HLA-B*5701: abacavir

HLA-B*5701-positive patients have a strongly increased risk of a hypersensitivity reaction to abacavir.

**Recommendation:**
Abacavir is contra-indicated for HLA-B*5701-positive patients.

1. Advise the prescriber to prescribe an alternative according to the current guidelines.

**Literature:**

14. SPC Ziagen.

Date 11-12-2008

CYP2C9 IM: acenocoumarol

No action is needed for this gene-drug interaction.

Genetic variation may lead to a decrease in the required maintenance dose. However, there is insufficient evidence that this causes problems when therapy is initiated as usual (i.e. with frequent INR monitoring).

**Literature:**

Literature:

NO action is needed for this gene-drug interaction.

Genetic variation may lead to a decrease in the required maintenance dose. However, there is insufficient evidence that this causes problems when therapy is initiated as usual (i.e. with frequent INR monitoring).

Literature:

27. Visser LE et al. The risk of overanticoagulation in patients with cytochrome P450 CYP2C9*2 or CYP2C9*3 alleles on acenocoumarol or phenprocoumon. Pharmacogenomics 2004;1427-33.
32. Thijssen HH et al. The possession of the CYP2C9*3 allele is associated with low dose requirement of acenocoumarol.

CYP2C9*1/*3: acenocoumarol

NO action is needed for this gene-drug interaction.

Genetic variation may lead to a decrease in the required maintenance dose. However, there is insufficient evidence that this causes problems when therapy is initiated as usual (i.e. with frequent INR monitoring).

Literature:

27. Visser LE et al. The risk of overanticoagulation in patients with cytochrome P450 CYP2C9*2 or CYP2C9*3 alleles on
acenocoumarol or phenprocoumon. Pharmacogenetics 2004;1427-33.

Date 14-05-2018

CYP2C9*2/*2: acenocoumarol

NO action is needed for this gene-drug interaction.

Genetic variation may lead to a decrease in the required maintenance dose. However, there is insufficient evidence that this causes problems when therapy is initiated as usual (i.e. with frequent INR monitoring).

Literature:

26. Visser LE et al. The risk of overanticoagulation in patients with cytochrome P450 CYP2C9*2 or CYP2C9*3 alleles on acenocoumarol or phenprocoumon. Pharmacogenetics 2004;1427-33.

Date 14-05-2018

CYP2C9*2*/3: acenocoumarol

NO action is needed for this gene-drug interaction.

Genetic variation may lead to a decrease in the required maintenance dose. However, there is insufficient evidence that this causes problems when therapy is initiated as usual (i.e. with frequent INR monitoring).

Literature:

CYP2C9*3/*3: acenocoumarol

NO action is needed for this gene-drug interaction.

Genetic variation may lead to a decrease in the required maintenance dose and possibly an increase in the time needed to reach a stable INR. However, there is insufficient evidence that this causes problems when therapy is initiated as usual (i.e. with frequent INR monitoring).

Literature:

VKORC1 -1639 AA: acenocoumarol

An INR ≥ 6, resulting in an increased risk of bleeding, occurs in 8-12% of these patients during the first weeks of treatment with standard regulation by the Anticoagulation Clinic. The genetic variation increases the sensitivity to acenocoumarol.

- Monitoring by the ANTICOAGULATION CLINIC (National INR Monitoring Service):
  - recommend to use 50% of the standard initial dose
- OTHERWISE:
  - recommend to use 50% of the standard initial dose
  - recommend more frequent monitoring of the INR

The initial dose and the maintenance dose can be calculated using an algorithm. However, for patients with two or more VKORC1 and/or CYP2C9 variations, the algorithm used in EU-PACT (see https://www.knmp.nl/patientenzorg/medicatiebewaking/farmacogenetica for a calculation tool in the form of an Excel file) did not result in a significant reduction in the incidence of INRs above the target range when compared to an algorithm without genetic information. We are therefore unable to recommend the use of this algorithm at this time.

A (non-validated) algorithm has been prescribed for children that should result in a better prediction of the maintenance dose for AA than the current guideline used by the Anticoagulation Clinic (Maagdenberg H et al. The pediatric acenocoumarol dosing algorithm: The Children Anticoagulation and Pharmacogenetics Study. J Thromb Haemost 2018 Jun 23 [Epub ahead of print]. PubMed PMID: 29935043).

