“Drug-Drug Interactions“

INTRODUCTION

The study of drug-drug interactions (DDIs) is a very complex field of clinical pharmacology/toxicology reaserch investigating the adverse events (ADRs) that can occur when two or more drugs are administered to patients. It also study interaction between drugs and herbal products as well as between drugs and food.

To note, interactions can also be exploited to obtain a better therapeutic outcome.

DDIs problems are destined to increase over time since:

- more and more new drugs are marketed
- there is increasing availability of over-the-counter (OTC) drugs for self-medication
- the average age of the population is increasing
- there is a growing use of herbal/alternative medicine products

Studies on DDIs present many problems of interpretation of data and translation to patients. One important parameter to establish is the clinical relevance of the DDI (i.e. the real impact of the DDI on the patient's health). Moreover, the mechanism of the DDI is not always identified.

Critical issues in DDI studies

- Studies using healthy volonteers
- Administration of single doses
- Acute administrations
- Interactions between two drugs only

Problems in identifying a DDI

- DDIs are often confused with phenomena of hyper/hypo-reactivity or idiosyncrasy
- Adverse events or treatment failure are often attributed to patient conditions
- There are frequent changes of drugs and/or posology

Key information a DDI study should provide

- Drug classes most likely involved in interactions
- Relationship between pharmacological interaction and clinical relevance
- Effect(s) of the interaction on patients
- Interaction dosing and latency of effects
- Prediction and prevention

Drug-Drug Interactions Among Elderly Patients Hospitalized for Drug Toxicity

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Context Drug-drug interactions are a preventable cause of morbidity and mortality, yet their consequences in the community are not well characterized.

Objective To determine whether elderly patients admitted to hospital with specific drug toxicities were likely to have been prescribed an interacting drug in the week prior to admission.

Design Three population-based, nested case-control studies.

Setting Ontario, Canada, from January 1, 1994, to December 31, 2000.

Patients All Ontario residents aged 66 years or older treated with glyburide, digoxin, or an angiotensin-converting enzyme (ACE) inhibitor. Case patients were those admitted to hospital for drug-related toxicity. Prescription records of cases were compared with those of controls matched on age, sex, use of the same medication, and presence or absence of renal disease to for receipt of interacting medications (co-trimoxazole with glyburide, clarithromycin with digoxin, and potassium-sparing diuretics with ACE inhibitors).

Main Outcome Measure Odds ratio for association between hospital admission for drug toxicity (hypoglycemia, digoxin toxicity, or hyperkalemia, respectively) and use of an interacting medication in the preceding week, adjusted for diagnoses, receipt of other medications, the number of prescription drugs, and the number of hospital admissions in the year preceding the index date.

Results During the 7-year study period, 909 elderly patients receiving glyburide were admitted with a diagnosis of hypoglycemia. In the primary analysis, those patients admitted for hypoglycemia were more than 6 times as likely to have been treated with co-trimoxazole in the previous week (adjusted odds ratio, 6.6; 95% confidence interval, 4.5-9.7). Patients admitted with digoxin toxicity (n = 1051) were about 12 times more likely to have been treated with clarithromycin (adjusted odds ratio, 11.7; 95% confidence interval, 7.5-18.2) in the previous week, and patients treated with ACE inhibitors admitted with a diagnosis of hyperkalemia (n=523) were about 20 times more likely to have been treated with a potassium-sparing diuretic (adjusted odds ratio, 20.3; 95% confidence interval, 13.4-30.7) in the previous week. No increased risk of drug toxicity was found for drugs with similar indications but no known interactions (amoxicillin, cefuroxime, and indapamide, respectively).

Conclusions Many hospital admissions of elderly patients for drug toxicity occur after administration of a drug known to cause drug-drug interactions. Many of these interactions could have been avoided.

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EXAMPLES OF DDIs STUDIES

- Evaluation of hospitalization risk for adverse events due to DDIs in a ≥ 65 year-old population
- 7 years of investigation di indagine
- Hospitalizations selected for:
  a) Hypoglicemia in patients treated with glyburide + co-trimoxazole
  b) Digoxin toxicity in patients treated with digossine + con digossina + clarithromycin
  c) Hyperkaliemia in patients treated with ACE inhibitors + K^+ sparing diuretics

Glyburide + Co-trimoxazole

Cotrimoxazole is a CYP2C9 inhibitor ⟹ glyburide conc. ⇑⟹ hypoglicemia

Result: hospitalization risk is 6 times higher for this association than for association with other antibiotics (e.g. glyburide + amoxicilline)

Digoxin + clarithromycin

Clarithromycin is a Pgp inhibitor ⟹ digoxin abosorption ⇑ ⟹ arrhythmia

Result: hospitalization risk is 12 volte times higher for this association than for association with other antibiotics (e.g. digoxin + cefuroxime)

ACE inhibitors + K^+ sparing diuretics

ACE inhibitors increase K^+ concentrations; K^+ sparing diuretics increase K^+ concentrations ⟹ Hyperkaliemia

Result: hospitalization risk is 20 volte times higher for this association than for association with other diuretics (e.g. ACE inhibitors + indapamide)

Risk factors for DDIs

- Number of drugs
- Age
- Dose
- Duration of therapy
- Genetic polymorphysm
- Multiple pathologies or degenerative pathologies
- Renal/epathic failure
- Number of medical specialists prescribing drugs
- Setting of prescription (GP surgery, hospital, nursing homes
- Self-medication

ADR incidence and number of drugs

Variables	Number of Drugs			
	0-5	6-10	11-15	16-20
Number of patients	4009	3861	1713	641
Number of ADRs	142	397	478	347
Incidence of ADRs	4%	10%	28%	53%

Adapted from: *"Interazioni tra Farmaci"*, S. Garattini e A. Nobili; Selecta Medica

Elderly have higher risks

- Patients aged 65 or older have twice the risk of developing iatrogenic pathologies
- 40% takes 5 or more drugs; 12% 10 or more drugs

Factors modifying drug response in elderly

Pharmacokinetics	Possible modifications
Absorption	Abs. surface reduction Blood perfusion reduction pH increase Alteration GI motility
Distribution	Reduction of serum albumin Reduction of lean body mass Increase of body fat mass Reduction of body fluids
Metabolism	Reduction of hepatic volume Reduction of hepatic blood flow Reduction of enzyme acttvity
Elimination	Reduction of renal blood flow Reduction of ultrafiltration Reduction of secretion

Adapted from: *"Interazioni tra Farmaci",* S. Garattini e A. Nobili; Selecta Medica

Neonates,infants and developing children are at risk

There are many pharmacokinetic parameters that are different:

- ✓ Higher % of body water
- ✓ Reduced amount of serum albumin
- ✓ Different metabolsim (e.g. reduced oxidative and glucuronidation, increased methylation)
- ✓ Reduced renal and hepatic elimination
- ✓ Reduced skin barrier

GENETIC POLYMORPHISM

The different pharmacokinetic and pharmacodynamic processes leading to drug effects are markedly influenced by genetic differences present in the treated population. The branch of science studying these differences is PHARMACOGENETICS.

