Drug Intractions

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What does the term drug interaction mean?

An interaction between drugs occurs when the response following the co-administration of two or more drugs is different from what we expected from the administration of a single drug. Put more simply, the consequences of a drug are changed by the presence of another drug.

What are the consequences of a drug interaction?

In assessing the consequences of an interaction, there are a number of factors that need to be considered, related to:

- **the drug:** the dose, the way it is administered (by mouth or into a vein), the way the drug is handled by the body (its "pharmacokinetics"), the effects it has on the body (its "pharmacodynamics"), the time that elapses between the administration of the different drugs and the duration of therapy.
- **the characteristics of the patient:** e.g. age, general fitness and other illnesses, whether they are taking other therapies (for example taking OTC, herbal products, etc..), whether they take their drugs on time.
- the setting in which drugs are prescribed (clinics, hospitals, retirement homes),
- the ability of the physician to recognize and diagnose a drug-drug interaction.

The effects of drug interactions may be the loss of effect of one of the drugs or the occurrence of more serious side effects than would have been anticipated. Both effects may have a detrimental impact on the health of the patient.

Anticancer drugs in most cases have what is referred to as a very small therapeutic index (the ratio of dose required to obtain the therapeutic effect and the dose at which toxic effects may occur) and, often, the dose required to achieve a therapeutic effect inevitably leads to a variety of adverse effects. These toxic effects can be induced or enhanced by interaction with other drugs in common use (such as antibiotics, antifungals, antidepressants, anticonvulsants and anticoagulants).

What are the mechanisms underlying the interaction?

To understand the mechanisms that are responsible for drug interactions it is essential to understand that a drug, before it reaches its target, must pass through several stages. If a drug is administered by mouth, it has to be taken up (absorbed) from the gastrointestinal tract, and pass in the blood through the liver. The liver changes (metabolises) the form of drugs through many enzyme systems (some called cytochromes). The transformed drug is then released into the blood stream, before reaching its target. From the blood stream, the drug can be eliminated from the body by the kidney or in the stool. Each of these steps may be the site of a drug interaction.

Some specific examples, illustrating each of these steps are:

- regarding drug absorption, antacids may reduce intestinal absorption of tetracycline, other antibiotics and bisphosphonates (drugs used to treat osteoporosis). There aren't any reported clinically significant interactions involving imatinib and sunitinib.
- many interactions are caused by the effect of a drug on the activity of enzymes in the liver, that are responsible for the metabolism of drugs. The most common interactions are induction (increased activity) and inhibition (reduction of activity) of these enzyme systems. This is the mechanism most commonly involved in interactions concerning imatinib and sunitinib. An increase of enzyme activity induced by some anticonvulsants, sedative hypnotics and oral anti-diabetic drugs can lead to a reduction in plasma concentrations, and therefore the pharmacological effects of imatinib and sunitinib.

  Reduction of activity of liver enzymes by drugs such as amiodarone (an antiarrythmic), some antifungals (fluconazole, miconazole, ketoconazole), certain antibiotics (erythromycin, clarithromycin) and cimetidine (a well-known anti-ulcer drug), may result in an increase in the plasma concentration of imatinib and sunitinib with an increased risk of adverse effects of these drugs.
- relating to the elimination of drugs, by the kidney, an increased or reduced elimination of a certain drug can lead to a lesser or greater availability of the drug in the bloodstream and its effects. For example, there is an interaction between some diuretics and lithium or some antiarrhythmics (quinidine, verapamil and amiodarone) and digoxin. There aren't any reported clinically significant interactions involving imatinib and sunitinib.
- finally, interactions may occur at the target site, enhancing the drug effect (for example an increase of sedative action after administration of benzodiazepines and antihistamines), or for antagonism between the drugs, that leads to a decrease or ablation of the effect of one of the drugs (for example, some diuretics and glucose lowering drugs). There aren't any reported clinically significant interactions of this type involving imatinib and sunitinib.

