Detection and Prevention of Drug–Drug Interactions in the Hospitalized Elderly: Utility of New Cytochrome P450–Based Software

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ABSTRACT

Background: Polypharmacy increases the risk of cytochrome P450–based drug–drug interactions (CYP450-DDIs), leading to decreased therapeutic efficacy or increased drug toxicity.

Objective: The aims of this study were to investigate the utility of a new CYP450-DDI software, InterMED-Rx, in aiding pharmacists in detecting CYP450-DDIs in hospitalized elderly patients and to ascertain pharmacists' agreement on how to intervene for each CYP450-DDI.

Methods: A consensus panel of geriatric pharmacists first established guidelines for managing clinically relevant pharmacokinetic CYP450-DDIs. A prospective study was then conducted of patients newly admitted to a geriatric hospital whose pharmaceutical profile underwent analysis with InterMED-Rx. Rates and types of interventions were recorded.

Results: Pharmacists' interrater agreement on how to manage CYP450-DDIs was initially only moderate (Cohen's κ, 0.51; 95% CI, 0.39–0.62), but improved subsequent to deliberation (Cohen's κ, 0.79; 95% CI, 0.70–0.88). Persistent disagreement involved interactions between 2 drugs with similar affinities for the same cytochrome. One hundred patients with polypharmacy (≥5 medications) aged 82.3 years (range, 65–96), with a mean (SD) of 12.2 (4.1) drugs (range, 5–27) were recruited for the prospective study. Eighty percent of patients had at least 1 CYP450 DDI detected with InterMED-Rx. A total of 238 CYP450-DDIs were identified involving CYP3A4 (70.2%), CYP2D6 (22.7%), and CYP2C9 (3.4%) substrates or inhibitors. Nineteen percent of patients received immediate medication adjustment, and 39% required follow-up of clinical signs, symptoms, and laboratory tests to determine whether future modification was needed. More than one half (56%) of all patients who required clinical follow-up had further medication adjustment prior to discharge.

Conclusions: Use of the InterMED-Rx software identified elderly patients at risk for pharmacokinetic interactions and facilitated interventions aimed at reducing adverse drug events. Although consensus can be reached among pharmacists on how to intervene for many CYP450-DDI scenarios, certain situations allow for multiple intervention strategies. (*Am J Geriatr Pharmacother*. 2011;9:461–470)

Key words: cytochrome, drug–drug interactions, hospitalized elderly, software.

Accepted for publication September 26, 2011.

doi:10.1016/j.amjopharm.2011.09.006
1543-5946/$ - see front matter

INTRODUCTION

Drug–drug interactions (DDIs) result from medication coadministration in the elderly, leading to hospitalization and adverse outcomes.[1,2] The prevalence of potentially relevant DDIs increases as a function of the number of prescribed drugs, with consumption of 5 to 7 and 8 to 10 drugs incurring a 4-fold and 8-fold greater risk of DDIs, respectively, compared with consumption of 2 to 4 drugs.[3] As rates of polypharmacy (≥5 drugs) continue to increase in the elderly population,[4–6] prevention of DDIs takes on critical importance as an essential component of appropriate prescribing.[7,8]

DDIs frequently involve isoenzymes of the hepatic cytochrome P450 (CYP450) system with resultant alterations in drug bioavailability that can lead to serious adverse events or decreased drug efficacy.[7,9] Although >30 cytochrome enzymes have been identified in humans, 90% of drug oxidation can be attributed to 6 main enzymes: CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4.[10] Drugs can be classified as inducers, inhibitors, or simple substrates of each isoenzyme, based on in vitro testing. Substrates can bind competitively or noncompetitively with low, moderate, or high affinity to their target isoenzyme(s). Genetic variants of some isoenzymes exist, with as many as 10% and 5% of the white population being poor or ultra-rapid metabolizers of CYP2D6 substrates, respectively.[11] In the majority of cases, however, it is coadministration of other drugs that leads to altered hepatic metabolism of isoenzyme substrates and a change in serum concentrations of these agents. An isoenzyme inhibitor or high-affinity substrate will increase the peak concentration of weaker affinity molecules that require oxidation by the same isoenzyme. The clinical significance of this increase will depend on several factors, including the baseline bioavailability of each agent. Agents with high bioavailability will not show immediate clinical effects of an increase in serum concentration, although later effects may develop over time. Agents with low bioavailability will display more immediate pharmacokinetic changes because of reduced isoenzyme metabolism. As a patient's pharmaceutical regimen becomes more complex, the added influence of multiple substrates competing for the same isoenzyme becomes more difficult to anticipate.