Literature:


Date 10-09-2018

VKORC1 -1639 GA: acenocoumarol

NO action is needed for this gene-drug interaction.

The genetic variation results in a reduction of the required dose, but with the current practice of initiating or reviewing treatment this results in little or no increased risk of bleeding or excessive anticoagulation.

Literature:

Date 10-09-2018

**CYP2D6 IM: amiodaron**

This is NOT a gene-drug interaction.

Literature:
-  

Date 24-08-2016

**CYP2D6 PM: amiodaron**

This is NOT a gene-drug interaction.

Literature:
-  

Date 24-08-2016

**CYP2D6 UM: amiodaron**

This is NOT a gene-drug interaction.

Literature:
-  

Date 24-08-2016

**CYP2D6 IM: amitriptyline**

The genetic polymorphism leads to decreased metabolic capacity of CYP2D6, which may cause an increase in the plasma concentrations of amitriptyline and its active metabolite nortriptyline and decreased plasma concentrations of the active metabolites E-10-OH-amitriptyline and E-10-OH-nortriptyline.

**Recommendation:**

1. Choose an alternative if possible
   Antidepressants that are not metabolised via CYP2D6 - or to a lesser extent - include, for example, citalopram and sertraline.
2. If an alternative is not an option: use 60% of the standard dose and monitor the plasma concentrations of amitriptyline and nortriptyline
As side effects are related to nortriptyline plasma concentrations and the efficacy to amitriptyline plus nortriptyline plasma concentrations, which are influenced to a lesser extent by CYP2D6, it is not known whether it is possible to reduce the dose to such an extent that the side effects disappear, but the efficacy is maintained.

Literature:

1. de Vos A et al. Association between CYP2C19*17 and metabolism of amitriptyline, citalopram and clomipramine in Dutch hospitalized patients. Pharmacogenomics J 2010 Jun 8 [Epub ahead of print]

Date 19-09-2007

CYP2D6 PM: amitriptyline

The genetic polymorphism leads to decreased metabolic capacity of CYP2D6, which may cause an increase in the plasma concentrations of amitriptyline and its active metabolite nortriptyline and decreased plasma concentrations of the active metabolites E-10-OH-amitriptyline and E-10-OH-nortriptyline.

Recommendation:

1. Choose an alternative if possible
   Antidepressants that are not metabolised via CYP2D6 - or to a lesser extent - include, for example, citalopram and sertraline.
2. If an alternative is not an option: use 50% of the standard dose and monitor the plasma concentrations of amitriptyline and nortriptyline
   As side effects are related to nortriptyline plasma concentrations and the efficacy to amitriptyline plus nortriptyline plasma concentrations, which are influenced to a lesser extent by CYP2D6, it is not known whether it is possible to reduce the dose to such an extent that the side effects disappear, but the efficacy is maintained.

Literature:

1. de Vos A et al. Association between CYP2C19*17 and metabolism of amitriptyline, citalopram and clomipramine in Dutch hospitalized patients. Pharmacogenomics J 2010 Jun 8 [Epub ahead of print]
The genetic polymorphism leads to increased metabolic capacity of CYP2D6, which may cause a decrease in the plasma concentrations of amitriptyline and its active metabolite nortriptyline and increased plasma concentrations of the active metabolites E-10-OH-amitriptyline and E-10-OH-nortriptyline.

Recommendation:

1. Choose an alternative if possible
   Antidepressants that are not metabolised via CYP2D6 - or to a lesser extent - include, for example, citalopram and sertraline.
2. If an alternative is not an option: increase the dose to 1.25 times the standard dose, monitor the plasma concentrations and be alert to potential therapy failure due to decreased amitriptyline plus nortriptyline plasma concentrations and to increased plasma concentrations of the potentially cardiotoxic, active hydroxy metabolites.

Literature:

1. de Vos A et al. Association between CYP2C19*17 and metabolism of amitriptyline, citalopram and clomipramine in Dutch hospitalized patients. Pharmacogenomics J 2010 Jun 8 [Epub ahead of print]


The heterozygously present genetic polymorphism “factor V Leiden” causes an increased tendency to coagulation, resulting in an increased risk of venous thromboembolism. Contraceptives containing oestrogens can increase this risk even further.