It is now well established that genetic polymorphisms affect both PK and PD processes and can greatly vary the response to drugs. In addition, they also can play a key role in DDIs.

The more common alterations are single nucleotide polymorphisms (SNPs) and can affect either coding sequence (modifying protein structure) or regulatory regions (modifyng levels of protein expression).

Therefore, SNPs are responsible for allelic variants.

One of the most common forms of genetic polymorphism involves metabolic enzymes and can lead to:

- absence of enzyme or inactive enzyme
- reduction of active enzymes
- enzyme with different substrate specificity
- increase of active enzymes (gene duplication/multiplication)

As a consequence, drugs can manifest excessive/toxic effects or reduced efficacy/inefficacy.

GENETIC POLYMORPHISM

In the case of genetic polymorphysm involving metabolic enzymes, four different phenotypes can be generated:

- Poor Metabolizers (PM). Possessing two non functional allels leading to no enzyme expression or to inactive enzyme
- Intermediate metabolizers (IM). Possessing one functional allele, thus showing reduced metabolism
- Extensive Metabolizers (EM). Possessing two functional alleles (wild type)
- Ultra-rapid Metabolizers (UM). Gene duplication/multiplication, increased metabolism

As for oxidative metabolism, there are many isoforms of the cytochrome P450 enzyme family that are identified by CYP folowed by a number representing the family (40% sequence homology), a capital letter representing the subfamily (55% sequence homology) and a final number representing the gene: **CYP1A2**

Subfamily	Isoenzyme	Hepatic content (%)
1A	CYP1A1	<1
	CYP1A2	8-15
2A	CYP2A6	5-12
2B	CYP2B6	1-5
2C	CYP2C8	10
	CYP2C9	15-20
	CYP2C19	1
2D	CYP2D6	2
2E	CYP2E1	7-11
3A	CYP3A4	30-40
	CYP3A5[b]	<1

Enzyme	Allelic variant	Effect
CYP2A6	CYP2A6*2	Inactive enzyme
	CYP2A6*4	Inactive enzyme
	CYP2A6*5	Defective enzyme
	CYPC8*2	Reduced activity
CYP2C8	CYPC8*3	Reduced activity
	CYPC8*4	Unknown
CYP2C9	CYP2C9*2	Reduced affinity and specificity
	CYP2C9*3	
CYP2C19	CYP2C19*2	Inactive enzyme
	CYP2C19*3	Inactive enzyme
CYP2D6	CYP2D6*2xn	Increased activity
	CYP2D6*4	Inactive enzyme
	CYP2D6*5	Absent enzyme
	CYP2D6*10	Unstable enzyme
CYP3A4	CYP3A4*2	Altered affinity
	CYP3A4*3	Unknown

Adapted from: *"Interazioni tra Farmaci"*; S. Garattini e A. Nobili; Selecta Medica

ACETYLATION POLIMORPHYSM

Prototype drug: isoniazide (antitubercolar drug)
Other drugs: sulphonamides, hydralazine, clonazepam, nitrazepam, caffeine

Phenotypes: Fast acetylators (EM; wild type gene); Slow acetylators (PM)
Polymorphism of the N-acetyltransferase 2
Effects in PM: Peripheral nerve damage and hepatotoxicity

OXIDATION POLYMORPHISM

Prototype drug: debrisoquine (antihypertensive drug)
Other drugs: tricyclic antidepressants, SSRI (paroxetine, fluoxetine), antipsychotics (haloperidol, risperidone), beta blockers (metoprolol), antiarrhythmics (flecainide, propafenone), oppiods (codeine, dextrometorphan).

Phenotypes: PM, EM, UM
Modifications of CYP2D6 gene
Effects: increased risk of ADR/toxicity in PMs; reduced therapeutic effect in UM

HYDROLYSIS POLYMORPHISM

Prototype drug: succinylcholine (miorelaxant)

Phenotypes: Poor metabolizers (PM) and Extensive metabolizers (EM)
Modification of Pseudocholinesterase
Effects in PM: increased risk of prolonged respiratory muscle paralysis

P GLYCOPROTEIN POLYMORPHISM

- SNPs of the MDR1 gene
- One of the most frequent is the polymorphism of the exon 26 with a C3435T variation

Genotype TT lower levels
Genotype CC higher levels
Genotype CT intermediate levels

Example
Digoxin levels higher in TT than in CC subjects

RECEPTOR POLYMORPHISM

40-70% of asthmatic patients show poor response to β_2 adrenergic bronchodilators
ADRb2 polymorphisms:

Arg16/Gly
Gln27/Glu
Thr164/Ile

The most relevant is Arg16/Gly: the Arg genotype is less responsive than the Gly genotype

GENETIC PLYMORPHISM AND DDIs

Isoniazide (antitubercular) and phenytoin (anti-epileptic).
Usually, this interaction is not clinically relevant but it can lead to severe toxicity in slow acetylators.

Isoniazide inhibits CYP2C9 that metabolizes phenytoin (CYP2C9), but in fast acetylators this inhibition dose not alter significantly phenytoin concentrations.

In slow acetylators, concentrations of isoniazide are higher ⇨ potent inhibition of CYP2C9 ⇨ higher phenytoin levels with toxic effects (ataxia, hyperreflexia, nystagmus, tremors).

MECHANISMS OF INTERACTIONS

- Pharmaceutical interactions
- Pharmacokinetic interactions
  - Absorbtion
  - Plasma protein binding
  - Metabolism
  - Elimination

- Pharmacodynamic interactions
  - Same receptors
  - Different receptors
  - Transporters
  - Modification of hydrosaline homeostasis

Pharmaceutical interactions

a) Incompatibility between two drugs
b) Incompatibility with solvents, additives, stabilisers
c) pH
d) Temperature
e) Light exposure

Some examples

Phenytoin (pKa 8-8.3) can precipitate at more acidic pH (solution with 0.9% NaCl rather than with dextrose 5%);

Amphotericin B can precipitate with electrolytic solutions (no NaCl solution, dextrose 5%)

Na Nitroprusside is inactivated by light exposure

Na Thiopental can precipitate if mixed with other drugs lowering pH (succinylcholine, pancuronium)

Pharmacokinetic interactions

Absorption

- Direct or chemical-physical interactions

1) Formation of chelates (iron and ciproflaxine; antiacids Al, Mg, Ca and tetracyclines; dicumarol and $Mg(OH)_2$)

2) Adsorption (colestipol/colestyramine/activated charcoal and digoxin, warfarin, tricyclic antidepressants, pravastatin)