No formal guidance exists for ascertaining the clinical significance of pharmacokinetic CYP450-DDIs, nor are algorithms readily available to suggest what type of interventions are necessary to prevent adverse outcomes. Guidance concerning acceptable levels of pharmacokinetic alteration can at best be extrapolated from regulatory definitions of bioequivalence for generic medication. According to the US Food and Drug Administration and regulations applicable in the European Economic Area and in Australia, bioequivalence is considered present when 90% CIs lie between 80% and 125% of the original drug's pharmacokinetic bioavailability parameters such as the AUC, its C_{max}, and T_{max}.[12–14]

InterMED-Rx, a new CYP450-based software program, was designed to detect CYP450-DDIs that produce pharmacokinetic alterations in bioavailability in excess of a conservative bioequivalence standard of ±30% in the context of polypharmacy. InterMED-Rx analyzes all drugs simultaneously, showing their relative affinities for the different CYP isoenzymes, as well as the expected baseline bioavailability of each medication. The output from InterMED-Rx is fueled by pharmacokinetic principles instead of case reports from the literature. Its advantage over other drug interaction alert software lies in its ability to show complex cytochromic interactions among all substrates of the same isoenzyme instead of simple 2-drug interactions. InterMED-Rx does not provide recommendations for medication adjustment; the software serves as an adjunct to pharmacists to aid medication risk assessment on an individual basis. The pharmacist must then use clinical acumen to decide whether each CYP450-DDI warrants clinical intervention.

The purpose of this study was 2-fold. The first objective was to reach agreement among an expert panel of geriatric pharmacists on guiding principles for intervention for CYP450-DDIs detected by the InterMED-Rx software. The second objective was to implement the InterMED-Rx software program in a geriatric hospital to determine the frequency of pharmacokinetic CYP450-DDIs as well as the proportion of interactions that necessitated intervention according to the formulated guidelines for preventing CYP450-DDI–related adverse outcomes.

METHODS

Consensus Development on CYP450-DDI

A consensus panel of 2 experienced geriatric pharmacists, 1pharmacokinetics expert, 1 geriatrician, and 2 graduate pharmacy residents was formed to agree on principles for intervention for CYP450-DDIs detected by the InterMED-Rx software. The first step of the process took place 2 weeks before the consensus meeting. Two pharmacy residents selected a convenience sample of 73 patients aged 65 years and older with polypharmacy (≥5 prescription drugs) admitted to the hospital wards of a large academic hospital and ran their drug profiles through InterMED-Rx for analysis of potential CYP450-DDIs. An InterMED-Rx printout for each patient was distributed to the 2 geriatric pharmacists on the panel, who were blinded to the patient identities.

Only the reason for hospital admission and the InterMED-Rx printouts were provided. All CYP450-DDIs identified by InterMED-Rx were pharmacokinetically significant, as defined by alterations in bioavailability of the weaker substrate in excess of a conservative bioequivalence standard of ±30%. Expected single-drug bioavailabilities for each medication were provided. Each pharmacist was asked to independently rate the clinical significance of the various CYP450-DDIs that were identified by InterMED-Rx. Clinical significance was defined as the need for monitoring or medication adjustment to reduce the risk of potential adverse outcomes. No restrictions were imposed on the type of adverse outcome that could occur. Any deleterious health event such as falls, confusion, and hemorrhagic stroke, as well as their heralding clinical signs, symptoms, or laboratory abnormalities (for example, tachycardia, dizziness, somnolence, increased international normalized ratio) were considered relevant. Based on the risk of adverse outcomes, the pharmacists were asked to rate whether each CYP450-DDI was clinically significant (yes or no), and to describe how they would intervene to reduce patient risk. Potential interventions included follow-up of clinical signs, symptoms, or laboratory tests; a change in the timing of administration of the drug; dose modification; substitution; and complete discontinuation of the drug class.