Recommendation:

- If the patient has a FAMILY HISTORY WITH A LOT OF THROMBOSIS, or has had a PREVIOUS THROMBOSIS:
  1. Advise the prescriber to avoid the use of contraceptives that contain oestrogens and prescribe a non-hormone contraceptive - such as a copper IUD - as an alternative. One could also opt for a progestogen-only contraceptive method, such as the depot injection, an IUD with levonorgestrel or an implant with etonogestrel.
- OTHER CASES:
  1. Advise the patient to avoid additional risk factors for thrombosis (obesity, smoking, etc.).

Literature:


Date 08-06-2005


The homozygously present genetic polymorphism “factor V Leiden” causes an increased tendency to coagulation, resulting in an increased risk of venous thromboembolism. Contraceptives containing oestrogens can increase this risk even further.

Recommendation:

- If the patient has a FAMILY HISTORY WITH A LOT OF THROMBOSIS, or has had a PREVIOUS THROMBOSIS:
  1. Advise the prescriber to avoid the use of contraceptives that contain oestrogens and prescribe a non-hormone contraceptive - such as a copper IUD - as an alternative. One could also opt for a progestogen-only contraceptive method, such as the depot injection, an IUD with levonorgestrel or an implant with etonogestrel.
- OTHER CASES:
  1. Advise the patient to avoid additional risk factors for thrombosis (obesity, smoking, etc.).

Literature:


Date 08-06-2005

**CYP2D6 IM: aripiprazol**

NO action is needed for this gene-drug interaction.

The genetic variation increases the plasma concentration of the sum of aripiprazole and the active metabolite dehydroaripiprazole to a limited degree. There is insufficient evidence that this increases the risk of side effects.

**Literature:**


Date 14-05-2018

**CYP2D6 PM: aripiprazol**

The risk of side effects is increased. The genetic variation leads to an increase in the sum of the plasma concentrations of aripiprazole and the active metabolite.

- administer no more than 10 mg/day or 300 mg/month (67-75% of the standard maximum dose of aripiprazole).

**Literature:**

4. Hendset M et al. Impact of the CYP2D6 genotype on steady-state serum concentrations of aripiprazole and dehydroaripiprazole.
NO action is needed for this gene-drug interaction.

The genetic variation decreases the plasma concentration of the sum of aripiprazole and the active metabolite dehydroaripiprazole to a limited degree. There is no evidence that this increases the risk of reduced effectiveness.

Literature:


This is NOT a gene-drug interaction.

Literature:


This is NOT a gene-drug interaction.

Literature:

CYP2D6 UM: atenolol

This is NOT a gene-drug interaction.

CYP2D6 IM: atomoxetine

The genetic variation increases the plasma concentration of atomoxetine and can thereby reduce the dose requirement.

Recommendation:

1. in the event of side effects occurring and/or a response later than 9 weeks: reduce the dose and check whether the effect is conserved
   The plasma concentration of atomoxetine is a factor of 2-3 times higher for IM than for EM at the same dose.

Literature:


CYP2D6 PM: atomoxetine

The genetic variation increases the plasma concentration of atomoxetine and thereby the risk of side effects.

Recommendation:

1. start with the normal initial dose, bearing in mind that an increase in this dose probably will not be required
2. advise the patient to seek contact if side effects occur (such as decreased appetite, vomiting, abdominal pain, constipation, insomnia, early waking, drowsiness, irritability, pupil dilation and itching)
3. if the medicine is effective, but side effects occur: reduce the dose and check whether the effect is conserved
   The plasma concentration of atomoxetine is a factor of 8-11 times higher for PM than for EM at the same dose.
CYP2D6 UM: atomoxetine

The genetic variation results in an increased conversion of atomoxetine to the active metabolite 4-hydroxyatomoxetine, which has a much lower plasma concentration. As the plasma concentration of the active ingredients decreases as a result, this gene variation can result in reduced efficacy.

Recommendation:

1. be extra alert to reduced efficacy of the treatment
2. advise the patient to contact their doctor in the event of inadequate effect
3. an alternative can be selected as a precaution
   Clonidine is not metabolised by CYP2D6.

SLCO1B1 521CC: atorvastatine

The genetic polymorphism may lead to reduced atorvastatin transport to the liver. This may increase atorvastatin plasma concentrations and therefore the risk of myopathy.

