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Beneficial Pharmacokinetic Drug Interactions

David J. Edwards

School of Pharmacy, University of Waterloo 200 University Avenue West, Waterloo, Ontario, Canada N2L 3G1, USA

Summary

Pharmacokinetic drug interactions are common, particularly in elderly patients taking multiple medications, and are generally unexpected with negative consequences for the patient. However, there are a number of reasons why clinicians may wish to strategically employ a combination of drugs to optimize response to treatment. Inhibitors of cytochrome P450-mediated drug metabolism in the liver and intestinal wall can improve oral bioavailability, reduce clearance and prolong half-life of co-administered therapeutic agents such as immunosuppressant's and protease inhibitors. Potential benefits include reduced daily dose and cost of therapy, less variability in plasma concentrations and longer dosing intervals for patient convenience and compliance. Inducers of metabolism such as phenytoin or St. John's wort may be of value when given with drugs whose effects are primarily mediated by active metabolites. Finally, inhibitors of the activity of drug transport proteins such as p-glycoprotein can have a similar effect as inhibitors of drug metabolism on the pharmacokinetic properties of co-administered drugs. In addition, uptake of drug into cancer cells or tissues such as the central nervous system may be disproportionately increased resulting in more effective treatment. This paper provides an overview of the theoretical rationale for beneficial drug interactions with specific examples of interactions that are currently being used clinically or actively undergoing research.

Keywords: Pharmacokinetics; Drug interactions; Cytochrome P450; p-glycoprotein; Inhibition; Induction

Introduction

A drug interaction occurs when the usual effects of a drug are enhanced or diminished by another drug being taken by the patient. In most cases, these interactions are unintentional and come to the attention of clinicians due to a therapeutic failure or adverse event that is undesirable. Polypharmacy and drug interactions are common particularly among seniors. A survey of elderly individuals living in the community reported that 29% were taking five or more prescription drugs regularly [1]. Although it is difficult to quantify how often a clinically significant drug interaction occurs, these investigators estimated that roughly 1 in 25 individuals were at risk. Juurlink et al. [2] found that many patients admitted to hospital with a variety of drug-related adverse events had experienced a drug interaction.

Mechanistically, drug interactions have either a pharmacodynamic or pharmacokinetic basis. The former may be easier to anticipate and avoid since additive effects are predictable when drugs having similar pharmacologic activity are taken together. For example, hyperkalemia is a potential consequence of the use of both ACE inhibitors and potassium-sparing diuretics. Not surprisingly, Juurlink et al. [2] found that patients treated with ACE inhibitors and admitted to hospital with a diagnosis of hyperkalemia were 20 times more likely to have received a potassium-sparing diuretic.

Pharmacokinetic drug interactions occur as a result of a change in the exposure to a given dose of one drug when given with another. This is best assessed by measuring area under the plasma concentration-time curve (AUC) but can be estimated in patients by measuring one or more plasma concentrations under steady state conditions. As indicated in Equation 1, steady-state plasma concentrations are a function of clearance (Cl), bioavailability (F), dose and dosing interval (τ):

$$C_{ss,av} = \frac{F \times Dose}{Cl \times \tau} \quad (1)$$

Drugs that act as inducers or inhibitors of cytochrome P450 enzymes in the enterocyte and hepatocyte may change exposure by altering oral bioavailability. The hepatic extraction ratio is also a determinant of hepatic clearance and for drugs subject to a significant degree of first-pass metabolism, large changes in plasma concentrations may occur when inducers or inhibitors alter hepatic extraction. The concomitant use of the CYP3A4 inducer phenytoin with itraconazole reduced itraconazole AUC by more than 90% with a decrease in half-life from 22 hours to less than 4 hours [3]. Whether a drug interaction will be clinically significant depends on both the magnitude of the change in exposure and the therapeutic index of the drug whose exposure has been altered. Large numbers of drug interactions have been reported with warfarin, digoxin, cyclosporine, and other narrow therapeutic index drugs.

A pharmacokinetic drug interaction is usually unwanted and typically viewed by clinicians as something to be avoided [4]. However, if done strategically, it is possible to administer drugs in combination for the express purpose of altering drug exposure to benefit the patient. Typically it is an increase in exposure that is desired since decreasing exposure can be achieved by reducing the dose or extending the dosing interval. This review focuses on the potential benefits of pharmacokinetic drug interactions.