The ratings for each CYP450-DDI were collected by the pharmacy residents, and concordance between the 2 pharmacists was calculated using Cohen's κ coefficient with 95% CIs to measure interrater agreement. Cohen's κ (weighted Fleiss coefficient) is a more robust measure than the simple percent agreement calculation between 2 raters because it takes into account the agreement occurring by chance.[15] A κ coefficient of 1 indicates perfect agreement and −1 indicates perfect disagreement. The members of the consensus panel then convened to discuss the cases in which disagreement occurred.

The last step of the consensus process entailed the creation of broad guidance for 4 different CYP450-DDI pharmacokinetic scenarios: CYP450-DDIs in which the substrates have the same affinity for a given isoenzyme, CYP450-DDIs in which the substrates have different affinities for a given isoenzyme, CYP450-DDIs that involve a cytochrome inhibitor, and CYP450-DDIs that involve a cytochrome inducer. The different scenarios were discussed and recommendations were made based on the pharmacists' experience, basic pharmacokinetic principles, and the risk–benefit ratio of each possible CYP450-DDI scenario within different patient contexts. In many instances, several possible interventions were posited for a given DDI scenario, including no change required.

Clinical Testing

The utility of InterMED-Rx was tested at a subacute care geriatric hospital in the Greater Montreal area, where standard drug alert software was already in place. The pharmaceutical profiles from a prospective cohort of consecutive new patients aged 65 years and older who were taking at least 5 different prescription medications were analyzed at admission with the InterMED-Rx software over an 11-week period in 2009. All routes of drug administration were considered. A research student recorded the frequency and type of CYP450-DDI identified by InterMED-Rx for each patient. The pharmacist on duty analyzed the InterMED-Rx printout according to the pharmacokinetic principles suggested in the guidelines and determined whether an intervention was required. The research student recorded the pharmacist's judgment for each CYP450-DDI and documented which of the following interventions were performed: follow-up of clinical signs, symptoms, or laboratory tests; a change in the timing of administration of the drug; dose modification; substitution; complete discontinuation of the drug class; or no change. Patients for whom clinical follow-up was recommended were reviewed at the time of discharge to determine whether further interventions were required. The study was approved by the Director of Professional Services at the hospital per the institution's ethics board requirements.

RESULTS

Consensus Development on CYP450-DDI

During the initial interrater concordance evaluation of CYP450-DDIs, 73 patient profiles with a total of 225 CYP450-DDI were presented to the 2 geriatric pharmacists. Medication profiles included a wide range of medication classes including selective serotonin reuptake inhibitors, β-blocking agents, antihistamines, antibiotics, antiarrhythmic drugs, cholinesterase inhibitors, tricyclic antidepressants, antiepileptic drugs, statins, antipsychotics, and calcium channel blockers, among others. The pharmacists were in agreement that 58% of CYP450-DDIs were potentially clinically significant and required an intervention, whereas 20% did not. The weighted κ coefficient was 0.51 with 95% CIs ranging from 0.39 to 0.62, indicating moderate agreement. Disagreement occurred in 22% of cases. We noted a trend in which pharmacists concurred that interventions were usually required when the CYP450-DDIs involved 1 medication that acted as a CYP450 inhibitor and another medication with affinity for the same cytochrome. Disagreement, on the other hand, occurred most frequently when same affinity substrates were coadministered. There was an insufficient sample size to conduct significance testing for concordance ratings according to different pharmacokinetic scenarios.

Reconciliation discussions with all members of the panel for the 22% (n = 50) of CYP450-DDIs for which there was disagreement about whether an intervention was required yielded an improvement in the concordance ratings. Twenty-seven percent of cases were determined to require monitoring, medication substitution, or separate dosing schedules, and in 33%, no pharmacologic change was deemed necessary. In 40% of cases (n = 20), no consensus was reached, and it was agreed that >1 course of action was acceptable. After discussion, the revised concordance coefficient for the CYP450-DDIs discussed by the panelists increased to 0.79 (95% CI, 0.71–0.88). Based on the panelists' experience and discussion, suggested guidance for managing the 4 most common CYP450-DDI pharmacokinetic scenarios was formulated and is presented in **Table I**.