Recommendation:

- Patient has ADDITIONAL SIGNIFICANT RISK FACTORS for statin-induced myopathy:
  1. Choose an alternative
     Rosuvastatin and pravastatin are influenced to a similar extent by SLCO1B1 polymorphisms but are not influenced by CYP3A4 inhibitors such as amiodarone, verapamil and diltiazem.
     Fluvastatin is not influenced by SLCO1B1 polymorphisms or CYP3A4 inhibitors.
  2. If an alternative is not an option: advise the patient to contact their doctor in the event of muscle symptoms.
- Patient has NO additional significant risk factors for statin-induced myopathy:
  1. Advise the patient to contact their doctor in the event of muscle symptoms.
The genetic polymorphism may lead to reduced atorvastatin transport to the liver. This may increase atorvastatin plasma concentrations and therefore the risk of myopathy.

Recommendation:

- Patient has ADDITIONAL SIGNIFICANT RISK FACTORS for statin-induced myopathy:
  1. Choose an alternative
     - Rosuvastatin and pravastatin are influenced to a similar extent by SLCO1B1 polymorphisms but are not influenced by CYP3A4 inhibitors such as amiodarone, verapamil and diltiazem.
     - Fluvastatin is not influenced by SLCO1B1 polymorphisms or CYP3A4 inhibitors.
  2. If an alternative is not an option: advise the patient to contact their doctor in the event of muscle symptoms.

- Patient has NO additional significant risk factors for statin-induced myopathy:
  1. Advise the patient to contact their doctor in the event of muscle symptoms.

Literature:


Date 27-11-2012

TPMT IM: azathioprine/mercaptopurine

The genetic variation reduces the conversion of azathioprine and mercaptopurine to mainly inactive metabolites. This increases the risk of serious, life-threatening adverse events such as myelosuppression.

Recommendation:

1. Start with 50% of the standard dose
   Adjustment of the initial dose should be guided by toxicity (monitoring of blood counts) and effectiveness.
   The frequency of monitoring should be increased.
   Dose adjustment is not required for doses lower than 1.5 mg/kg per day for azathioprine or 0.75 mg/kg per day for mercaptopurine.

Literature:

16. Gearry RB et al. Thiopurine S-methyltransferase (TPMT) genotype does not predict adverse drug reactions to thiopurine drugs in

Date 27-05-2015

TPMT PM: azathioprine/mercaptopurine

The genetic variation reduces the conversion of azathioprine and mercaptopurine to mainly inactive metabolites. This increases the risk of serious, life-threatening adverse events such as myelosuppression.

Recommendation:

1. Choose an alternative or start with 10% of the standard dose.
   Any adjustment of the initial dose should be guided by toxicity (monitoring of blood counts) and effectiveness.
   The frequency of monitoring should be increased.
2. If the dose is decreased: advise patients to seek medical attention when symptoms of myelosuppression (such as severe sore throat in combination with fever, regular nosebleeds and tendency to bruising) occur

Literature:

27. SPC’s Imuran en Puri-Nethol.

Date 27-05-2015

**CYP2D6 IM: bisoprolol**

This is NOT a gene-drug interaction.

Literature:

Date 26-05-2009

**CYP2D6 PM: bisoprolol**

This is NOT a gene-drug interaction.
Literature:

1. Deroubaix X et al. Comparative bioavailability of a metoprolol controlled release formulation and a bisoprolol normal release tablet after single oral dose administration in healthy volunteers.

CYP2D6 UM: bisoprolol

This is NOT a gene-drug interaction.

Date 26-05-2009

CYP2D6 IM: carvedilol

NO action is required for this gene-drug interaction.

The plasma concentration of carvedilol can be elevated. This does not, however, result in an increase in side effects.

Date 26-05-2009

CYP2D6 PM: carvedilol

NO action is required for this gene-drug interaction.

The plasma concentration of carvedilol can be elevated. This does not, however, result in an increase in side effects.

Literature:


Date 24-08-2016

CYP2D6 PM: carvedilol

NO action is required for this gene-drug interaction.

The plasma concentration of carvedilol can be elevated. This does not, however, result in an increase in side effects.
Literature:

6. SPC’s Carvedilol Sandoz (Nederland) en Coreg (VS).

Date 24-08-2016

**CYP2D6 UM: carvedilol**

NO action is required for this gene-drug interaction.

