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Clinical-Pharmacological Strategies to Assess Drug Interaction Potential During Drug Development

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Abstract

Drug interactions in patients receiving multiple drug regimens are a constant concern for the clinician. With the increased availability of new drugs and their concomitant use with other drugs, there has been a rise in the potential for adverse drug interactions as demonstrated by the recent withdrawals of newly marketed drugs because of unacceptable interaction profiles. Therefore, the interaction potential of a new compound has to be assessed in detail, starting with preclinical *in vitro* and *in vivo* studies at candidate selection and continuously followed up through preclinical and clinical development. Since formal *in vivo* studies of all possible drug interactions are neither practicable nor suggestive, a careful selection of a limited number of drug combinations to be investigated *in vivo* during the development phase is indicated. Based on knowledge of pharmacokinetic and biopharmaceutical properties, a well balanced link between *in vitro* investigations and carefully selected *in vivo* interaction studies allows full assessment of the potential of a new drug to cause clinically relevant pharmacokinetic drug-drug interactions, prediction of a lack of interactions and derivation of the proper dose recommendations.

Clinical pharmacology plays a number of key roles within the process of collecting information on drug interactions during preclinical and clinical development: addressing issues and/or favourable properties to be expected, thus contributing to the scientific assessment of development potential; setting up a rational *in vivo* drug-drug interaction programme; performing early mechanistic studies to link *in vitro* with *in vivo* information (employing 'cocktail' approaches if possible); reviewing co-medication sections for clinical trials; and conducting labelling-oriented interaction studies after proof of concept.

The fact that interactions can occur between various active substances should by itself be a conclusive argument against unnecessary polypharmacy. Prescribing fewer drugs on a rational basis can reduce the risk of adverse effects secondary to drug interactions and may help to improve the quality of drug treatment and to save costs.

Drug interactions in patients receiving multiple drug regimens are a constant concern for the clinician. When any 2 drugs are prescribed together, the potential for interaction has been reported as approximately 6%.[1,2] The risk of drug interactions increases exponentially with the number of drugs the patient takes.[3-6] Reviews of hospital and outpatient prescribing suggest that when an interaction is reported an average of between 4 and 8 drugs are being taken by the patient.[7-16] Adverse effects of drugs are one major cause for hospital admissions. In different studies, the reported incidence of drug-related hospital admissions ranges from 2 to 10% of all general admissions involving the elderly population.[17-22] Fatal adverse drug effects rank between the fourth and sixth leading cause of death in the US.[23] Up to 20 to 30% of all adverse drug reactions are assumed to be caused by drug interactions.[24,25] Therefore, every multiple drug regimen must have a sound rationale for use. Use of drug combinations where only 1 of the drugs or not all of the drugs are necessary is no longer acceptable.

1. Definition of Drug-Drug Interactions

Interactions between 2 or more concomitantly administered drugs may intensify or reduce desired as well as undesired effects. Only when the combined effects of the interacting drugs are greater or less than the arithmetic sum of their individual actions can the event be considered a true interaction.[16,26,27] This eliminates many 'potential interactions' which in reality merely describe the summation of similar or opposing but independent drug effects. While the desired increase of effectiveness with an associated decrease in risk of therapy is well known, the magnitude of the additional risk posed by the drug-drug interactions is often underestimated. The number of available agents provides enormous scope for such interference and ensures that no physician can be completely familiar with all eventualities. However, experimental findings and clinical experience have shown that the great majority of interactions occur through a small number of relatively specific basic mechanisms.

An understanding of a particular interaction in terms of the site and mechanisms is essential for interpreting, preventing and treating adverse interactions. It also provides a means of recording and classifying the large number of individually reported interactions. Drugs can interact with one another at any point from their incorporation into a pharmaceutical formulation to their final elimination from the body. They can be divided into the pharmaceutical, pharmacokinetic or pharmacodynamic phases (table I).