Clinical Testing

A total of 100 patients aged 82.3 (8.0) years (range, 65–96 years) were evaluated during the clinical implementation of InterMED-Rx. The mean (SD) frequency of medication use was 12.2 (4.1) drugs per patient (range, 5-27). Patient characteristics and the reason for their hospital admission are documented in **Table II**. Eighty percent of patients had at least 1 CYP450 interaction detected with InterMED-Rx. A total of 238 different DDIs were detected, with CYP3A4-based DDIs accounting for 70% of interactions (**Table III**). Immediately after InterMED-Rx analysis, 15 of 80 patients (19%) received medication adjustment, 31 patients (39%) required follow-up of clinical signs, symptoms, and laboratory tests to determine whether a future adjustment was needed, and 34 patients (42%) needed no change. More than one half (56%) of the patients who required clinical follow-up had further medication adjustment performed before discharge to reduce the risk of adverse clinical events. In all, 32 of 80 (40%) of this sample of frail hospitalized patients with polypharmacy and CYP450-DDIs detected by InterMED-Rx on admission received dosing schedule changes, medication substitution, or discontinuation to reduce the risk of adverse outcomes.

Figure 1 is an example of an InterMED-Rx analysis of the medication profile of an 84-year-old man with behavioral symptoms of dementia who was concomitantly being treated for symptoms of benign prostatic hypertrophy. The analysis revealed 4 medications involved in CYP3A4 interactions: atorvastatin 20 mg/d, a moderate affinity substrate, with donepezil 5 mg/d, finasteride 5 mg/d, and tamsulosin 0.4 mg/d, all weak substrates. As a result, atorvastatin was replaced by rosuvastatin, which is metabolized by CYP2C9, and the patient was monitored for hypotension related to tamsulosin before increasing the dose of donepezil from 5 mg to 10 mg. Three medications with potential CYP2D6 interactions were also noted: metoprolol 25 mg BID, haloperidol 0.5 mg BID, both moderate affinity substrates, with donepezil 5 mg/d. The pharmacist's intervention was to discontinue haloperidol and replace it with a trial of behavioral management of dementia because the risk of bradycardia/fatigue/hypotension with metoprolol and extrapyramidal symptoms with haloperidol was considered high.

The case analysis of a 78-year-old woman with congestive heart failure is shown in **Figure 2**. Five medications were involved in CYP3A4 interactions: amiodarone 200 mg/d, a strong affinity substrate, and amlodipine 5 mg/d, repaglinide 2 mg TID, domperidone 10 mg QID, and prednisone 5 mg/d. The pharmacist decided to discontinue repaglinide and increase the patient's insulin dose. The patient's electrocardiogram was monitored for prolongation of the QT interval due to potentially increased levels of domperidone, and the dosing of domperidone was decreased to TID. The administration times for amiodarone and amlodipine were separated by 12 hours to minimize first-pass effects. CYP2D6 interactions were also noted between amiodarone 200 mg/d, acting as an inhibitor, and amitriptyline 25 mg BID and dimenhydrinate 50 mg BID. Amitriptyline and dimenhydrinate were discontinued due to unclear indication, lack of effectiveness, and an associated risk of hypotension and sedation. To minimize potential CYP2C9 interactions between amiodarone 200 mg/d and irbesartan 300 mg/d, irbesartan was replaced with valsartan, which is less likely to be involved in DDIs through CYP2C9 metabolism.

DISCUSSION

Experience with the use of InterMED-Rx, a new CYP450-DDI detection software, suggests that potentially significant CYP450-DDIs occur in as many as 80% of hospitalized frail older adults taking ≥5 different medications. Detection of these CYP450-DDIs is the first step toward appropriate management. The second step requires a customized decision for each patient, whether specific interventions are warranted, to reduce the risk of an adverse outcome. Findings from this study indicate that on initial assessment, there is only moderate concordance between geriatric pharmacists whether or not specific CYP450-DDIs require clinical intervention. Through reconciliation with an expert panel and discussion of cases in which disagreement occurred, guidance on when and how to manage certain pharmacokinetic interactions was clarified. Given the complexity of geriatric patients, their different comorbidities,

Table I. Recommendations for management of different cytochrome-based drug– drug interactions.