- Indirect interactions

1) Alteration of gastric pH

Agents changing gastric pH	Absorption reduction	Absorption increase
Antacids	Amprenavir, atenolol, capropril, cimetidine, digoxin, fosfomycin, gabapentin, iron, itraconazole, levothyroxine	Glyburide, glipizide, tolbutamide
Antacids containing Al	Allopurinol, bisphosphonates, quinolones, isoniazid	
Antacids containing Ca^{2+}	Quinolones, tetracyclines	
Antacids containing Mg^{2+}	Bisphosphonates, quinolones	
Antacids containing $NaHCO_3$	Ketoconazole	
Antacids containing $Al(OH)_3$ $Mg(OH)_2$	Acetylsalycilic acid, ketoconazole, propranolol, tetracyclines	Mefenamic acid
H2 receptor antagonists (e.g. Nizatidine)	Cyclosporine, clarithromycin, ketoconazole, itraconazole	Glyburide, glipizide, tolbutamide
PPIs (e.g. Omeprazole)	Ampicillin, ketoconazole, itraconazole	Glyburide, glipizide, tolbutamide

Adapted from: *"Interazioni tra Farmaci"*; S. Garattini e A. Nobili; Selecta Medica

2) Alteration of gastric emptying and GI motility ($Al(OH)_3$, beta agonists, cholinergic antagonists, opioids; metoclopramide, cisapride)

3) Competition with GI transporters (levodopa, methyldopa, beta-lactam antibiotics)

4) Alteration of intestinal bacterial flora: reduction of bacterial-mediated hydrolysis of drug conjugates eliminated via the bile and reduction of the enterohepatic circulation (antibiotics and ethinylestradiol)

Distribution

- Plasma protein (PP) binding

Acid drugs ⇒ albumin
Basic drugs ⇒ alpha-1 acidic glycoprotein
Lipophilic drugs ⇒ lipoproteins

Two or more drugs can compete for the binding to plasma proteins. The drug with higher affinity can displace the other drug, thus increasing its blood-free concentration. This interaction may have clinical relevance for drugs with PP binding > 90% (e.g. coumarins, sulfonylureas, sulphonamides, salicylates), narrow therapeutic index (digitalis drugs), small distribution volume, slow elimination rate.

- Binding to tissue proteins

Also in this case, two or more drugs can compete for binding to tissue protein. Displacement of one drugs will reduce the distribution volume of the displaced drug, leading to its increase in blood (e.g. quinidine-digoxin).

Metabolism

- Enzyme inhibition

Drug A inhibits the metabolism of drug B

1) Competitive/non competitive inhibition
2) Inhibition of enzyme synthesis
3) Enzyme destruction

Effect: increased plasmatic level of drug B

Some examples: a) Inhibition of the metabolism of some antihistamines (terfenadine and astemizole) by antibiotics/antifungals (erythromycin, clarithromycin, ketoconazole, itraconazole). 20-30 fold increase of plasmatic levels. Possible toxicity: severe arrhythmia (*torsades de pointes)*

b) Inhibition of the metabolism of some medium-acting benzodiazepines (midazolam, lorazepam) by calcium antagonists (diltiazem, verapamil) e antifungals (ketoconazole, itraconazole). Effect: increased degree of sedation and of duration.
c) Inhibition of codeine bioactivation by CYP2D6 inhibitors (e.g. fluoexetine). Effect: reduced analgesia

- Enzyme induction

Drug A increase the metabolism of drug B

In general, enzyme induction requires repeated administration.

Effect: decrease of plasmatic levels of drug B

Some examples: Barbiturates, phenytoin, carbamazepine increase metabolism of oral contraceptives (e.g, ethinylestradiol). Possible effects: intermestrual bleeding, mestrual irregularities, unintended pregnancy.

Cyt P450 isoforms	Substrates	Inhibitors	Inducers
CYP1A2	haloperidol, amitriptyline, caffeine, clomipramine, cyclobenzaprine, clozapine, fluvoxamine, estradiol, imipramine, mexiletine, naproxen, ondasetron, phenacetin, propranolol, riluzole, ropivacaine, theophylline, verapamil, warfarin, zileuton, zolmitriptan	amiodarone, cimetidine, fluoroquinolones, fluvoxamine, interferon, metoxalene, mibefradil, mexiletine, grapefruit juice, theophylline, ticlopidine	omeprazole, rifampicin, phenobarbital, phenytoin, broccoli, Brussels sprouts, grilled foods, cigarette smoke, insulin, methylcholanthrene, nafcillin, omeprazole, rifampicin
CYP2C9	amitriptyline, celecoxib, diclofenac, phenytoin, fluoxetine, fluvastatin, glipizide, ibuprofen, irbesartan, losartan, naproxen, piroxicam, rosiglitazone, sulfamethoxazole, suprofen, tamoxifen, torasemide, tolbutamide, warfarin	amiodarone, phenylbutazone, fluconazole, fluvastatin, fluvoxamine, isoniazid, itraconazole, ketoconazole, lovastatin, metronidazole, paroxetine, probenecid, ritonavir, sertraline, sulfaphenazole, temiposide, trimethoprin, zafirlukast	rifampiciN, secobarbital

Cyt P450 isoforms	Substrates	Inhinitors	Inducers
CYP2D6	haloperidol, alprenolol, amitriptyline, carvedilol, clomipramine, codeine, debrisoquine, desipramine, dexfenfluramine, dextromethorphan, encainide, phenacetin, phenformin, flecainide, fluoxetine, fluvoxamine, imipramine, lidocaine, metoprolol, mexiletine, minaprine, nortriptyline, ondasetron, perexiline, perphenazine, propafenone, propranolol, risperidone, sparteine, tamoxifen, timolol, thioridazine, tramadol, venlafaxine	aimalina, amiodarone, halofantrine, celecoxib, quinidine, cimetidine, clomipramine, chlorpheniramine, cocaine, doxorubicin, fluoxetine, levomepromazine, methadone, moclobemide, nicardipine, paroxetine, ranitidine, ritonavir, sertraline, terbinafine	dexamethasone, rifampicin
CYP2E1	acetaminophen, halothane, aniline, enflurane, ethanol, isoflurane, isoniazid, methanol, methoxiflurane, sevoflurane, theophylline, fatty acids (linolenic, linoleic, arachidonic	disulfiram	ethanol, isoniazid, ketoconazole
CYP3A (4, 5, 7)	alfentanil, haloperidol, alprazolam, astemizole, atorvastatin, azithromycin, buspirone, caffeine, quinidine, quinine, cyclosporine, cisapride, clarithromycin, chlorpheniramine, cocaine, codeine, dapsone, dextromethorphan, diazepam, diltiazem, erythromycin, estradiol, felodipine, fentanyl, finasteride, hydrocortisone, indinavir, lercanidipine, lidocaine, lovastatin, methadone, midazolam, nelfinavir, nifedipine, nisoldipine, nitrendipine, ondasetron, pimozide, progesterone, propranolol, ritonavir, salmeterol, saquinavir, sildenafil, simvastatin, tacrolimus, taxol, terfenadine, testosterone, trazodone, triazolam, verapamil, vincristina, zaleplon, zolpidem	amiodarone, azithromycin, cimetidine, ciprofloxacin, clarithromycin, diltiazem, erythromycin, fluconazole, fluvoxamine, gestodene, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, norfloxacin, ritonavir, saquinavir, setralina, grapefruit juice	barbiturates, carbamazepine, efavirenz, phenytoin, glucocorticoids, hypericum, nevirapine, pioglitazone, rifampicin, troglitazone

Adapted from: *"Interazioni tra Farmaci",* S. Garattini e A. Nobili; Selecta Medica

Pharmacokinetic interactions

Elimination

Renal excretion

A) Glomerular ultrafiltration
B) Tubular secretion
C) Tubular reabsorption

- Tubular secretion interactions

This process is mediated by transporters (for anions and cations). Therefore, two drugs can compete for the same transporter, thus leading to accumulation of one of the two and potential toxicity.