Studies have also identified new mechanisms underlying drug interactions, such as the level of drug transporters in the gut and the cancer cells (a common one is P-glycoprotein). These transporters have a role in absorption and also drug uptake by cancer cells. The level of the drug transporters can be altered due to inter-individual genetic diversity and variability. Further studies like this may allow the identification of people that, from a genetic point of view, are more at risk for drug interactions through the classification of liver enzyme activity and drug transporters.

What are the most common drug interactions?

The risk of interactions between drugs is greatest for those drugs in most common use (for example, drugs for cardiovascular disease or disorders such as arthritis, depression, anxiety and insomnia) and those which are used for long periods of time (for example, oral contraceptives, anticoagulants). Oral contraceptives are a particular problem as people often forget to mention them to other doctors, and the risk is also related to the number of drugs being taken.

Who are subjects most at risk?

- Some categories that are most at risk of interactions are patients with chronic diseases (heart failure, depression, psychosis, chronic liver disease and nephropathy, osteoarthritis) requiring multiple prolonged therapies and patients with impaired liver or kidney function In these cases, a close attention must also be given to drugs available "Over the Counter" (OTC) because laxatives, painkillers and antacids can cause serious drug interactions.
- Women who use oral contraceptives may lead to a risk of unplanned pregnancy, as result of drug interactions, especially with antibiotics, antifungals, antivirals and laxatives.
- Elderly persons are vulnerable because they generally suffer from multiple illnesses and are prescribed multiple therapies. They are also affected by age-induced changes in drug metabolism and elimination.
- In relation to children, the risk of mechanism related drug interactions is not different from the adult population.
- In relation to the use of drugs during pregnancy, this should be restricted to situations in which the underlying disease is a serious risk to the mother and unborn child

Interactions between medications and food

Food can have an effect on both the rate of absorption and the amount of drug absorbed. Dairy products (milk, cheese, yogurt), as rich in calcium, can reduce the absorption of many antibiotics, so antibiotics should be taken 1 hour before or 2 hours after consumption of these foods. Good advice is to refer to the patient information leaflet where it will state whether the drug has to be taken with or without food. There is no evidence to support clinically significant interactions between food, vitamins, supplements, coffee and other beverages containing caffeine and imatinib or sunitinib.

The important interaction between drugs and grapefruit juice

Grapefruit juice can significantly increase the amount of some drugs found in the blood stream, including imatinib and sunitinib. Grapefruit juice reduces the activity of enzymes that, in the liver (the cytochromes), are responsible for the processing of drugs. The result is in most cases an increase in the side effects of the drug. Other drugs which are affected by this are: calcium antagonists (amlodipine, felodipine, nicardipine, nifedipine, nimodipine, nisoldipine, and nitrendipina verapamil) used for the treatment of hypertension and other cardiovascular diseases, some oral cholesterol lowering drugs (atorvastatin, lovastatin, simvastatin), astemizole and terfenadine (known anti-histaminics), cisapride (commonly used to treat indigestion), carbamazepine (an anticonvulsant, but also used for nerve pain), some minor tranquilizers (buspirone, diazepam, midazolam, triazolam) used for the treatment of sleep disorders and anxiety and certain antidepressants (clomipramine and sertraline). The advice is

to avoid all intake of grapefruit juice, because small amounts of grapefruit juice, especially when highly concentrated, are sufficient to cause these interactions.

Interactions between drugs and alcohol

Subjects treated with drugs that operate on the central nervous system (antidepressants, barbiturates, antipsychotics, benzodiazepines, anti-convulsants, opiate analgesics) or drugs such as anti-histamines, paracetamol, some antibiotics and anti-mycotics should avoid drinking alcoholic beverages. In fact alcohol can increase, even at small doses, the effects of depression on the central nervous system produced by these drugs, resulting in sedation, decreased vigilance and attention span, reduced reflexes and in some cases lethargy to coma.