The plasma concentration of carvedilol can be reduced. This does not, however, result in a decrease in the effectiveness.

Literature:


Date 24-08-2016

**CYP2C19 IM: citalopram**

The risk of QT prolongation and torsades de pointes is theoretically increased because the gene variation leads to an increased citalopram plasma concentration. If you follow the dose recommendation below, the increased plasma concentration and the theoretically increased risk of QT prolongation will be offset.

- Do not exceed the following daily doses:
  1. adults up to 65 years: 30 mg as tablets or 22 mg as drops
  2. adults 65 years or older: 15 mg as tablets or 10 mg as drops

Literature:


Date 14-05-2018

CYP2C19 PM: citalopram

The risk of QT prolongation and therefore also the theoretical risk of torsades de pointes is increased as the gene variation leads to an increased citalopram plasma concentration. If you follow the dose recommendation below, the increased plasma concentration and the increased risk of QT prolongation will be offset.

- do not exceed the following daily doses (50% of the standard maximum dose):
  1. adults up to 65 years: 20 mg as tablets or 16 mg as drops
  2. adults 65 years or older: 10 mg as tablets or 8 mg as drops

Literature:

13. SPC’s Cipramil en Celexa (VS).
CYP2C19 UM: citalopram

NO action is needed for this gene-drug interaction.

The gene variation increases conversion of citalopram to a weakly active metabolite. However, there is no significant effect on the plasma concentration of citalopram, the tolerance or the response.

Literature:


Date 14-05-2018

CYP2D6 IM: citalopram/escitalopram

This is NOT a gene-drug interaction.

Literature:

10. SPC Cipramil.

Date 14-05-2018

CYP2D6 PM: citalopram/escitalopram

This is NOT a gene-drug interaction.
Literature:

9. SPC’s Cipramil, Lexapro (NL en VS) en Celexa (VS).

Date 14-05-2018

CYP2D6 UM: citalopram/escitalopram

This is NOT a gene-drug interaction.

Literature:

5. SPC Cipramil.

Date 14-05-2018

CYP2D6 IM: clomipramine

The risk of side effects may be increased, because the gene variation leads to increased plasma concentrations of clomipramine and the active metabolite desmethylclomipramine.

- use 70% of the standard dose and monitor the effect and side effects or the plasma concentrations of clomipramine and desmethylclomipramine
  For depression, the therapeutic range is 200-400 ng/mL for the sum of the plasma concentrations of clomipramine and desmethylclomipramine.
  For anxiety disorders, the therapeutic plasma concentration of clomipramine is approximately 100 ng/mL, in combination with a plasma concentration of desmethylclomipramine lower than 200 ng/mL. For obsessive compulsive disorder, the therapeutic plasma concentration of clomipramine is higher than 200 ng/mL, in combination with a plasma concentration of desmethylclomipramine that is as low as possible.
  A sum of the plasma concentrations of clomipramine and desmethylclomipramine higher than 600 ng/mL is considered toxic.

Literature:
The risk of side effects may be increased, because the gene variation leads to increased plasma concentrations of clomipramine and the active metabolite desmethylclomipramine.

- **Indication DEPRESSION:**
  - use 50% of the standard dose and monitor the effect and side effects or the plasma concentrations of clomipramine and desmethylclomipramine in order to set the maintenance dose. The therapeutic range is 200-400 ng/mL for the sum of the plasma concentrations of clomipramine and desmethylclomipramine. Values higher than 600 ng/mL are considered toxic.

- **Indication ANXIETY DISORDERS or OBSESSIVE COMPULSIVE DISORDER:**
  - if side effects occur: use 50% of the standard dose and monitor the effect and side effects or the plasma concentrations of clomipramine and desmethylclomipramine in order to set the maintenance dose. It is not known whether it is possible to reduce the dose to such an extent that the side effects disappear while the effectiveness is retained. Clomipramine and desmethylclomipramine both contribute to the side effects. Only clomipramine contributes to the effectiveness. For anxiety disorders, the therapeutic plasma concentration of clomipramine is approximately 100 ng/mL, in combination with a plasma concentration of desmethylclomipramine lower than 200 ng/mL. For obsessive compulsive disorder, the therapeutic plasma concentration of clomipramine is higher than 200 ng/mL, in combination with a plasma concentration of desmethylclomipramine that is as low as possible. A sum of the plasma concentrations of clomipramine and desmethylclomipramine higher than 600 ng/mL is considered toxic, whilst the therapeutic upper limit for depression is 400 ng/mL.
  - if dose reduction does not have the desired effect: avoid clomipramine

Antidepressants that are not metabolised by CYP2D6, or to a lesser extent, include citalopram and sertraline.