Theoretical Rationale for Beneficial Pharmacokinetic Drug Interactions

Many drugs have less than desirable pharmacokinetic properties for optimal use in patients. Compounds that are highly extracted by the liver or intestine have poor and highly variable oral bioavailability. In addition, clearance is high and half-life tends to be short. Plasma concentrations

***Corresponding author:** David J. Edwards, PharmD, MPH, Hallman Director and Professor, School of Pharmacy, University of Waterloo 200 University Avenue West, Waterloo, Ontario, Canada N2L 3G1, USA, Tel: 519-888-4408; Fax: 519-883-7580; E-mail: david.edwards@uwaterloo.ca

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for a given dose vary widely between patients and multiple daily doses are required to maintain concentrations at therapeutic levels. Many of these drugs are substrates for CYP3A4, the most abundant form of cytochrome P450 in the liver and the predominant P450 enzyme in the enterocyte. Inhibitors of drug metabolism can improve bioavailability, lower clearance, reduce variability in plasma concentrations and prolong half-life. All of these factors make it easier to achieve and maintain therapeutic concentrations. Less frequent dosing is required which can potentially promote patient adherence. In addition, the total daily dose can be reduced. For expensive medications, this results in significant cost-savings to patients, insurance companies or governments that are responsible for paying for medications. This may be particularly valuable in making medications more accessible in developing countries with limited budgets for high-priced pharmaceuticals [5]. This strategy of adding an enzyme inhibitor to produce a clinically beneficial drug interaction is being successfully utilized in treating transplant patients and patients with HIV infection.

In contrast to the effects of inhibitors of cytochrome P450 activity, inducers of drug metabolism will have the opposite effect and typically cause undesirable drug interactions. However, for drugs whose effectiveness is primarily dependent on the generation of active metabolites, the addition of an enzyme inducer could be of benefit. Co-administration of drugs such as phenytoin, rifampin and the herbal product St. John's wort with medications that essentially act as prodrugs would be expected to increase the ratio of active metabolite to parent drug and potentially maximize circulating concentrations of the active moiety. The potential benefits of this approach may be offset if the inducer also increases the clearance of the metabolite. There has been little clinical application of this type of beneficial drug interaction but studies examining the potential role of inducers to overcome resistance to clopidogrel have been reported.

When plasma concentrations of a drug are increased by a change in bioavailability or clearance, tissue concentrations typically increase proportionately with the potential for a proportionate increase in adverse events. An ideal drug interaction would selectively increase concentrations at the site of action. This can theoretically be achieved by a pharmacokinetic interaction involving modulation of the activity of drug transporters in the cell membrane. Transporters such as P-glycoprotein (PGP) influence the effects of drugs in two ways. The plasma concentrations associated with a given dose are altered because PGP can influence bioavailability, hepatic clearance and renal clearance. In addition, tissue concentrations are affected since PGP acts to restrict drug entry into vulnerable tissues such as the central nervous system. PGP is also over-expressed in many types of cancer leading to the phenomenon of multi-drug resistance. There is enormous potential for therapeutic benefit in cancer and other diseases if an inhibitor of PGP-mediated transport could be effectively combined with a therapeutic agent to enhance drug delivery to cancer cells or other target organs.

The following discussion provides additional background on selected examples of beneficial drug interactions that are currently being used clinically in patients or are the subject of ongoing research.

Beneficial Drug Interactions: Selected Examples

Dose-sparing of immunosuppressant drugs in transplantation

The development of effective immunosuppressant drugs such as cyclosporine has been a significant contributor to the improved outcomes associated with transplantation over the past 25 years. However, with the cost of cyclosporine averaging several thousand dollars annually in the late 1980's, there was considerable interest in finding a way to reduce costs. The pharmacokinetics of cyclosporine is characterized by poor and variable bioavailability averaging around 30% [6]. Intestinal and hepatic extraction by CYP3A4 as well as transport by PGP in the enterocyte contributes to the low bioavailability. A number of inhibitors of CYP3A4 were identified which could potentially be combined with cyclosporine to improve bioavailability, reduce clearance and reduce the required daily dose. An ideal inhibitor for this purpose would need to be inexpensive and have minimal toxicity at the doses required for clinically significant inhibition of metabolism. Ketoconazole met all of these criteria with the added bonus that its antifungal activity could be of value given the potential for fungal infections associated with immunosuppression. Clinical trials demonstrated significant benefits from the ketoconazole-cyclosporine interaction. Keogh et al. [7] reported that the dose of cyclosporine required to reach targeted blood concentrations was reduced by 80% one year after transplantation. Itraconazole and diltiazem have subsequently been shown to be effective for cyclosporine dose-sparing as well. Florea et al. [8] reported a 48% decrease in the total daily dose of cyclosporine when administered with itraconazole while another study found that cyclosporine dose could be reduced by 23%, 40%, 75% and 80% when combined with diltiazem, itraconazole, ketoconazole or ketoconazole plus diltiazem, respectively [9]. Gerntholtz et al. [5] reported an 85% reduction in cyclosporine dose with ketoconazole and suggested that this combination was critical in making transplantation more affordable in developing countries. A similar assertion was made by Egyptian investigators who used the combination for the treatment of nephrotic syndrome in children [10].