Table I. Different phases for possible drug interactions

Pharmaceutical phase
Galenic formulation
Physical intolerability
Gastrointestinal tract
Pharmacokinetic phase
Mechanism of absorption
Distribution
Biotransformation
Elimination
Pharmacodynamic phase
Direct
Indirect

Pharmaceutical interactions pertain to intravenous formulations and physical or chemical interactions. Pharmacokinetic interactions may affect gastrointestinal absorption, distribution (plasma and/or tissue protein binding), metabolism or excretion processes. Pharmacodynamic changes that can result in drug interactions include competition for receptor site, alteration of a receptor at the site of action, and additive or opposite effects of a drug on other biological systems.

In particular, newly launched drugs will have had little or no testing in combination with most other drugs. Therefore, the study of drug-drug interactions has become an important aspect of the development process of new drugs. The studies should focus on both the effect of the new drug on already approved drugs and the effect of already approved drugs on the new drug.

The importance of such studies has been demonstrated impressively with the withdrawal of the calcium channel antagonist mibefradil from the market,

almost exactly a year after the drug had been given marketing approval in Europe and the US. The withdrawal was based on new reports about serious interactions with other commonly used drugs.[28,29] Mibefradil inhibits the action of cytochrome P450 (CYP) 3A4. Therefore, when given concurrently with drugs that are metabolised by this enzyme, concentrations of these drugs could reach toxic concentrations with normal doses as has been shown, for example, for cyclosporin, tacrolimus, metoprolol and several hydroxymethylglutaryl co-enzyme A (HMG-CoA) reductase inhibitors.[30] In retrospect, it can be concluded that these interactions could have been predicted on the basis of the pharmacokinetic and pharmacological data available for mibefradil before its introduction to the market.[31]

2. General Strategy to Address Interaction Potential of New Drug Candidates

The interaction potential of a new compound has to be assessed in detail, starting with preclinical *in vitro* and *in vivo* studies at candidate selection and continuously followed up during preclinical and clinical development (fig. 1).

Before clinical interaction studies can be designed and performed the following important questions have to be answered.

2.1 Which Drug Interactions Should Be Investigated?

As a consequence of the scientific development within the areas of pharmacokinetics (particularly drug metabolism) and pharmacodynamics, the focus of interaction studies has changed from *ad hoc* observational studies to rationally designed studies.[32-34]

The key information to assess metabolic inhibitory or inducing drug-drug interactions can already be obtained by *in vitro* studies investigating metabolic pathways, involved CYP isozymes or drug transporters, such as P-glycoprotein, and CYP enzyme/drug transporter affinities of a new drug candidate. A set of *in vivo* interaction studies – including both potent inhibitors/inducers and relevant substrates of the identified CYP isoforms and/or drug transporters – are then selected to complement the *in vitro* data with respect to mechanistic information and especially focusing on the mutual pharmacokinetic effects of the new drug candidate and CYP inhibitors/inducers or substrates, respectively. In addition, the rationale for the formal pharmaco-

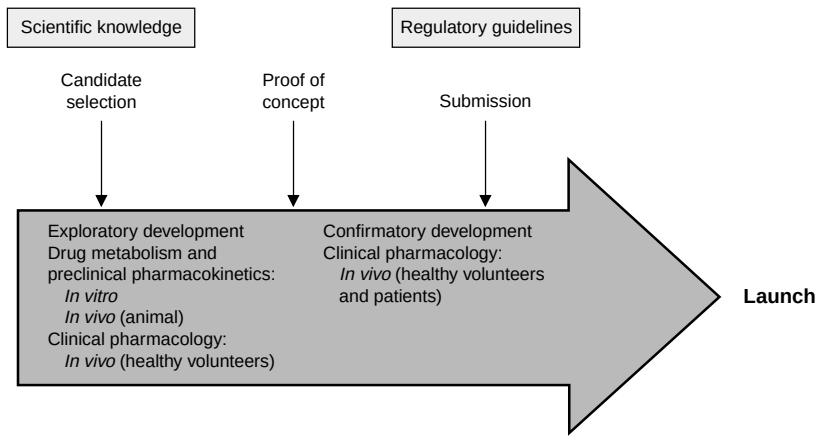

Fig. 1. General strategy to address drug interaction potential from drug development to launch.

kinetic interaction programme may cover *in vitro* investigations related to displacement interactions at the protein binding site and interaction studies with co-medications affecting absorption or renal elimination.