**Literature:**

12. SmPC Anafranil (VS).
CYP2D6 UM: clomipramine

The risk of ineffectiveness and cardiotoxic side effects may be increased. The gene variation leads to reduced plasma concentrations of clomipramine and the active metabolite desmethylclomipramine and to increased concentrations of the potentially cardiotoxic hydroxy metabolites.

- use 1.5 times the standard dose and monitor the effect and side effects of the plasma concentrations of clomipramine and desmethylclomipramine to set the maintenance dose.
  For depression, the therapeutic range is 200-400 ng/mL for the sum of the plasma concentrations of clomipramine and desmethylclomipramine.
  For anxiety disorders, the therapeutic plasma concentration of clomipramine is approximately 100 ng/mL, in combination with a plasma concentration of desmethylclomipramine lower than 200 ng/mL.
  For obsessive compulsive disorder, the therapeutic plasma concentration of clomipramine is higher than 200 ng/mL, in combination with a plasma concentration of desmethylclomipramine that is as low as possible.
- if a dose increase is not wanted due to potential cardiotoxic hydroxy metabolites: avoid clomipramine.
  Antidepressants that are not metabolised by CYP2D6, or to a lesser extent, include citalopram and sertraline.

Literature:


CYP2D6 IM: clonidine

This is NOT a gene-drug interaction.

Literature:

CYP2D6 PM: clonidine

This is NOT a gene-drug interaction.

Literature:
CYP2D6 UM: clonidine

This is NOT a gene-drug interaction.

Literature:

CYP2C19 IM: clopidogrel

The risk of serious cardiovascular and cerebrovascular events is increased in patients undergoing balloon angioplasty or stent placement (percutaneous coronary intervention) and in patients with a stroke or TIA, as the genetic variation reduces the activation of clopidogrel. No negative clinical consequences have been observed in other patients.

- PERCUTANEOUS CORONARY INTERVENTION, STROKE or TIA:
  - choose an alternative or double the dose to 150 mg/day (600 mg loading dose)
    Prasugrel, ticagrelor and acetylsalicylic acid/dipyridamole are not metabolised by CYP2C19 (or to a lesser extent).
- OTHER INDICATIONS:
  - no action required

Literature:


**CYP2C19 PM: clopidogrel**

The risk of serious cardiovascular and cerebrovascular events is increased in patients undergoing balloon angioplasty or stent placement (percutaneous coronary intervention) and in patients with a stroke or TIA, because the genetic variation reduces the activation of clopidogrel. No negative clinical consequences have been proved in other patients.

- **PERCUTANEOUS CORONARY INTERVENTION, STROKE or TIA:**
  - avoid clopidogrel
Prasugrel, ticagrelor and acetylsalicylic acid/dipyridamole are not metabolised by CYP2C19 (or to a lesser extent).

- OTHER INDICATIONS:
  - determine the level of inhibition of platelet aggregation by clopidogrel
  - consider an alternative in poor responders

Prasugrel and ticagrelor are not metabolised by CYP2C19 (or to a lesser extent).

Literature:

42. FDA Drug Safety Communication: Reduced effectiveness of Plavix (clopidogrel) in patients who are poor metabolizers of the drug. 03-12-10.
43. SPC’s Clopidogrel Sandoz en Plavix (VS).

Date 19-11-2018

**CYP2C19 UM: clopidogrel**

NO action is required for this gene-drug interaction.

The genetic variation results in increased conversion of clopidogrel to the active metabolite. However, this can result in both positive effects (reduction in the risk of serious cardiovascular and cerebrovascular events) and negative effects (increase in the risk of bleeding).

**Literature:**


Date 19-11-2018
CYP2D6 IM: clozapine

This is NOT a gene-drug interaction.

