.

Conclusion

Taken together, data from our virtual clinical trial exemplarily demonstrate how PBPK modeling can be used as a valid tool to gain deeper insight into pharmacokinetic properties of tamoxifen and its metabolites in early breast cancer patients. The simulation data indicate a novel dosing strategy of concomitant use of tamoxifen standard dosage plus CYP2D6 phenotype-adjusted endoxifen dosing as a feasible approach to overcome differences in tamoxifen metabolite levels. Thus, the tamoxifen-plus-endoxifen approach versus tamoxifen or endoxifen monotherapy offers a new avenue in treatment of early breast cancer women. Future proof-of-concept clinical trials are warranted.

Competing interests

K.D., T.E. and S.W. are employees of Bayer Technology Services (BTS) GmbH that owns and commercializes the simulation software platform (PK-Sim® and MGB®). T.E. and S.W. are potential stock owners of Bayer Technology Services GmbH. A patent for fixed-dose combinations of tamoxifen and endoxifen has been filed by K.D., T.E. and S.W. G.H. and K.D. during her PhD received funding from Bayer Technology Services GmbH. The authors acknowledge financial support by the Federal Ministry for Education and Research (BMBF), Germany (grant 0315747 [Virtual Liver]), the German Research Foundation (DFG, MU1727/2-1), the 7FP EU Marie Curie
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Authors’ contributions
K.D. developed the coupled tamoxifen-endoxifen model and performed all simulations. M.S. and T.M. provided clinical data for the establishment and qualification of the model. The concept for the virtual clinical trial was developed by K.D., T.E., and S.W. The results of the simulations were jointly discussed between all authors. The presented work was part of K.D.'s PhD thesis under the supervision of G.H. All authors contributed to the writing of the manuscript and read and approved the final manuscript.