Interactions between medications and herbal products

The increasing usage of herbal and homeopathic products has led to the identification of drug interactions between these products and precribed drugs. The best known case is that of *hypericum perforatum* (better known as "St. John's wort"), used for the treatment of mild or moderate depression. Recent studies have shown that the St John's wort interacts with many drugs, including imatinib and sunitinib, by increasing their metabolism in the liver.

In particular interactions have been described with:

- certain antidepressants (fluoxetine, fluvoxamine, paroxetine, citalopram, trazodone, and sertraline nefazodone),
- triptans (sumatriptan, zolmitriptan and rizatriptan) used to treat headache and migraine: causing an increase in serotonergic effects (agitation, tremors, cognitive disorders, hypertension),
- warfarin (an oral anticoagulant): reducing its effectiveness,
- oral contraceptives: reducing their effect and increasing the risk of unplanned pregnancies,
- digoxin: reducing its cardioprotective effects
- some antiviral drugs used for the treatment of AIDS.

The advice is then to avoid the use of St John’s wort and to exercise caution when combining conventional medicines with so-called alternative therapies.

What should be done to reduce the risk of drug interactions?

Helpful tips for the safer use of drugs and the prevention of drug interactions are as follows:

- ask the doctor who prescribes a new drug when it should be taken, what the dose is and what are the risks of any interaction with existing therapies or medicines available “over the counter”.
- learn to consult the patient information leaflet carefully, even if at first sight it appears a bit complex.
- be aware that the more drugs you take, the greater is the risk of interactions and side effects. Therefore rational prescribing based on necessity should be the first rule of preventing interactions. For many disorders it may be better to modify life style factors such as diet, before resorting to drugs.

- for the possible interactions with food, read the administration instructions in the patient information leaflet carefully, especially to see whether you need to take the drug with or without food.
- for people who, as a consequence of chronic illness are required to take several drugs, the addition of another drug or OTC medicine is a potential hazard. It is always recommended that you point out to the doctor or pharmacist a list of the drugs (prescribed or purchased OTC) that you are taking.
- if the addition of a new drug causes you to experience new symptoms, point this out to your doctor. You should play close attention to these changes, especially in the initial weeks of therapy.
- remember that grapefruit juice interacts with many drugs, and it should be avoided
- do not assume that herbal or other "natural" products are free of the risk of interaction with conventional drugs.

Finally:
Knowledge of drug interactions is often limited or comes from experimental models or studies on healthy volunteers, from which it may be difficult to extrapolate to the clinical setting. Reporting (through special adapter voluntary reports) by the patient and doctor of adverse situations/events that might have occured during the administration of imatinib or sunitimib as a result of a drug interaction is of fundamental importance to the acquisition of knowledge regarding combinations of drugs that may cause changes in therapeutic response or the incidence of side effects.

Each patient and doctor should be responsible for monitoring and reporting any suspected drug interactions

If you have any doubt on new prescriptions contact your doctor or pharmacist.

Summary tables of the main interactions related to imatinib and sunitinib are attached.

Clinically relevant drug interactions with Imatinib (Glivec)
(update on December 18, 2007)