Since formal *in vivo* studies of all possible pharmacodynamic interactions are neither practicable nor advisable, a careful selection of a limited number of drug combinations to be investigated during the development phase is indicated. Priorities should be based on the likelihood of certain combinations occurring in clinical practice as well as on risks associated with them. A general principle may be that clinical drug interaction studies should be performed during drug development with the standard therapy for the proposed indication and/or with drugs frequently co-medicated with the new drug in clinical use, based on the knowledge of clinically relevant interactions. Cardiac glycosides, antiarrhythmics, anticoagulants, antihypertensives (especially β-blockers), anticonvulsants, antidiabetics, antifungals, histamine H_2 receptor blockers, antacids, psychotropic agents (e.g. lithium salts and monoamine oxidase inhibitors) as well as theophylline and cytostatics belong to these substance groups.[35]

If interactions are: suspected from animal data; expected from structural and physico-chemical characteristics; expected from pharmacological properties; expected from human *in vitro* data; known from similar compounds; or if adverse drug reactions, suspected to result from drug interactions have been observed during clinical trials, selective clinical studies to assess drug interactions with a new substance are indicated. Based on results from such studies, the risk of clinically relevant interactions may be predicted.

2.2 When Should Drug Interaction Studies Be Performed?

Normally clinical drug interaction studies are performed during later phases of clinical development after adequate information on safety and tolerability, pharmacokinetics, efficacy and therapeutic dose range has been established during the exploratory phase of drug development (phase I and phase IIa). If a co-medication with drugs affecting a vital process such as clotting, respiration, cardiac rhythm, blood pressure or glucose homeostasis is necessary during larger clinical trials, clinical interaction studies should be conducted at an early stage of development, e.g. at the end of phase I or during phase IIa to minimise the patients' risk during the wide spread clinical investigations. Other factors increasing the risk of a clinically relevant drug interaction are summarised in table II.

Another advantage of performing drug interaction studies early in the drug development process is that knowledge of causes for variability can be taken into consideration in the design of later clinical studies. In some situations the results of interaction studies may be crucial for the decision to develop the drug or not. Thus, extensive investigation of potential interactions at an early stage of drug development is encouraged.

2.3 How and in Whom Should Drug Interaction Studies Be Performed?

Drug-drug interactions can either be investigated in formal studies or by a sub-analysis of those patients from phase II or III safety, efficacy and comparative trials receiving the study drug concomitantly with a potentially interacting drug. Sometimes a combination of both methods is favourable.

2.4 Formal Drug-Drug Interaction Studies

If one of the drugs characterised by the aforementioned selection criteria is often used in com-

Table II. Factors increasing the risk of drug-drug interactions

Steep course of the dose-response curve
Highly specific effect
Accumulation of analogous effects
Small therapeutic range
Problematic pharmacokinetics
Necessary long term therapy with different drugs
Simultaneous prescription of several drugs by different physicians
Increasing self-medication by the patient

bination with the new drug under development and if interactions are expected on the basis of their structural and physico-chemical characteristics, their pharmacokinetic and/or pharmacological behaviour during preclinical studies, or if interactions from similar compounds are known, then the clinical relevance should be investigated in a formal study in humans as early as possible during clinical development and, whenever possible, the mechanism should be elucidated.

2.5 Nonformal Drug-Drug Interaction Studies

For all other drugs often administered together an initial screen for pharmacokinetic and/or pharmacodynamic (efficacy and safety) interactions during phase II or III of clinical trials with plasma concentration measurements and a possible concentration-effect relationship might be sufficient. On the basis of these data it should be critically estimated whether this screening itself is sufficient for an estimation of risk/benefit or if an additional formal study is necessary.