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References
Ahmad A, Shahabuddin S, Sheikh S, Kale P, Krishnappa M, Rane RC, Ahmad J (2010) Endoxifen, a new cornerstone of breast cancer therapy: demonstration of safety, tolerability, and systemic bioavailability in healthy human subjects. Clin Pharmacol Ther 88(6):814–7
Barginear MF, Jaremkó M, Peter I, Yu C, Kasai Y, Kemeny M, Rapits G, Desnick RJ (2011) Increasing tamoxifen dose in breast cancer patients based on CYP2D6 genotypes and endogenous levels: effect on active metabolite isomers and the antiestrogenic activity score. Clin Pharmacol Ther 90(4):626–11
Borges S, Desta Z, Li L, Skaar TC, Ward BA, Nguyen A, Jin Y, Storniolo AM, Nikoloff DM, Wu L, Hillman G, Hayes DF, Steams V, Flockhart DA (2006) Quantitative implication for CYP2D6 genotype and inhibitors on tamoxifen metabolism: implication for optimization of breast cancer treatment. Clin Pharmacol Ther 80(1):61–74
Boura DH, Saraf D, Schwartz SD (2007) Peripheral retinopathy and maculopathy in high-dose tamoxifen therapy. Ann J Ophthalmol 144(1):126–8
Brauch H, Schwab M (2013) Prediction of tamoxifen outcome by genetic variation of CYP2D6 in postmenopausal women with early breast cancer. Br J Clin Pharmacol 77(4):695–703
Brauch H, Murdter TE, Eichelbaum M, Schwab M (2009) Pharmacogenomics of tamoxifen therapy. Chem Clin 55(10):1770–82
Brauch H, Schroth W, Goetz MP, Murdter TE, Winter S, Ingle JN, Schwab M, Eichelbaum M (2013a) Tamoxifen use in postmenopausal breast cancer: CYP2D6 matters. J Clin Oncol 31(2):76–80
Brauch H, Schroth W, Goetz MP, Murdter TE, Winter S, Ingle JN, Schwab M, Eichelbaum M (2013b) Reply to A.-S. Dieudonne et al. and J.M. Rae et al. Kuepfer L (2012) A mechanistic, model-based approach to safety assessment of tamoxifen endoxifen metabolites in women of different CYP2D6 phenotypes provides new insight into the tamoxifen mass balance. Front Pharmacol 2012 May 21 3:92 Edginton AN, Willmann S (2008) Physiology-based simulations of a pathological condition: prediction of pharmacokinetics in patients with liver cirrhosis. Clin Pharmacokinet 47(11):731–52
Edginton AN, Schmitt W, Willmann S (2006) Development and evaluation of a genetic physiologically based pharmacokinetic model for children. Clin Pharmacokinet 45(10):1013–34
Eissing T, Kuepfer L, Becker C, Block M, Coboekens K, Gaub T, Goerlitz L, Jaeger J, Loosen R, Ludewig B, Meyer M, Niederert C, Sevestre M, Siegmund HU, Solodenko J, Thelen K, Telle U, Weiss W, Wendt T, Willmann S, Lippert J (2011) A computational systems biology software platform for multiscale modeling and simulation: integrating whole-body physiology, disease biology, and molecular reaction networks. Front Physiol 2:4
Eissing T, Lippert J, Willmann S (2012) Pharmacogenomics of codeine, morphine, and morphine-6-glucuronide: model-based analysis of the influence of CYP2D6 activity, UGT2B7 activity, renal impairment, and CYP3A4 inhibition. Mol Diagn Ther 16(1):45–53
Gjerde J, Hasuglid M, Breileid H, Lundgren S, Varhaug JE, Kaisa ER, Mellingen G, Steen VM, Lien EA (2008) Effects of CYP2D6 and SULT1A1 genotypes including SULT1A1 gene copy number on tamoxifen metabolism. Ann Oncol 19(1):56–61
Gjerde J, Geisler J, Lundgren S, Ekse D, Varhaug JE, Mellingen G, Steen VM, Lien EA (2010) Associations between tamoxifen, estrogen, and FSH serum levels during steady state tamoxifen treatment of postmenopausal women with breast cancer. BMC Cancer 10:313
Huang SM, Rowland M (2012) The role of physiologically based pharmacokinetic modeling in regulatory review. Clin Pharmacol Ther 91(3):542–9
Irwin WJ Jr, Walco KM, Weck KE, Ibrahim JG, Chiu WK, Dees EC, Moore SG, Olajide OA, Graham ML, Canale ST, Raab RE, Corso SW, Peppercorn JM, Anderson SM, Friedman KJ, Ogbum ET, Desta Z, Flockhart DA, McLeod HL, Evans JP, Carey LA (2011) Genotype-guided tamoxifen dosing increases active metabolite exposure in women with reduced CYP2D6 metabolism: a multicenter study. J Clin Oncol 29(24):3322–32
Kersting G, Willmann S, W urthwein G, Lippert J, Boos J, Hempel G (2012) Physiologically based pharmacokinetic modelling of high- and low-dose etoposide from adults to children. Cancer Chemother Pharmacol 69(2):397–405
Kiyotani K, Mishirodta T, Iramura CK, Hosono N, Tsunoda T, Kubo M, Tanigawa Y, Flockhart DA, Skaar TC, Lim YC, Desta Z, Flockhart DA, Skaar TC, Aki F, Hirata K, Takatsuka Y, Okazaki M, Ohsumi S, Yamakawa T, Sasa M, Nakamura Y, Zembutsu H (2010) Significant effect of polymorphisms in CYP2D6 and ABC2C2 on clinical outcomes of adjuvant tamoxifen therapy for breast cancer patients. J Clin Oncol 28(8):1287–93
Kiyotani K, Mishirodta T, Iramura CK, Tanigawa Y, Hosono N, Kubo M, Sasa M, Nakamura Y, Zembutsu H (2012) Dose-adjustment study of tamoxifen based on on CYP2D6 genotypes in Japanese breast cancer patients. Breast Cancer Res Treat 131(1):137–45
Loe ng R, Veiera ML, Zhao P, Mulugeta Y, Lee CS, Huang SM, Burkett GJ (2012) Regulatory experience with physiologically based pharmacokinetic modeling for pediatric drug trials. Clin Pharmacol Ther 91(5):526–31
Lim YC, Desta Z, Flockhart DA, Skaar TC (2005) Endoxifen (4-hydroxy-N-desmethyl-tamoxifen) has anti-estrogenic effects in breast cancer cells with potency similar to 4-hydroxy-tamoxifen. Cancer Chemother Pharmacol 56(5):471–8
Lim JS, Chen XA, Singh O, Yap YS, Ng RC, Wong NS, Wong M, Lee EJ, Chowbay B (2011) Impact of CYP2D6, CYP3A5, CYP2C9 and CYP2C19 polymorphisms on tamoxifen pharmacokinetics in Asian breast cancer patients. Br J Clin Pharmacol 71(5):731–50
Lippert J, Broich M, von Kampen O, Meyer M, Siegmund HU, Schaafmayer C, Becker T, Laffert B, Görtitz L, Schreiber S, Neuvonen PJ, Niemi M, Hampe J, Kuepfer L (2012) A mechanistic, model-based approach to safety assessment in clinical development. CPT Pharmacometrics Syst Pharmacol 1:13
Madsen L, Natarajan L, Tchou S, Pu M, Mortimer J, Flatt SW, Nikoloff DM, Hillman G, Fontecha MR, Lawrence JH, Parker BA, Wu AH, Pierce JP (2011) Tamoxifen metabolite concentrations, CYP2D6 genotype, and breast cancer outcomes. Clin Pharmacol Ther 89(5):718–26
Maximov PY, McDaniel RE, Jordan VC, Brauch H (2013) Modeling the pharmacological importance of endoxifen for the treatment of ER-positive breast cancer in premenopausal patients. Cancer Res 73(8):5682
Mürdter TE, Schroth W, Bacchus-Gerybadze L, Winter S, Heinkele G, Simon W, Fasching PA, Fehm T, German T, AI Clinicians Group, Eichelbaum M, Schwab
M, Brauch H (2011) Activity levels of tamoxifen metabolites at the estrogen receptor and the impact of genetic polymorphisms of phase I and II enzymes on their concentration levels in plasma. Clin Pharmacol Ther 89(5):708–17