Rationale	Acute toxicity (<24 hours) can occur for drug A with bioavailability ≤70% when a second drug that inhibits its metabolism is introduced due to an immediate first-pass effect and subsequent increase in drug A's C_{max} by ≥30%. An increase <30% in C_{max} for a drug with an initial bioavailability >70% will likely not lead to acute toxicity. Chronic toxicity (over 5–7 days) can develop for drug A if a gradual increase in C_{ss} evolves due to inhibition of its metabolism by other substrates of the same cytochrome. Long-term toxicity may also occur for drugs with an initial bioavailability >70% if C_{ss} increase gradually over time.	
Type of CYP450-DDI	Anticipated Effect	Management Recommendation
≥2 drugs with the same affinity for the same cytochrome	Drugs with the same affinity will undergo competitive inhibition. Drugs given in higher doses will likely inhibit the metabolism of drugs given in lower doses. Over the long term, a new C_{ss} for each drug will be reached that will be higher than if no interaction was present. When one of the drugs is discontinued, the C_{ss} of the remaining drug will decrease until a new steady state is reached.	Follow-up at 24 hours and again after 5–7 half-lives for signs of toxicity or reduced efficacy when introducing or removing a drug. Adjust the dose according to the clinical response or predicted increase in serum concentration Reassess whether one of the drugs can be discontinued or substituted with a drug that does not undergo oxidative metabolism. Consider substituting one of the drugs with another drug from the same class that is not metabolized by the same cytochrome. If discontinuation or substitution is not possible, separate the time of administration of the 2 drugs to minimize the effects of first-pass hepatic metabolism. Administer the medication with the lowest dose 4 to 5 hours before the medication with the higher dose.

(continued)

Table I (continued).

≥2 drugs with different affinity for the same cytochrome	The drug with the higher affinity will competitively inhibit metabolism of drugs with weaker affinity. A partial increase in the C_{max} of drugs with weaker affinity may occur acutely. As the number of drugs with higher affinity for the same cytochrome increases, metabolism of the drug with the weakest affinity will be progressively inhibited. Over the long term, a new C_{ss} for the drugs with weaker affinity will be reached that will be higher than if no interaction was present. When a drug with higher affinity is discontinued, the C_{ss} of the remaining drug will decrease until a new steady state is reached.	Same recommendations as above except for the following: If discontinuation or substitution is not possible, separate the time of administration of the 2 drugs to minimize the effects of first-pass hepatic metabolism: Administer the medication with the weaker affinity 4 to 5 hours before the medication with the higher affinity.
Presence of an inhibitor*	An inhibitor will significantly inhibit the metabolism of other drugs with affinity for the same chromosome, regardless of their affinity Administering an inhibitor over the long term is discouraged. If this cannot be avoided, a new C_{ss} for drugs undergoing metabolism by the same chromosome will be reached that will be much higher than if no interaction was present.	Same recommendations as above. If discontinuation or substitution of either drug is not possible, reduce the dose of the weaker affinity substrate and monitor for toxicity. Be aware that separating administration times or decreasing the dose of the inhibitor will not minimize the interaction.
Presence of an inducer	Induction of a cytochrome is a slower process than inhibition. It may take several days or weeks to see the full effects of the interaction. Clearance of drugs undergoing a CYP450-DDI by induction will be higher, and the efficacy of these drugs will be reduced once the induction is complete.	Follow up for signs of diminished efficacy over days or weeks of the drug being metabolized by a cytochrome that is undergoing induction. Adjust the dose of the substrate according to clinical response or the anticipated decrease in serum concentration.

CYP450-DDI = cytochrome P450–based drug–drug interaction.

*Because total drug clearance is equal to the sum of its renal clearance and hepatic clearance, it is important to assess the proportion of hepatic clearance for each drug. For instance, if renal clearance is 10%, then hepatic clearance will account for 90% of the drug's total clearance. If hepatic metabolism is fully inhibited by a cytochrome inhibitor, significant drug accumulation will occur.

Table II. Patient characteristics.