- Tubular reabsorption interactions

Drugs are reabsorbed mainly by passive diffusion, a process that is possible only for the undissociated fraction of an weak electrolyte (weak acid or base). Therefore, it is influenced by tubular pH (average 6.4) and by the drug pKa/pKb.
In this case, some drugs can alter tubular pH (acidification, alkalinization) and can influence the elimination of other drugs. If the elimination of a drug is reduced, there can be increase of its effect and duration of action.

Drugs altering tubular pH

A) Alkalinizing agents: sodiun bicarbonate ($NaHCO_3$), some diuretics (e.g. acetazolamide, thiazides)
B) Acidifying agents: Ammonium chloride (NH_4Cl)

Reduced elimination due to drug-induced renal failure

Drugs that reduce glomerular filtration rate GFR (NSAIDS, aminoglycoside antibiotics).

Pharmacokinetic interactions

P GLYCOPROTEIN (P-gp)

Encoded by the *Multidrug Resistance 1 (MDR1)* gene.
It limits drug absorption, distribution and reabsorption.
There are many drugs that are P-gp substrates, inhibitors and inducers

Substrates	Inhibitors	Inducers
Amiodarone, Quinidine, Lidocaine, Ciprofloxacin, Erythromycin, Mitomycin, Pristinamycin, Rifampicin, Amprenavir, Indinavir, Nelfinavir, Ritonavir, Saquinavir, Actinomycin D, Daunorubicin, Docetaxel, Doxoractoxanitone, Enoxosidexanitis, Enoxosidex , Vincristina, Vindesina, Fexofenadina Terfenadine, Diltiazem, Mibefradil, Nicardipine, Verapamil, Cyclosporin A, FK506, Rapamycin, Atorvastatin, Lovastatin, Pravastatin, Aldosterone, Corticosterone, Cortisol, Dexamethasone, Hydrocortisone, Methylprednisone, Amitripeticanyl, Cymperacid Ivermectin, Loperamide, Methadone, Morphine, Nadolol, Ondasentrone, Ranitidina, Tacrolimus, Talinolol, Timolol	Amiodarone, Quinidine, Lidocaine, Propafenone, Claritrimycin, Erythromycin, Ofloxacin, Rifampicin, Amitriptyline, Desipramine, Imipramine, Trimipramine, Indinavir, Nelfinavir, Ritonavir, Saquinavir, Itroconazole, Ketblizastolo, Dabate, Tremazole, Tifenemastene, Tremzil Felodipine, Gallopamil, Mibefradil, Nicardipine, Nifedipine, Nitrendipine, Verapamil, Cyclosporin A, FK506, Rapamycin, Biricodar, Valspodar, Atorvastatin, Lovastatin, Cortisol, Hydrocortisone, Testosterone, Aloperidine, Chlperidol, Carvedilol , Fluphenazine, Gibenclamide, Ivermectin, Maprotiline, Mefloquine, Midazolam, Mefiprostone, Prochlorperazine, Progesterone, Propranolol, Reserpine, Sarulimus, Grapefruit juice, Tacrolimus, Tamoxifen, Trifluoperazine	Acetylaminofluorene, Amitriptyline Bromocriptine, Clotrimazole, Delavirdine, Dexamethasone, Doxorubicin, Phenobarbital, Phenothiazines, Nefazodone, Hypericum perforatum, Paclitaxel, Prazosin, Progesterone, Reserpine, Ritonavir, Rifampicin, Trazodone, Verapamil, Vinblastine

Adapted from: *"Interazioni tra Farmaci",* S. Garattini e A. Nobili; Selecta Medica

Pharmacodynamic interactions

These interactions take place at the level of drug mechanism of action.
To understand pharmacodynamic interactions, it is important to highlight that most drugs, besides acting on the main target, can also act on other sites of action (off-targets).

- Interactions on the same receptors
- Interactions on different receptors
- Interference with cell transporters
- Interactions modifying hydrosaline homeostasis

Main effects on receptors

- Additivity/summation
  Effect of drugs A+B = effect of drug A + effect of drug
- Synergism
  Effect of drugs A+B >> effect of drug A + effect of drug B
- Antagonism
  Physiological or pharmacological (receptor) antagonism. Effect: reduction/loss of efficacy of one of the two drugs.

Some examples

Benzodiazepines+antihistamines,tricyclic antidepressants, some antiepileptics ⇨ increased sedation

NSAIDs+oral anticoagulants (warfarin) ⇨ hemorrhage

Anti MAO-A + SSRI ⇨ serotonin syndrome

Digoxin + kaliuretic diuretics ⇨ cardiac arrhythmias

DRUG-HERBAL PRODUCT INTERACTIONS

- Increasing use of herbal products (> 20% of the population in Italy).
- Erroneous belief that natural products are safe and do not cause toxic effects. On the contrary, herbal products contain chemicals that have pharmacological effects and can lead to serious interactions.

THE HYPERICUM CASE

- *Hypericum Perforatum* (HP; St John's wort) can be used to treat mild forms of depression. Antidepressant effects are due to the presence of hypericin, hyperforin and flavonoids that can act on serotonergic, dopaminergic and noradrenergic systems in the CNS.

- Different studies have demonstrated that HP preparations cause induction of CYP3A4, CYP1A2, CYP2C9 and also P-gp. Reduction of efficacy of many drugs (e.g. anti-HIV drugs, oral contraceptives, digoxin, warfarin, etc).

- HP can also have dangerous additive effects with serotonergic drugs (serotonin syndrome).

THE HYPERICUM CASE

Drugs	Hypericum (mg/day x weeks)	Effect and possible mechanism
Amitriptyline	900 x 2	↓AUC; CYP3A4 induction
Cyclosporine	900 x 3 900 x 24 1800 x 2	↓plasmatic levels ↓↓ plasmatic levels ↓↓↓ plasmatic levels; CYP3A4/P-gp induction
Digoxin	900 x 1.5	↓AUC; ↓C_{MAX}; P-gp induction
Oral contraceptives	900 x 8	↑Clearance
Indinavir	900 x 2	↓AUC; ↓C_{MAX}; CYP3A4 induction

Adapted from: *"Interazioni tra Farmaci"*; S. Garattini e A. Nobili; Selecta Medica

DRUG-FOOD INTERACTIONS

- Pharmacokinetic interactions

Absorption.
Food can influence both the absorption rate and the absorbed amount of drugs
Food influences:

a) gastric pH
b) gastrointestinal secretions
c) gastric emptying
d) splanchnic and hepatic circulation

Other factors to consider:
• amount and state of food (liquid/solid)
• food composition (fats, proteins, minerals)

Empty stomach; at least 1 hour before – 2 hours after meal

Metabolism.
It has been found that many cruciferous vegetables (cauliflowers, broccoli, Brussels sprouts) can induce Cyt P450 isoenzymes and some phase II enzymes. The relevance of this possible interaction is not yet clear.