Puchner MJ, Giese A, Lohmann F, Cristante L (2004) High-dose tamoxifen treatment increases the incidence of multifocal tumor recurrences in glioblastoma patients. Anticancer Res 24(8):4195–203

Willmann S, Edginton AN, Coboeken K, Ahr G, Lippert J (2009) Risk to the breast-fed neonate from codeine treatment to the mother: a quantitative mechanistic modeling study. Clin Pharmacol Ther 86(6):634–43

Willmann S, Becker C, Burghaus R, Coboeken K, Edginton A, Lippert J, Siegmund HU, Thelen K, Muck W (2013) Development of a paediatric population-based model of the pharmacokinetics of rivaroxaban. Clin Pharmacokinet 53(1):89–102

Wu X, Hawse JR, Subramaniam M, Goetz MP, Ingle JN, Spelsberg TC (2009) The tamoxifen metabolite, endoxifen, is a potent antiestrogen that targets estrogen receptor alpha for degradation in breast cancer cells. Cancer Res 69(5):1722–7

Zanger UM, Schwab M (2013) Cytochrome P450 enzymes in drug metabolism: regulation of gene expression, enzyme activities, and impact of genetic variation. Pharmacol Ther 138(1):103–41

Zhao P, Rowland M, Huang SM (2012) Best practice in the use of physiologically based pharmacokinetic modeling and simulation to address clinical pharmacology regulatory questions. Clin Pharmacol Ther 92(1):17–20

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