2.6 What are the Assessment Criteria?

It is important in the drug development phase to differentiate between detectable interaction and clinically relevant interactions.[16,27] An interaction is 'clinically relevant':

- when the therapeutic activity and/or toxicity of a drug is changed to such an extent that a dosage adjustment of the medication or medical intervention may be required
- when concomitant use of the 2 interacting drugs could occur when both are used as therapeutically recommended.[32]

A special problem of the sample size estimation for interaction studies is the fact that in most cases clearly defined criteria to assess a clinically relevant interaction do not exist.[35] From a statistical viewpoint, considering different drug treatments in a drug interaction study, one should test for 'non-equivalence' by demonstrating 'equivalence' or a lack of interaction by the confidence interval approach established for bioequivalence studies. A lack of interactions is concluded if the 90% confidence interval for the difference of the means or medians of the test and reference treatments is entirely within the equivalence range (range of clinically acceptable variation). This decision procedure ensures that the consumer risk, incorrectly concluding 'no interaction', is limited to 5%.[36] However, in classical hypothesis testing the consumer risk is not controlled because a nonsignificant result does not imply that there is 'no interaction' and a significant result does not imply a 'clinically relevant interaction'. For drug interactions these limits may be wider or narrower depending on the therapeutic range of the drug and the pharmacokinetic and pharmacodynamic variability of the affected drug. According to the limits for analysis the contraindication for a combination must be defined early. Otherwise the clinical relevance of possible interactions has to be investigated in additional, nonformal clinical studies in patients.

3. Recommendations for Drug Interaction Studies

Suitable study design and clear targets will improve our ability to determine whether the combined effect is a true interaction or simply the result of additive pharmacological effects. By optimisation of experimental protocols the maximum amount of information may be obtained from experiments performed in a limited number of healthy volunteers or patient volunteers. Determination of plasma drug concentrations is an essential part of drug interaction studies allowing the interpretation of a possible interaction in terms of a pharmacokinetic-pharmacodynamic interaction. If feasible, the oral route of drug administration is preferable in the initial evaluation or screen for suspected interactions in man, because it is the most common route of administration, it is the only way to detect interaction involving absorption, and the magnitude of the interaction may be much greater than after intravenous administration, for example, for drugs eliminated by metabolism.

Special questions concerning the study design of drug interaction studies are:[32-34]

- Should formal studies be performed in healthy volunteers or patient volunteers?
- Should single or multiple dose regimens be preferred?
- Should a crossover or group comparison design be used?

Formal studies can be performed either in healthy volunteers or in volunteers with the target indication. In view of their greater clinical relevance, drug interaction studies involving patients with the target indication are usually to be preferred. However, for practical reasons this is not always possible and the decision on the study population has to be taken on a case by case basis.

In general, it is beneficial for the elucidation of drug-drug interactions for studies to be conducted during long term oral administration when steady state conditions are observed. The healthy volunteer/patient can serve as his or her own control by using pretreatment and post-treatment control periods. Transient interactions can be detected and the time course of events can be seen. Furthermore, this is the only feasible way to study patients who may require continuous administration of the test drug to control their disease. Moreover, it may be important to investigate a drug interaction in the patient for whom a given treatment is intended because it is the only way in which the effects of the disease state on such drug interactions can be assessed.

Formal interaction studies in healthy volunteers should primarily be conducted in a randomised 2-fold or 3-way (to investigate any mutual interaction potential) crossover design. The duration of the study periods depends on the duration of the efficacy and the pharmacokinetic half-life, respectively. It is absolutely necessary to keep a washout period of at least 4 to 5 half-lives between the single study periods.

Studies in patients who need basic treatment have to be conducted without washout periods between the study periods. In this situation, a run-in phase to obtain steady state of basic treatment will be followed by a period to estimate the pharmacokinetics and pharmacodynamics of basic treatment and subsequently of combination therapy.