Characteristic	N = 100
Age, y	
Mean (SD)	82.3 (8.0)
Range	65–96
Female sex, %	68
No. of medications/patient	
Mean (SD)	12.2 (4.1)
Range	5–27
Proportion of patients with a CYP450 drug–drug interaction, %	80
Reason for admission, %	
Stroke	19.0
Dementia/cognitive impairment	17.1
Multifactorial	14.3
Fracture	11.4
Rehabilitation	10.5
Loss of autonomy	9.5
General deterioration	5.7
Falls	4.8
Parkinson's disease	3.8
Pain management	1.9
Lung disease	1.9
Admitted to, %	
Acute care geriatrics	32.0
Rehabilitation ward	44.0
Long-term care	24.0

body distributions, reduced hepatic and renal function, and individualized treatment preferences, developing a simple algorithm for managing CYP450-DDIs, or developing a list of CYP450-DDIs to avoid for all patients is recognizably unachievable. However, by applying sound pharmacokinetic principles and weighing the risks of medication modification versus the potential clinical consequences of each CYP450-DDI, an appropriate decision can be made on a case-by-case basis. The experiences, deliberations, and consensus decisions of the expert panel of pharmacists for the current study can help guide CYP450-DDI management for other older hospitalized patients with similar clinical profiles.

In the present study, the use of a CYP450-DDI software resulted in risk-reduction medication management interventions in 40% of patients with CYP450-DDIs detected by InterMED-Rx on admission. Different types of interventions were implemented to reduce the risk of adverse events from pharmacokinetically significant CYP450-DDIs. Separating drug administration times to favor cytochrome-mediated metabolism of a weaker affinity substrate, monitoring a patient for the emergence of clinically relevant signs and symptoms, and drug substitution or discontinuation were all conceivable options. Situations when it was most difficult to make a management decision regarding risk reduction for potentially significant CYP450-DDIs involved concomitant administration of 2 medications with equally weak or moderate affinities for the same cytochrome. Such situations will arise frequently among geriatric patients with polypharmacy and will likely involve substrates metabolized by CYP3A4, as evidenced in our sample of 100 patients admitted to a geriatric hospital. In such cases, >1 course of action may be deemed acceptable or the consequences of the interaction too minimal to warrant intervention. In other cases, there may be no safer alternative, with the benefit of continuing the 2 medications outweighing the risk. Only by giving due consideration to each CYP450-DDI will the right decision be reached for each patient.

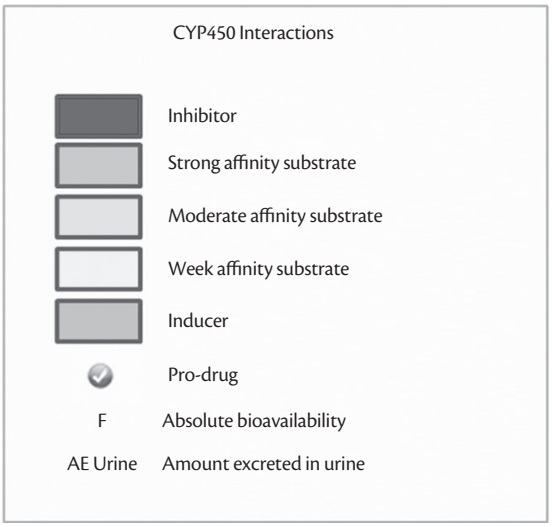
InterMED-Rx is a software program that provides information on potential CYP450-DDIs as well as general information on non–CYP450-DDIs. However, it does not render judgments on whether the DDIs will become clinically significant. The decision support tool only has an impact on the pharmacist's assessment of each patient's clinical situation and the subsequent decision to intervene. A major limitation of the InterMED-Rx software and its accompanying management recommendations proposed by the consensus panel relates to the fact that the motivation for a clinical intervention is driven not only by the knowledge and evidence of the potential interaction, but also by the clinical status and characteristics of the patient. Furthermore, appropriate interpretation of the information provided by InterMED-Rx requires robust knowledge of the pharmacokinetic properties of each drug involved in the interaction, such as their bioavailability and clearance.

Table III. Frequency of CYP450 interactions identified with InterMED-Rx.

Cytochrome	Frequency of Interaction, No.	Proportion of Interactions, %
3A4	167	70.1
2D6	54	22.7
2C9	8	3.4
2C19	5	2.1
1A2	4	1.7
2B6	0	0
Total	238	100.0

CYP450 = cytochrome P450.