The strategy of combining CYP3A4 substrates with ketoconazole continues to be utilized currently despite some changes in immunosuppressant regimens over the past 20 years. Many transplantation teams now consider tacrolimus to be the immunosuppressant of choice [11]. Tacrolimus shares many of the same pharmacokinetic properties as cyclosporine [12] including poor and variable bioavailability which can be enhanced by co-administration of inhibitors such as ketoconazole and diltiazem [12,13]. This interaction may be more complex with tacrolimus, however, since metabolism is mediated by CYP3A5 in addition to CYP3A4. As reviewed by Barry and Levine [14], not all adults express CYP3A5 and expression appears to be most prevalent in blacks and least common in those of white European or American ethnicity. CYP3A5 expression is associated with higher tacrolimus clearance and dose requirements [14]. Chandel et al. [15] reported that ketoconazole produced 30% more inhibition of tacrolimus in patients lacking the CYP3A5*1 allele while another study found that diltiazem had no significant tacrolimus dose-sparing effects in CYP3A5 nonexpressors [16].

Boosted regimens for treating HIV infection

The development of the protease inhibitors represented a significant advance in the treatment of HIV. Drugs such as saquinavir, indinavir, nelfinavir and ritonavir have significant antiviral activity but less desirable pharmacokinetic properties. Bioavailability is poor and highly variable as a result of significant first-pass metabolism by CYP3A4 and transport by PGP in the intestinal wall and liver. The half-life of these drugs is short requiring frequent dosing and the combination of high pill burden and inconvenient dosing schedules led to poor adherence with early treatment regimens. A number of studies in the late 1990's reported significant drug interactions with the combination of ritonavir and saquinavir. Merry et al. [17] found that mean peak plasma concentrations of saquinavir were increased more than 30-fold when administered with ritonavir 300 mg twice daily. Saquinavir AUC

was increased from 470 to 27,458 ng·h/mL in the presence of ritonavir, an increase of greater than 50-fold reflecting a substantial increase in oral bioavailability. These findings were confirmed by Hsu et al. [18] who also reported that intersubject variability in saquinavir AUC was reduced by half when given with ritonavir. The half-life of saquinavir could not be accurately estimated when given alone but was about 6 hours when given with ritonavir.

Ritonavir-boosted protease inhibitors have now become a standard component of treatment for patients with HIV disease [19]. Ritonavir is used in combination with lopinavir and saquinavir as well as with the newer protease inhibitors atazanavir, fosamprenavir, darunavirand tipranavir [20-22]. The typical dose of ritonavir for combination with most other protease inhibitors is 100 mg twice daily, significantly lower than the doses of 1200 mg daily used for anti-viral effects. The use of these sub-therapeutic doses minimizes the risk of gastrointestinal and other adverse events associated with the addition of ritonavir, lowers costs and makes it easier to co-formulate with other drugs. Lopinavir is particularly sensitive to the inhibitory effects of ritonavir with a 77-fold increase in lopinavir AUC after a single 50 mg dose of ritonavir [23]. These drugs have been co-formulated in a fixed-dose combination of 200 mg lopinavir with 50 mg ritonavir (Kaletra®) offering the convenience of reduced pill burden with the potential for improved adherence.

Unlike saquinavir and lopinavir, atazanavir has relatively little first-pass metabolism and bioavailability approaches 70% [24]. The addition of ritonavir, however, reduces the clearance of atazanavir and increases its half-life to nearly 11 hours. Minimum plasma concentrations are increased more than ten-fold allowing boosted atazanavir to be administered once a day. Inhibition of clearance and prolongation of half-life also occurs when darunavir and fosamprenavir are given with ritonavir and the substantial increase in minimum plasma concentrations with chronic dosing also allows these drug combinations to be administered once daily [25,26]. The ability to maintain high trough concentrations of protease inhibitors with boosted regimens is a key factor in decreasing resistance to these drugs with chronic treatment.