The number of volunteers/patients involved in such a study depends on:

- study design
- variability of pharmacodynamic and pharmacokinetic parameters
- criteria to assess a clinically relevant difference
- additional ethical considerations/limitations.

4. Cerivastatin: an Example How to Set Up a Drug-Drug Interaction Programme Within Clinical Development

Rationale and conduct of a drug-drug interaction programme within clinical development may be briefly illustrated by using the example of the HMG-CoA reductase inhibitor cerivastatin which has been recently introduced to the market.[37-39] The programme was primarily based on the pharmacokinetic profile of cerivastatin as derived from *in vitro* and *in vivo* studies, on the common co-medications, and on the information available from other drugs in the same therapeutic class. Based on this knowledge, a well balanced link between *in vitro* investigations and carefully selected mechanism-based *in vivo* approaches has been chosen to elucidate the risk for drug-drug interactions with cerivastatin (fig. 2).[40]

Briefly, the key properties of cerivastatin with respect to pharmacokinetic drug-drug interactions will now be outlined.[38,40,41]

4.1 Absorption

Cerivastatin possesses a carboxylic acid functional group. Therefore, the objectives of the clinicopharmacological investigations were to investigate whether there was a possible influence on the extent and rate of absorption of cerivastatin by:

- an antacid preparation containing 600mg magnesium and 900mg aluminium hydroxide by an increase in gastric pH or by adsorption;
- the gastric acid secretion inhibitor omeprazole or the H_2 antagonist cimetidine (by rise in gastric pH).

Also it was necessary to define the effect on cerivastatin absorption due to adsorption to the bile acid sequestrant cholestyramine, a basic co-medication

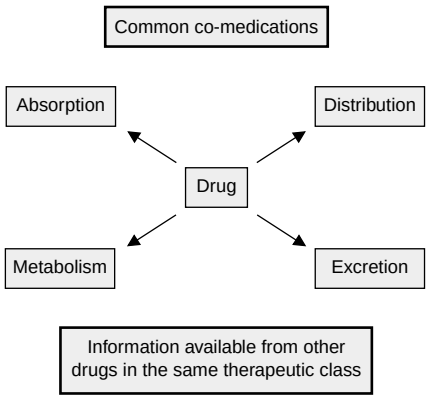

Fig. 2. Rationale for a drug-drug interaction programme.

in patients with hypercholesterolaemia, or due to altered solubility by the lipase inhibitor orlistat, which is becoming increasingly popular as anti-obesity drug.

The coadministration of the antacid preparation did not affect plasma concentrations of cerivastatin. Steady-state comedication with cimetidine or omeprazole did not lead to a statistically significant interaction with cerivastatin.

Concomitant administration of cerivastatin 0.2mg and cholestyramine 12g resulted in a 21% reduction in bioavailability. By separating the intake of the 2 drugs by 1 or 5 hours the loss in bioavailability could be reduced to 16 or 8%, respectively. The concomitant administration of orlistat 120mg 3 times daily for 7 days and cerivastatin 0.8mg did not affect the bioavailability of concurrently administered cerivastatin.

4.2 Distribution

Cerivastatin is highly bound to plasma proteins, mainly albumin (99.1 to 99.5%), resulting in the potential for drug-drug interaction by mutual displacement from binding sites. Lack of interaction could be established by *in vitro* displacement experiments using free fatty acids or drugs, well known themselves for their high plasma protein binding [i.e. warfarin, phenylbutazone, clofibrate, ibuprofen, propranolol, imipramine, gemfibrozil, nifedipine, salicylic acid, nicotinic acid, furosemide (frusemide), phenytoin, digitoxin and glibenclamide (glyburide)]. These experiments could then be confirmed via an *in vivo* interaction study investigating both pharmacodynamics and pharmacokinetics of the oral anticoagulant warfarin.