- Pharmacodynamic interactions

DRUG-FOOD INTERACTIONS

Drugs	Food	Effects	What to do
ACE-inhibitors	Food rich in potassium (bananas, oranges, several vegetables)	Hyperkalemia	Limit the consumption of this type of food
Antibiotics (penicilline, quinolones, cephalosporines tetracyclines, rifampin)	Most common food	Reduction of drug absorption	Take drugs on an empty stomach (at laet 1 hour before or meals or 2 hours after meals). Avoid simultaneous intake of food products that contain calcium (milk, yogurt), vitamins and micronutrients containing iron
Anticoagulants (wasrfarin)	Food rich in vitamin K (cauliflowers, spinach, broccoli, garlic, lattice, fish)	Reduced anticoagulant efficacy	Limit the consumption of this types of food
Antifungal drugs (fluconazole, ketoconazole, itraoconazole)	Dairy products (milk, cheese, yogurt)	Increased drug absorption	Do not take the drug with this type of food
Digoxin	Common foods	Reduction of drug absorption	Take drugs on an empty stomach
Lipid-lowering drugs (statins)	Common foods	Increase drug absorption	Take drugs with or after food to enhance absorption

Adapted from *"Interazioni tra Farmaci",* S. Garattini e A. Nobili; Selecta Medica

THE CASE OF GRAPEFRUIT

Grapefruit contains different compounds such as flavonoids (naringin, naringenin) and furanocumarins (bergamottin, 6',7'-dihydroxybergamottin) that inhibit CYP3A4, CYP1A2 and also P-gp (intestine).
The first interaction was discovered between grapefruit juice and felodipine.

The effect is influenced by:

A) quali-quantitative composition of juice (the higher the % of fruit juice, the more potent the inhibition is. Relevant interactions occur with a single glass (≅ 250 ml) of 100% fruit juice or one fruit.
B) PK characteristics of the drug
C) individual susceptibility

Grapefruit causes inhibition and also reduced expression of CYP3A4. The effects manifest after 4 hours and can last up to 24 hours.
Repeated consumption causes a more sustained increase in the plasmatic concentration of different drugs.

Table 2: Case reports of serious adverse events related to grapefruit–drug interaction[18–26]

Serious adverse event	Drug	Amount of grapefruit consumed
Torsade de pointes	Amiodarone[18]	Juice, 1–1.5 L/d on a regular basis
	Quinine in tonic water[19]	Juice, high volume during preceding days
Complete heart block	Verapamil[20]	Juice, high volume during preceding days
Rhabdomyolysis	Atorvastatin[21,22]	Juice, 1–2 glasses/d for 5 d; juice from fresh grapefruit daily for 2 mo
	Simvastatin[23]	Whole fruit, 1 fruit/d for 2 wk
Nephrotoxicity	Tacrolimus[24]	Marmalade, 1.5 kg eaten during preceding 1 wk
Myelotoxicity	Colchicine[25]	Juice, 1 L/d for preceding 2 mo
Venous thrombosis	Ethinylestradiol[26]	Whole fruit, 1 fruit/d for breakfast for preceding 3 d