The success of ritonavir-protease inhibitor combinations in improving treatment of HIV infection has led to a search for other compounds that can enhance the effectiveness of other antiviral drugs. Cobicistat (GS-9350) is a more specific inhibitor of CYP3A4 than ritonavir and has the necessary physicochemical properties for co-formulation with other drugs. Elion et al. [27] observed that AUC, maximum and trough concentrations of atazanavir were all increased to a comparable extent after co-administration with either ritonavir 100 mg or cobicistat 150 mg. Since it is not a protease inhibitor, cobicistat is preferable to ritonavir for combination with other classes of antiviral agents used in treating HIV. Cobicistat has been combined with elvitegravir, an investigational integrase inhibitor, emtricitabine and tenofovir in a single tablet designed for once-daily administration. Results from a Phase 3 trial comparing this product to a standard treatment regimen have been encouraging [28].

Enzyme induction for enhanced generation of active metabolites

Clopidogrel is a widely used inhibitor of platelet aggregation whose activity is primarily due to the formation of an active metabolite that is generated through the activity of the cytochrome P450 enzymes CYP3A4 and CYP2C19. Patients who have a genetic deficiency in CYP2C19 activity have poorer cardiovascular outcomes when treated with clopidogrel [29] and drug interactions with cytochrome P450 inhibitors such as ketoconazole, itraconazole, omeprazole and atorvastatin have been reported to reduce clopidogrel effectiveness [30]. Approximately 25% of patients exhibit hyporesponsiveness to clopidogrel which can lead to serious cardiovascular events including myocardial infarction and coronary stent thrombosis.

A beneficial pharmacokinetic interaction has been observed between clopidogrel and the cytochrome P450 inducer rifampin. Lau et al. [31] reported improved platelet aggregation in healthy volunteers who were nonresponders to clopidogrel after treatment with rifampin. Judge et al. [32] found that in healthy volunteers treated with rifampin, plasma concentrations of the active metabolite of clopidogrel were increased from 89 to 335 ng·hr/mL accompanied by greater inhibition of platelet aggregation. St. John's wort, a natural product used by many patients for the treatment of mild depression, is also an inducer of drug metabolism and is typically much better tolerated than rifampin. It has been demonstrated that treatment with St. John's wort for 14 days improved the effectiveness of clopidogrel in both healthy volunteers and patients resistant to clopidogrel alone [33]. Percent platelet inhibition improved from 28% with clopidogrel alone to 41% when St. John's wort was added [33].

A theoretical case can be made for this strategy with tamoxifen, a widely used drug in the treatment of estrogen-receptor positive breast cancer. The tamoxifen metabolite endoxifen is many times more potent as an estrogen-receptor blocker than the parent compound and is formed primarily via the activity of the cytochrome P450 enzyme CYP2D6. Patients who have a genetic deficiency in CYP2D6 activity may exhibit a poorer response to tamoxifen treatment although the results of clinical studies have been mixed [34]. Similarly, patients treated with antidepressants such as paroxetine which inhibit CYP2D6 activity have been reported to have poorer clinical outcomes [35]. Induction of CYP2D6 metabolism could lead to an increase in generation of active metabolites for a given dose and potentially greater clinical effect. Rifampin has been reported to reduce AUC of tamoxifen by 86% [36]. Although peak concentrations of the N-desmethyltamoxifen metabolite were elevated, the AUC was reduced and half-life was shortened suggesting induction by rifampin. N-desmethyltamoxifen is further metabolized to the more active species endoxifen. This raises the possibility that endoxifen concentrations could be elevated by induction although there are no published reports documenting this or describing the clinical use of this type of drug interaction.

Optimizing drug delivery to target cells and tissues

Increasing the concentration of active drug in the cells and tissues at the site of action and not elsewhere would be highly desirable. The intracellular to extracellular transport of drugs is primarily mediated by the ATP-binding cassette (ABC) family of proteins of which the most widely studied has been PGP. PGP plays an important role in protecting the body from potentially toxic foreign compounds and is highly localized in tissues such as the intestine, liver, and kidney where its ability to efflux drug limits oral bioavailability and enhances hepatic and renal clearance of substrates [37]. In the testes, ovaries, placenta and blood-brain barrier, PGP fulfills a barrier function limiting penetration of drugs into vulnerable tissues such as the fetus and central nervous system [37]. Knockout mice that lack PGP show a dramatic increase in brain concentrations of drugs whose ability to cross the blood-brain barrier is normally limited [38]. PGP shares many substrates with CYP3A4 and inducers and inhibitors of CYP3A4 often have a similar effect on PGP activity [39].