Interacting drug	Brand name	Clinical relevance	Possible effects	Clinical conduct
Aprepitant	***EMEND***	intense	Increased plasma levels of imatinib	Reduce doses of imatinib
Carbamazepine	***EPIMAZ*** ***TEGRETOL*** ***TEGRETOL RETARD*** ***TERIL CR***	intense	Decreased plasma levels of imatinib	Monitor the plasma levels of imatinib and if necessary, increase the dose up to 50%
Ciclosporin	***SANDIMMUN*** ***NEORAL***	mild	Increased plasma levels of cyclosporine	Use this association with caution
Clarithromycin	***KLARICID*** ***KLARICID XL*** ***CLAROSIP***	mild	Increased plasma levels of imatinib	Reduce doses of imatinib
Dexamethasone	***DEXAMETHASONE*** ***DEXSOL*** ***MAXIDEX*** ***MAXITROL*** ***OTOMIZE*** ***TOBRADEX*** ***SOFRADEX***	intense	Decreased plasma levels of imatinib	Monitor the plasma levels of imatinib and if necessary increase the dose up to 50%
Eletriptan	***RELPAX***	mild	Increased plasma levels of eletriptan	Use this association with caution and, if needed, monitor blood pressure and pulsation
Erythromycin	***AKNEMYCIN PLUS*** ***ERYACNE*** ***ERYMAX*** ***ERYTHROCIN*** ***ERYTHROPED*** ***ERYTHROPED A*** ***ERYTHROPED PI*** ***ERYTHROPED FORTE*** ***KERYMAX*** ***RETCIN*** ***ROMMIX*** ***STIEMYCIN*** ***TILORYTH*** ***ZINERYT TOPICAL SOLUTION***	mild	increased plasma levels of imatinib	Use this association with caution
Phenytoin	***EPANUTIN*** ***DILANTIN*** ***PHENYTOIN***	low	Increased plasma levels of imatinib	Monitor plasma levels of imatinib

Phenobarbital	***PHENOBARBITAL*** ***LUMINAL*** ***GARDENAL***	intense	Decreased plasma levels of imatinib	Monitor the plasma levels of imatinib and if necessary increase the dose up to 50%
***Hypericum perforatum* or St.John's wort**	***KIRA***	intense	Decreased plasma levels of imatinib	Monitor the plasma levels of imatinib and if necessary increase the dose up to 50%
Itraconazole	***SPORANOX*** ***ITRACONAZOLE***	mild	Increased plasma levels of imatinib	Use this association with caution
Ketoconazole	***NIZORAL*** ***DANDRAZOL***	mild	Increased plasma levels of imatinib	Use this assosiation with caution
L-Thyroxine	***ELTROXIN*** ***LEVOTHYROXINE***	mild	Decreased effect of levothyroxine and worsening of hypothyroidism	Increase dose of levothyroxine
Pimozide	***ORAP***	mild	Increased plasma levels of pimozide	Use with caution the association and, if needed, increase dose of imatinib
Rifabutin	***MYCOBUTIN***	mild	Decreased plasma levels of imatinib	Monitor the plasma levels of imatinib and if necessary increase the dose up to 50%
Rifampicin	***RIFADIN*** ***RIFAMPICIN*** ***RIFATER*** ***RIFINAH*** ***RIMACTAZID***	intense	Decreased plasma levels of imatinib	Monitor the plasma levels of imatinib and if necessary increase the dose up to 50%
Simvastatin	***INEGY*** ***SIMVASTATIN*** ***ZOCOR***	low	Increased plasma levels of imatinib	Reduce dose of imatinib
Voriconazole	***VFEND***	mild	Increased plasma levels of imatinib	Use this association with caution
Warfarin	***WARFARIN*** ***COUMADIN***	intense	Increased risk of bleeding	Use low weight heparins in alternative of warfarin. Otherwise closely monitor the INR or prothrombine time.

Note: *The formulations for topical or local as ointments, creams and drops and all those in which the concentration of active ingredient is low with a modest risk of interactions if the doses used in accordance with the directions recommended*

Clinically relevant drug interactions with Sunitinib (Sutent)
(update on December 18, 2007)