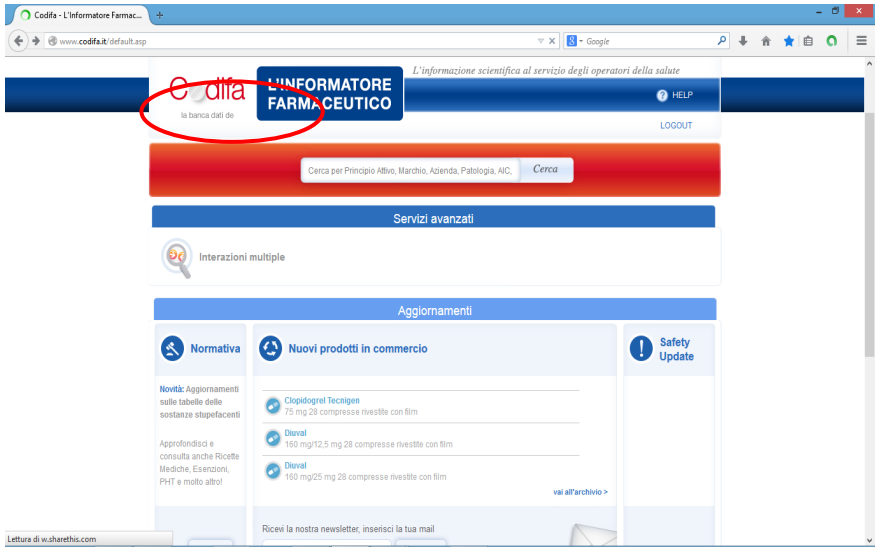
Bailey et al. (2013) CMAJ 185: 309-316

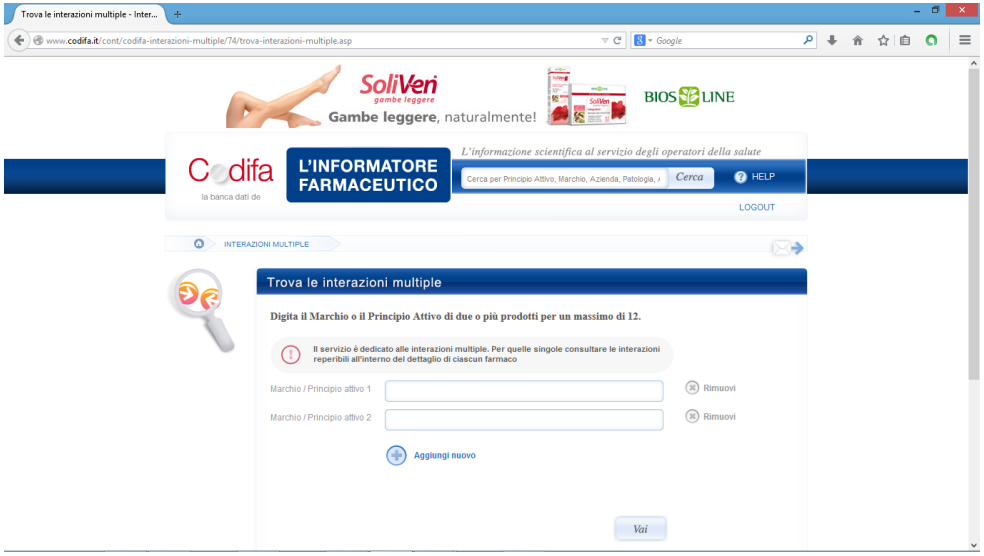
DRUG-ETHANOL INTERACTIONS

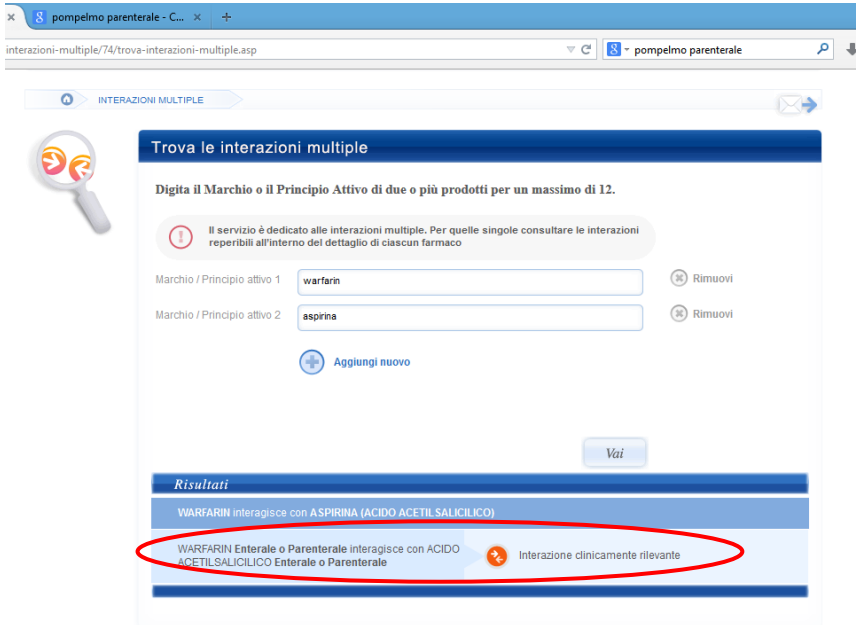
- Acute consumption ⇨ aldehyde dehydrogenase saturation ⇨ reduction of the metabolism of drugs by this enzymatic pathway ⇨ increased drug effects

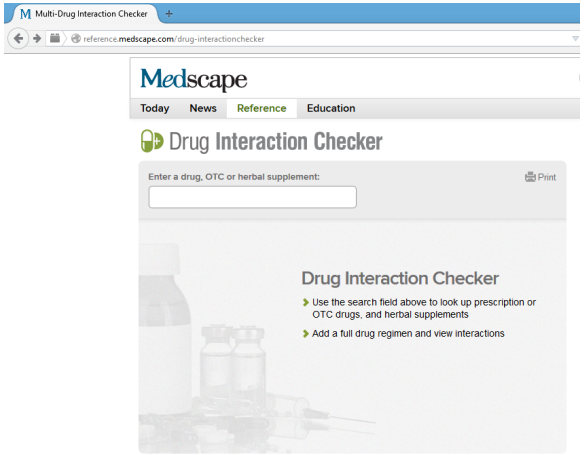
- Chronic consumption ⇨ CYP2E1 induction ⇨ reduced effects of drugs metabolized by this enzymatic pathway.

DRUG-DRUG INTERACTION DATABASES








Multi-Drug Interaction Checker
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Enter a drug, OTC or herbal supplement:
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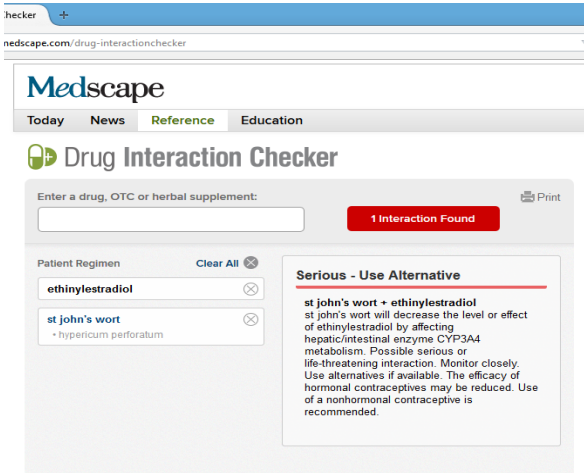
Add a full drug regimen and view interactions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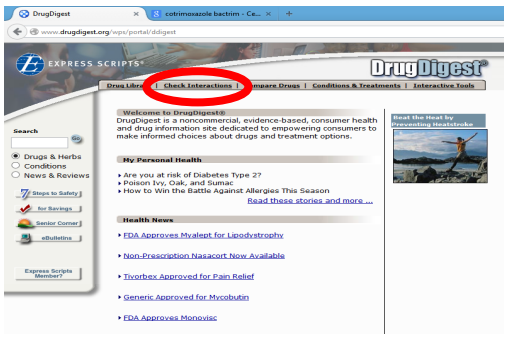
Drug Interaction Checker
Enter a drug, OTC or herbal supplement:
1 Interaction Found
Print
Patient Regimen
Clear All
ethinylestradiol
st john's wort
• hypericum perforatum
Serious - Use Alternative
st john's wort + ethinylestradiol
st john's wort will decrease the level or effect of ethinylestradiol by affecting hepatic/intestinal enzyme CYP3A4 metabolism. Possible serious or life-threatening interaction. Monitor closely. Use alternatives if available. The efficacy of hormonal contraceptives may be reduced. Use of a nonhormonal contraceptive is recommended.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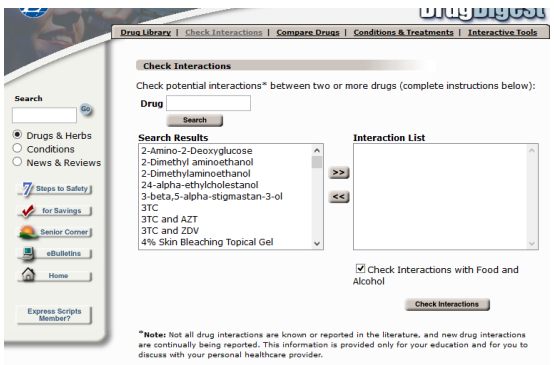
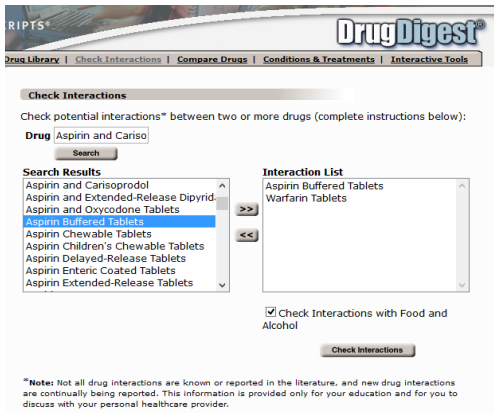
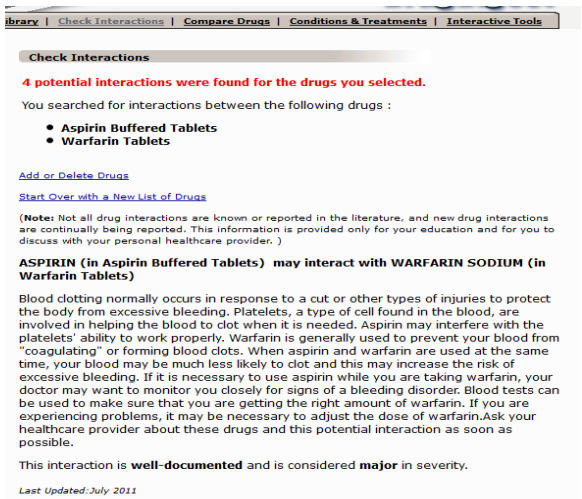
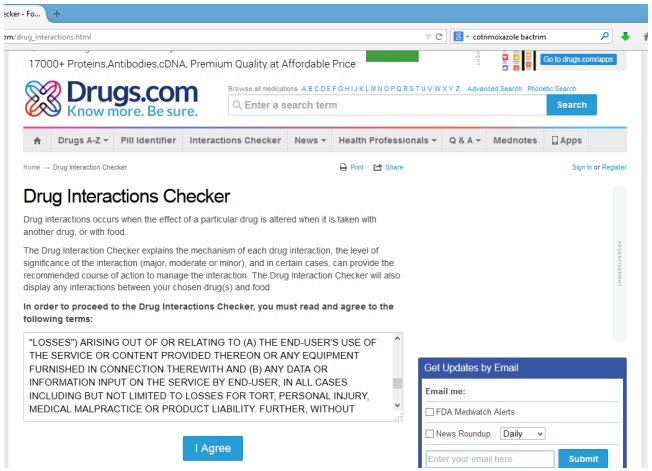