PGP primarily came to the attention of clinicians and researchers when it was recognized that it was largely responsible for the phenomenon of multi-drug resistance in cancer cells. Over-expression of PGP has been reported in several different types of cancer leading to resistance to a wide spectrum of structurally unrelated anti-cancer compounds. As a result of these observations, considerable research has been conducted into strategic drug interactions in which anticancer drugs are co-administered with a PGP inhibitor to overcome resistance by allowing more effective uptakeby cancer cells [40-42]. It was recognized almost 30 years ago that drugs such as verapamil and cyclosporine inhib it PGP and early attempts to identify specific PGP inhibitors were based on finding more potent and specific analogues of these drugs. Valspodar emerged from these efforts and is structurally related to cyclosporine with approximately 10-fold more potency as a PGP inhibitor. Despite promising early results, a Phase III study published in 2006 found that the addition of valspodar to vincristine, doxorubicin and dexamethasone did not improve the treatment of multiple myeloma [43]. Disappointing results were also obtained with valspodar in the treatment of ovarian and peritoneal cancer [44].

One of the challenges with the development of PGP inhibitors has been to find compounds that do not also inhibit cytochrome P450 and cause undesirable drug interactions in addition to the beneficial interaction with PGP. Adverse events have been a problem as well at the doses needed for clinically significant inhibition of PGP. The most recent generation of PGP inhibitors include compounds such as zosuquidar which is a highly potent and specific inhibitor of PGP with minimal toxicity. Similar to results with valspodar, however, zosuquidar did not improve outcome in a large placebo-controlled trial of patients with acute myeloid leukemia [45]. It is not clear, however, whether PGP was primarily responsible for drug resistance in these patients.

There is also considerable interest in the use of natural products as PGP inhibitors [41,42]. There are a diverse range of bioactive compounds in fruits and vegetables that presumably have minimal toxicity since they are consumed as food on a regular basis. Curcurmin is found in the spice turmeric and has been identified as a PGP inhibitor. Unfortunately, it has poor bioavailability which limits its use for therapeutic purposes. Many flavonoids also have PGP inhibitory activity although there are no clinical studies demonstrating a beneficial drug interaction with anticancer drugs.

The activity of PGP in the blood-brain barrier also presents a challenge in attaining therapeutic concentrations of drug in the central nervous system to treat cancer, HIV and diseases such as depression [46,47]. Khaliq et al. [48] found that co-administration of ketoconazole, an inhibitor of PGP as well as CYP3A4, with ritonavir resulted in a disproportionate increase in the concentration of ritonavir in cerebrospinal fluid (CSF). The CSF concentration of ritonavir was increased by almost three-fold while unbound plasma concentration was unchanged suggesting that ketoconazole was blocking efflux of ritonavir from CSF. It has been suggested that patients with depression may exhibit over-expression of PGP in the blood-brain barrier potentially leading to treatment resistance given that a number of widely used antidepressants are PGP substrates [49]. The combination of a PGP inhibitor with an antidepressant in the treatment of refractory depression has been proposed.

The availability of an effective non-toxic PGP inhibitor remains an active area of research despite the lack of success to date. Polymorphic expression of PGP as well as variation in level of expression between patients may contribute to the difficulty in achieving clinically effective PGP inhibition. It has been proposed that PGP activity might be more effectively modulated by targeting factors affecting regulation as opposed to inhibiting transporter activity [50]. Irrespective of how it is achieved, altering PGP function has the potential to improve the treatment of a broad range of diseases.

Conclusion

It is clear from this discussion that there are therapeutic advantages to be gained through the strategic and deliberate use of drug combinations. In the treatment of transplant patients with immunosuppressant drugs or the treatment of HIV infected patients with antiviral drugs, these benefits have already been realized. The use of drug interactions to modulate the activity of PGP or other transporters for the purpose of improving drug access to tissues or cells has proven to be much more challenging to date. Further research is needed to identify appropriate drugs or compounds that can improve the tissue/plasma concentration ratio of the primary therapeutic agent for more effective treatment of diseases such as cancer or those affecting the central nervous system. In addition, exploration of the potential benefits of interactions involving the combination of an enzyme inducer and a therapeutic agent with active metabolites is warranted.

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