4.3 Metabolism/Excretion

In vitro investigations using human hepatic microsomes and cells expressing human CYP isoforms and an *in vivo* mass balance study, employing ^{14}C-labelled drug in humans, enabled the metabolic pathways of cerivastatin to be elucidated, the CYP isozymes catalysing these biotransformation reactions to be identified and the major route of elimination to be defined.

Detailed *in vitro* investigations, determining the inhibitory constant (K_i) excluded any inhibitory potential of cerivastatin and its major metabolites on all of the common CYP enzyme classes.

All subsequent *in vivo* investigations with specific 'probe drugs' were then targeted to confirm pathways and CYP isoform profile information.

No pharmacokinetic interaction was noted for either cerivastatin or its immuno-active metabolites when a single dose of cerivastatin 0.2mg was administered alone or on the fourth day of pre- and co-treatment with cimetidine 400mg twice daily as an example for an unspecific CYP inhibitor (see also section 4.1).

The pre- and co-treatment with erythromycin 500mg three times daily or itraconazole 200mg twice daily (both specific and potent CYP3A4 inhibitors) slightly increased the area under the plasma concentration-time curve of cerivastatin by 21 and 15%, respectively, whereas the maximum plasma drug concentration was marginally elevated by 13 and 3%, respectively. Dosage adjustment of cerivastatin is not necessary.

There was no mutual pharmacokinetic drug-drug interaction with warfarin, a drug mainly cleared via CYP2C9-mediated biotransformation, or with omeprazole, mainly cleared via CYP2C19-mediated biotransformation (see also section 4.1).

Lack of interaction could also be demonstrated for the concurrent administration of cerivastatin 0.3mg and slow-release nifedipine 60mg, a known CYP3A4 substrate.

4.4 Common Co-Medications

Primary attention was paid to address *in vivo* whether there are any safety issues relating to the coadministration of cerivastatin with digoxin, warfarin, or cyclosporin, all of which have a narrow therapeutic range and/or respective interactions that been reported for other HMG-CoA reductase inhibitors.

There was no evidence of any mutual interaction either on warfarin or cerivastatin pharmacokinetics (see also section 4.3); the pharmacodynamic parameters prothrombin time and factor VII activity remained unaffected. Lack of interaction could also be demonstrated for the concurrent administration of cerivastatin 0.2mg and digoxin. In kidney transplant patients (n = 12), coadministration of cervastatin 0.2mg every day with individual doses of cyclosporin and other immuno-suppressive agents resulted in a 3- to 5-fold increase in cerivastatin and active metabolite plasma concentrations when compared with a control group receiving cerivastatin alone. Cerivastatin elimination was unaffected and no significant accumulation occurred under multiple-dose conditions. Cerivastatin had no influence on the steady-state whole-blood concentration/time profiles of either cyclosporin or cyclosporin metabolites in these patients.

4.5 *In Vivo* Pharmacodynamic Interaction Studies

All investigations targeted at identifying additive and/or synergistic effects on lipid parameters were conducted in the patient population and were addressed within the clinical efficacy and safety programme for cerivastatin. Combination trials of cerivastatin with cholestyramine or the fibrates bezafibrate and fenofibrate demonstrated beneficial pharmacodynamic interactions.[42]

In summary, based on the pharmacokinetic profile of cerivastatin and the information available from the currently marketed HMG-CoA reductase inhibitors, the formal interaction programme for cerivastatin covered the major concerns for drug-drug interactions when administered to the target population and appropriate information to guide the prescriber could be collected.[41]

5. Current Status

In 1998, 2 out of the 5 drugs withdrawn from the US market, i.e. mibefradil and terfenadine were withdrawn because of serious drug-drug interaction issues. At least partially due to these experiences, which raised public health concerns, both the US Food and Drug Administration and the European regulatory authorities have issued guidance documents over the past years, emphasising the need for a detailed assessment of the interaction potential of drug development candidates.[32-34]