Drug Library | Check Interactions | Compare Drugs | Conditions & Treatments | Interactive Tools
Search
Drugs & Herbs
Conditions
News & Reviews
Steps to Safety
for Savings
Senior Corner
eBulletins
Home
Express Scripts Member?
Check Interactions
Check potential interactions* between two or more drugs (complete instructions below):
Drug
Search
Search Results
2-Amino-2-Deoxyglucose
2-Dimethyl aminoethanol
2-Dimethylaminoethanol
24-alpha-ethylcholestanol
3-beta,5-alpha-stigmastan-3-ol
3TC
3TC and AZT
3TC and ZDV
4% Skin Bleaching Topical Gel
Interaction List
Check Interactions with Food and Alcohol
Check Interactions
*Note: Not all drug interactions are known or reported in the literature, and new drug interactions are continually being reported. This information is provided only for your education and for you to discuss with your personal healthcare provider.


DrugDigest
Drug Library | Check Interactions | Compare Drugs | Conditions & Treatments | Interactive Tools
Check Interactions
Check potential interactions* between two or more drugs (complete instructions below):
Drug
Aspirin and Cariso
Search
Search Results
Aspirin and Carisoprodol
Aspirin and Extended-Release Dipyrid
Aspirin and Oxycodone Tablets
Aspirin Buffered Tablets
Aspirin Chewable Tablets
Aspirin Children's Chewable Tablets
Aspirin Delayed-Release Tablets
Aspirin Enteric Coated Tablets
Aspirin Extended-Release Tablets
Interaction List
Aspirin Buffered Tablets
Warfarin Tablets
Check Interactions with Food and Alcohol
Check Interactions
*Note: Not all drug interactions are known or reported in the literature, and new drug interactions are continually being reported. This information is provided only for your education and for you to discuss with your personal healthcare provider.