MEDICATION	F (%)	AE urine (%)	CYP1A2	CYP2B6	CYP2C8	CYP2C9	CYP2C19	CYP2C6	CYP3A4	NON-CYP
Acetaminophen	75	5								-
Atorvastatin	13	2								-
Donepezil	100	17								-
Finasteride	63	0								-
Furosemide	65	90	NON- P450							- 1
Haloperidol	60	1								-
Meropenem	-	65	NON-P450							-
Metoprolol	45	10								-
Morphine	25	10	NON-P450							-
Pantoprazole	77	0								-
Ramipril	28	2	NON-P450							- 1
Tamsulosin	100	9								-



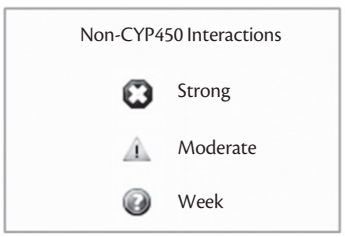


Figure 1. InterMED-Rx analysis of an 84-year-old man with behavioral symptoms of dementia.

The results of this study must be interpreted with several caveats in mind. First, the results are only applicable to a frail older population of hospitalized adults. Second, the geriatric pharmacists who interpreted the InterMED-Rx analyses were experts specialized in care of the elderly. Their knowledge and experience may not reflect the knowledge and experience of community-based pharmacists or hospital pharmacists who do not specialize in geriatric care. Third, pharmacist time constraints, hospital budget restrictions, software compatibility issues, and the phenomenon of alert fatigue from other drug-interaction software alert programs may make CYP450-DDI software assistance prohibitive in other busy clinical settings.

CONCLUSIONS

In summary, use of a new CYP450-DDI detection software program identified elderly patients at risk for pharmacokinetic interactions and facilitated preventive interventions to circumvent the potential for adverse drug events. The process of using the software elicited discussion and produced guidance on how to intervene for different CYP450-DDI scenarios. Although consensus can be reached among pharmacists on how to intervene for many CYP450-DDI scenarios, certain situations allow for multiple intervention strategies. Future research will aim to validate the consensus recommendations for the manage-

MEDICATION	F (%)	AE urine (%)	CYP1A2	CYP2B6	CYP2C8	CYP2C9	CYP2C19	CYP2D6	CYP3A4	NON-CYP
Acetylsalicylic acid	75	25				NON-P450				-3
Acetaminophen	75	5								-
Amiodarone	46	1								-
Amitriptyline	45	5								-
Amlodipine	70	10								-
Dimenhydrinate	-	2								-
Docusate Sodium	-	-				NON-P450				-
Domperidone	16	0								-
Enoxaparin	92	-				NON-P450				- 1
Furosemide	65	90				NON-P450				- 1
Hydralazine	25	10				NON-P450				-
Hydrochlorothiazide	70	95				NON-P450				- 1
Insulin	-	5				NON-P450				- 1
Irbesartan	70	2								- 1
Levothyroxine	-	-				NON-P450				-
Metformin	55	40				NON-P450				-
Oxanzepam	90	1				NON-P450				-
Pantoprazole	77	0								-
Pregabalin	90	90				NON-P450				-
Repaglinide	60	0								-
Spironolactone	100	0				NON-P450				- 2
Prednisone	80	3								-

Figure 2. InterMED-Rx analysis of a 78-year-old woman with congestive heart failure.

ment of CYP450-DDIs with a larger outside group of geriatric prescribing experts. A randomized, controlled trial for testing the clinical value of a CYP450-DDI detection software program for averting CYP450-DDI–induced adverse drug events is also required.

ACKNOWLEDGMENTS

We acknowledge the Department of Pharmacy at the Institut universitaire de geriatrie de Montreal for their participation in this study, as well as Suzanne Gilbert and Lucie Gosselin for taking part in the consensus panel discussions.

This study was funded by the Michel-Saucier Endowed Chair in Geriatric Pharmacology, Health, and Aging. The sponsor had no role in the conduct, analysis or interpretation of the study results. J. Turgeon developed, currently markets, and has a proprietary interest in the InterMED-Rx software. None of the other authors have a proprietary interest in the software. The authors have indicated that they have no other conflicts of interest regarding the content of this article. Mr. Zakrzewski-Jakubiak and Ms. Doan participated in the study design, data collection, data interpretation, and writing of the manuscript. Ms. Lamoureux participated in the study design, data collection, and data interpretation phases of this study. Dr. Singh contributed to the data interpretation and writing of manuscript. Mr. Turgeon participated in data interpretation and figure reproduction. Dr. Tannenbaum was involved in the study design, data interpretation and writing of the manuscript.

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