The advance of *in vitro* techniques to elucidate metabolic patterns and to identify the enzymes catalysing the involved biotransformation steps (e.g. assays based on liver microsomes, hepatozytes, cell systems expressing single CYP isoforms, etc.) has strongly encouraged rationale mechanistic approaches to detect and/or predict interaction potential,[43-46] particularly in the area of mutual metabolic drug interactions, where most of pharmacokinetic interactions are actually reported in the literature.[28,47-49] Reviewing package insert information of recently launched drugs, such as celecoxib, moxifloxacin, rosiglitazone and sildenafil to mention only a few,[50-53] demonstrates that pharmaceutical scientists have readily adopted these concepts, as detailed in the guidance documents (section 2) and illustrated in the provided example (section 4), to decrease uncertain safety for patients in clinical trials. In addition, pharmaceutical companies have now implemented *in vitro* assays to screen for interaction issues at the candidate selection stage.

Critical appraisals of these approaches and first regulatory experiences have been recently published.[54-56]

In summary, clinical pharmacology plays a key role within the process of collecting information on

drug interactions during the preclinical and clinical development:

- addressing issues and/or investigating possible favourable properties, thus contributing to an early scientific assessment of developability
- setting up a rational *in vivo* drug-drug interaction programme
- performing early mechanistic studies to link *in vitro* with *in vivo* information (employing 'cocktail' approaches if possible)[57]
- reviewing co-medication sections for clinical trials
- conducting labelling-oriented interaction studies after proof of concept.

6. Conclusions and Future Directions

Multiple drug therapy, properly managed, is a major hope for the treatment of complex diseases. As it is impossible to carry out studies of all possible interactions of drugs concomitantly given with a new drug in order to detect an interaction, each formal clinical interaction study requires a strict benefit/risk estimation which takes into consideration all preclinical and clinical results available at the respective phase of development. Accordingly, a clinical interaction study is not necessary if the physico-chemical, pharmacokinetic or pharmacological properties of the new substance exclude the possibility of an interaction with a potential combination partner. For instance, although antacids and cimetidine will be frequently co-administered in the indication of the drug under development in the future, an interaction study is not necessary, if the possibility of interactions can be excluded due to the physico-chemical properties (e.g. no indication as to the formation of complexes) or due to the pharmacokinetic properties (e.g. pH-independent solubility, no marked enzymatic metabolism in the liver).

The design of a clinical interaction study should be based upon a detailed knowledge of the pharmacokinetic and pharmacodynamic properties of the drugs being investigated. Recent experience, especially in the area of drug metabolism, encourages the extensive use of *in vitro* methodologies and their continuous refinement. *In vivo* studies should then portray a scenario as clinically realistic as possible, and every effort should be made to quantify changes in pharmacodynamic response.

A physician cannot and should not try to remember all the documented or potential drug interactions. The astute clinician can lessen the risk of adverse consequences of drug interactions by being aware of the clinical settings in which the risk of adverse drug interactions is increased.

To avoid hazardous drug interactions the clinician needs knowledge of:

- the drug at risk
- the pharmacological mechanisms involved
- the patient groups with the greatest potential
- the resulting practical consequences.

According to Bates et al.[58] drug interactions, one of the leading causes of medication errors, were found to be potentially preventable by computerised order checking. Computerised approaches are ideal for this because reliability can approach 100% while methods that rely on human inspection will always miss some errors. Even if computers can never replace clinical judgement, computer-based tools assist prescribing in various ways.[59,60]

Furthermore, patient-held medication record cards may be useful to avoid medication errors due to drug interactions. These medication records provide assistance to the patients in the identification, organisation and self-administration of their medications, and provide clinicians with a list of medications taken by the patient.[61,62] Drugs for which patient-orientated information strategies may decrease the likelihood of drug interactions tend to those with a narrow therapeutic ratio, and have interaction potential with other drugs commonly used in combination or available without prescription.[63,64]

The fact that interactions can occur between various active substances should by itself be a conclusive argument against unnecessary polypharmacy. Prescribing fewer drugs on a rational basis can reduce the risk of a patient experiencing an adverse effect secondary to a drug interaction and may help to improve the quality of drug treatment and to save costs.

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