ibrary | Check Interactions | Compare Drugs | Conditions & Treatments | Interactive Tools
Check Interactions
4 potential interactions were found for the drugs you selected.
You searched for interactions between the following drugs :
Aspirin Buffered Tablets
Warfarin Tablets
Add or Delete Drugs
Start Over with a New List of Drugs
(Note: Not all drug interactions are known or reported in the literature, and new drug interactions are continually being reported. This information is provided only for your education and for you to discuss with your personal healthcare provider.)
ASPIRIN (in Aspirin Buffered Tablets) may interact with WARFARIN SODIUM (in Warfarin Tablets)
Blood clotting normally occurs in response to a cut or other types of injuries to protect the body from excessive bleeding. Platelets, a type of cell found in the blood, are involved in helping the blood to clot when it is needed. Aspirin may interfere with the platelets' ability to work properly. Warfarin is generally used to prevent your blood from "coagulating" or forming blood clots. When aspirin and warfarin are used at the same time, your blood may be much less likely to clot and this may increase the risk of excessive bleeding. If it is necessary to use aspirin while you are taking warfarin, your doctor may want to monitor you closely for signs of a bleeding disorder. Blood tests can be used to make sure that you are getting the right amount of warfarin. If you are experiencing problems, it may be necessary to adjust the dose of warfarin.Ask your healthcare provider about these drugs and this potential interaction as soon as possible.
This interaction is well-documented and is considered major in severity.
Last Updated:July 2011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Drug Interactions Checker
Drug interactions occurs when the effect of a particular drug is altered when it is taken with another drug, or with food.
The Drug Interaction Checker explains the mechanism of each drug interaction, the level of significance of the interaction (major, moderate or minor), and in certain cases, can provide the recommended course of action to manage the interaction. The Drug Interaction Checker will also display any interactions between your chosen drug(s) and food.
In order to proceed to the Drug Interactions Checker, you must read and agree to the following terms:
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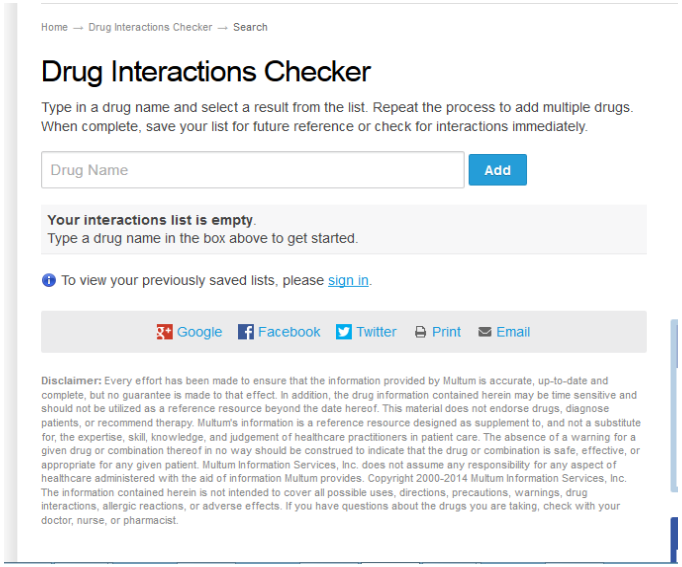
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Drug Interactions Checker
Type in a drug name and select a result from the list. Repeat the process to add multiple drugs.
When complete, save your list for future reference or check for interactions immediately.
Drug Name
Add
Your interactions list is empty.
Type a drug name in the box above to get started.
To view your previously saved lists, please sign in.
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Facebook
Twitter
Print
Email
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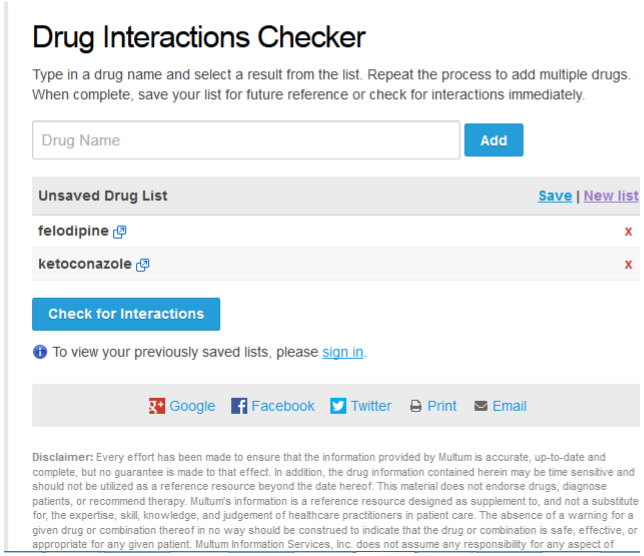
Drug Interactions Checker
Type in a drug name and select a result from the list. Repeat the process to add multiple drugs.
When complete, save your list for future reference or check for interactions immediately.
Drug Name
Add
Unsaved Drug List
Save | New list
felodipine
x
ketoconazole
x
Check for Interactions
To view your previously saved lists, please sign in.
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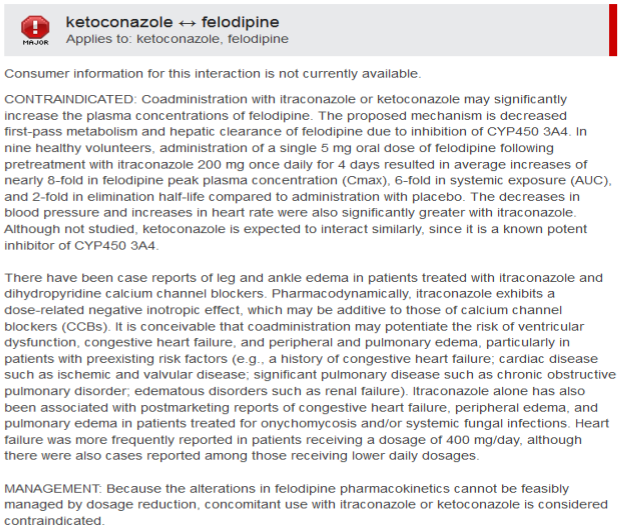
MAJOR
ketoconazole ↔ felodipine
Applies to: ketoconazole, felodipine
Consumer information for this interaction is not currently available.
CONTRAINDICATED: Coadministration with itraconazole or ketoconazole may significantly increase the plasma concentrations of felodipine. The proposed mechanism is decreased first-pass metabolism and hepatic clearance of felodipine due to inhibition of CYP450 3A4. In nine healthy volunteers, administration of a single 5 mg oral dose of felodipine following pretreatment with itraconazole 200 mg once daily for 4 days resulted in average increases of nearly 8-fold in felodipine peak plasma concentration (Cmax), 6-fold in systemic exposure (AUC), and 2-fold in elimination half-life compared to administration with placebo. The decreases in blood pressure and increases in heart rate were also significantly greater with itraconazole. Although not studied, ketoconazole is expected to interact similarly, since it is a known potent inhibitor of CYP450 3A4.
There have been case reports of leg and ankle edema in patients treated with itraconazole and dihydropyridine calcium channel blockers. Pharmacodynamically, itraconazole exhibits a dose-related negative inotropic effect, which may be additive to those of calcium channel blockers (CCBs). It is conceivable that coadministration may potentiate the risk of ventricular dysfunction, congestive heart failure, and peripheral and pulmonary edema, particularly in patients with preexisting risk factors (e.g., a history of congestive heart failure; cardiac disease such as ischemic and valvular disease; significant pulmonary disease such as chronic obstructive pulmonary disorder; edematous disorders such as renal failure). Itraconazole alone has also been associated with postmarketing reports of congestive heart failure, peripheral edema, and pulmonary edema in patients treated for onychomycosis and/or systemic fungal infections. Heart failure was more frequently reported in patients receiving a dosage of 400 mg/day, although there were also cases reported among those receiving lower daily dosages.
MANAGEMENT: Because the alterations in felodipine pharmacokinetics cannot be feasibly managed by dosage reduction, concomitant use with itraconazole or ketoconazole is considered contraindicated.

DRUG-DRUG INTERACTION TEXT-BOOK

ANALGESICI ANTIPIRETICI

Acido acetilsalicilico

interagisce con:

Principio interagente	Rilevanza clinica	Possibili effetti	Meccanismo	Documentazione	Comportamento clinico
ace-inibitori	moderata	riduzione dell'efficacia dell'ACE-inibitore	inibizione della sintesi delle prostaglandine	scarsa	monitorare la risposta terapeutica
acenocumarolo	maggiore	aumento del rischio di emorragie	ipoprotrombinemia, inibizione dell'aggregazione piastrinica, spiazzamento dell'acenocumarolo dalle proteine plasmatiche	eccellente	se ne sconsiglia la cosomministrazione
acetazolamide	moderata	aumento del rischio di tossicità da salicilato (vomito, tachicardia, iperpnea, confusione mentale) o tossicità da acetazolamide (senso di fatica, letargia, sonnolenza, confusione, acidosi metabolica ipercloremica)	aumento della concentrazione di acetazolamide e passaggio dei salicilati nei tessuti	discreta	monitorare i segni di tossicità da salicilati
acido alendronico	minore	disturbi gastrointestinali (nausea, dolore addominale, dispepsia, costipazione, diarrea, rigurgito acido)	non noto	discreta	monitorare l'insorgenza dei sintomi gastroenterici
acido ascorbico	minore	aumento del fabbisogno di acido ascorbico	inibizione dell'assorbimento dell'acido ascorbico	buona	aumentare l'assunzione di acido ascorbico con la dieta
acido valproico	moderata	aumento del rischio di tossicità da acido valproico (depressione del sistema nervoso centrale, disturbi gastrointestinali)	alterazione del legame proteico e del metabolismo	scarsa	se ne sconsiglia la cosomministrazione in caso di terapia cronica con acido acetilsalicilico
alcool	moderata	aumento del rischio di emorragie gastrointestinali	prolungamento del tempo di sanguinamento e irritazione gastointestinale	eccellente	evitare l'ingestione di alcool entro 12 ore dall'assunzione del farmaco
alluminio fosfato	moderata	riduzione dell'effetto dell'acido acetilsalicilico solo per antiacidi contenenti magnesio idrossido o alluminio idrossido	riduzione dell'assorbimento e aumento della clearance renale dell'acido acetilsalicilico	buona	monitorare la risposta terapeutica all'acido acetilsalicilico