Interacting drug	Brand name	Clinical relevance	Possible effects	Clinical conduct
Atazanavir	***REYATAZ***	intense	Increased plasma levels of sunitinib	Reduce dose of sunitinib to at least 37.5 mg (*)
Carbamazepine	***EPIMAZ*** ***TEGRETOL*** ***TEGRETOL RETARD*** ***TERIL CR***	intense	Decreased plasma levels of sunitinib	Monitor the plasma levels of sunitinib and, if necessary, increase the dose by 12.5 up to 87.5 mg max, depending on the endurance of the patient
Clarithromycin	***KLARICID*** ***KLARICID XL*** ***CLAROSIP***	mild	Increased plasma levels of sunitinib	Reduce doses of sunitinib to at least 37.5 mg. (*)
Dexamethasone	***DEXAMETHASONE*** ***DEXSOL*** ***MAXIDEX*** ***MAXITROL*** ***OTOMIZE*** ***TOBRADEX*** ***SOFRADEX***	intense	Decreased plasma levels of sunitinib	Monitor the plasma levels of sunitinib and, if necessary, increase the dose by 12.5 to 87.5 mg max, depending on the endurance of the patient
Indinavir	***CRIXIVAN***	intense	Increased plasma levels of sunitinib	Reduce doses of sunitinib to at least 37.5 mg (*)
Phenytoin	***EPANUTIN*** ***DILANTIN*** ***PHENYTOIN***	intense	Decreased plasma levels of sunitinib	Monitor the plasma levels of sunitinib and, if necessary, increase the dose by 12.5 to 87.5 mg max, depending on the endurance of the patient
Phenobarbital	***PHENOBARBITAL*** ***LUMINAL*** ***GARDENAL***	intense	Decreased plasma levels of sunitinib	Monitor the plasma levels of sunitinib and, if necessary, increase the dose by 12.5 to 87.5 mg max, depending on the endurance of the patient
***Hypericum perforatum* or St.John's wort**	***KIRA***	intense	Decreased plasma levels of sunitinib	Monitor the plasma levels of sunitinib and if necessary to increase the dose
Itraconazole	***SPORANOX*** ***ITRACONAZOLE***	intense	Increased plasma levels of sunitinib	Reduce dose of sunitinib to at least 37.5 mg (*)
Ketoconazole	***NIZORAL*** ***DANDRAZOL***	intense	Increased plasma levels of sunitinib	Reduce dose of sunitinib to at least 37.5 mg (*)
Methadone	***METHADOSE*** ***PHYSEPTONE*** ***SYNASTONE***	intense	Increased risk of cardiac QT prolongation	Monitor heart function
Rifabutin	***MYCOBUTIN***	intense	Decreased plasma levels of sunitinib	Monitor the plasma levels of sunitinib and, if necessary, increase

				the dose by 12.5 to 87.5 mg max, depending on the endurance of the patient
Rifampicin	***RIFADIN*** ***RIFAMPICIN*** ***RIFATER*** ***RIFINAH*** ***RIMACTAZID***	intense	Decreased plasma levels of sunitinib	Monitor the plasma levels of sunitinib and, if necessary, increase the dose by 12.5 to 87.5 mg max, depending on the endurance of the patient
Ritonavir	***NORVIR***	intense	Increased plasma levels of sunitinib	Reduce dose of sunitinib to at least 37.5 mg (*)
Saquinavir	***INVIRASE***	intense	Increased plasma levels of sunitinib	Reduce dose of sunitinib to at least 37.5 mg (*)
Telithromycin	***KETEK***	intense	Increased plasma levels of sunitinib	Reduce dose of sunitinib to at least 37.5 mg (*)
Grapefruit juice		mild	Increased plasma levels of sunitinib	Monitor the plasma levels of sunitinib and, if necessary, decrease the dose
Voriconazole	***VFEND***	intense	Increased plasma levels of sunitinib	Reduce dose of sunitinib to at least 37.5 mg (*)

Note: *The formulations for topical or local as ointments, creams and drops and all those in which the concentration of active ingredient is low with a modest risk of interactions if the doses used in accordance with the directions recommended.*

(*) Current available data suggest dose reduction to 37.5 mg/day in case the patient is taking 50 mg/day under intermitted therapy (four week on, two weeks off cycles). There are no data in the published literature indicating reduction of Sunitinib under continuous dose therapy of 37.5 mg/day, but patients must be aware that some drugs can increase Sunitinib plasma levels and it is necessary to monitor possible adverse effects.

Data suggest, on a general approach, always to monitor possible adverse effects arising from drugs which could cause increase or decrease of Imatinib and Sunitinib plasma levels.

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