Literature:


Date 25-05-2016

CYP2D6 PM: clozapine

This is NOT a gene-drug interaction.

Literature:


Date 25-05-2016

CYP2D6 UM: clozapine

This is NOT a gene-drug interaction.

Literature:

CYP2D6 IM: codeine

The genetic variation reduces the conversion of codeine to morphine. This can result in reduced analgesia.

Recommendation:

- For COUGH: 1. no action required
- For PAIN:
  1. be alert to a reduced effectiveness
  2. if this does not work: choose an alternative
     a. Do not select tramadol, as this is also metabolised by CYP2D6
     b. Morphine is not metabolised by CYP2D6.
     c. Oxycodone is metabolised by CYP2D6 to a limited extent, but this does not result in differences in analgesia in patients.
  3. if no alternative is selected: advise the patient to report inadequate analgesia

Literature:

7. SPC Codeinefosfaat Ratiopharm.
Literature:

16. SPC Codeïnefosfaat Ratiopharm.

Date 20-11-2017

CYP2D6 UM: codeine

The genetic variation increases the conversion of codeine to morphine. This can result in an increase in side effects. Death has occurred in children who received analgesic doses. One adult with reduced kidney function and co-medication with two CYP3A4 inhibitors became comatose after use of codeine for a cough.

Recommendation:

- **DOSES HIGHER THAN 20 mg every 6 hours for adults and 10 mg every 6 hours for children aged 12 years or older AND/OR ADDITIONAL RISK FACTORS**, such as co-medication with CYP3A4 inhibitors and/or reduced kidney function:
  - Codeine is contra-indicated
    - if possible, select an alternative
      - For PAIN: do not select tramadol, as this is also metabolised by CYP2D6.
        - Morphine is not metabolised by CYP2D6. Oxycodone is metabolised by CYP2D6 to a limited extent, but this does not result in differences in side effects in patients.
      - For COUGH: noscapine is not metabolised by CYP2D6.
    - **DOSES LOWER THAN OR EQUAL TO 20 mg every 6 hours for adults and 10 mg every 6 hours for children aged 12 years or older AND NO ADDITIONAL RISK FACTORS**, such as co-medication with CYP3A4 inhibitors and/or reduced kidney function:
      - no action required

Literature:

15. SPC Codeinefosfaat Ratiopharm.
16. SPC Codeine Sulfate Tablets (VS).

Date 20-11-2017

CYP2D6 IM: disopyramide

This is NOT a gene-drug interaction.

Literature:
-

Date 24-08-2016

CYP2D6 PM: disopyramide

This is NOT a gene-drug interaction.

Literature:
-

Date 24-08-2016

CYP2D6 UM: disopyramide

This is NOT a gene-drug interaction.
CYP2D6 IM: doxepine

The risk of side effects may be increased, because the gene variation leads to increased plasma concentrations of doxepin and the active metabolite nordoxepin.

• use 80% of the standard dose and monitor the effect and side effects or the plasma concentrations of doxepin and nordoxepin in order to set the maintenance dose
  The therapeutic range is 100-250 ng/mL for the sum of doxepin and nordoxepin plasma concentrations. Values higher than 400 ng/mL are considered toxic.

Literature:


CYP2D6 PM: doxepine

The risk of side effects may be increased, because the gene variation leads to increased plasma concentrations of doxepin and the active metabolite nordoxepin.

• use 40% of the standard dose and monitor the effect and side effects or the plasma concentrations of doxepin and nordoxepin in order to set the maintenance dose
  The therapeutic range is 100-250 ng/mL for the sum of doxepin and nordoxepin plasma concentrations. Values higher than 400 ng/mL are considered toxic.

Literature:

6. SmPC Silenor (VS).

CYP2D6 UM: doxepine

The risk of ineffectiveness and cardiotoxic side effects may be increased. The gene variation leads to reduced plasma concentrations of
doxepin and the active metabolite nordoxepin and an increase in the plasma concentrations of the potentially cardiotoxic hydroxy metabolites.

- double the standard dose and monitor the effect and side effects or the plasma concentrations of doxepin and nordoxepin in order to set the maintenance dose.
  The therapeutic range is 100-250 ng/mL for the sum of doxepin and nordoxepin plasma concentrations. Values higher than 400 ng/mL are considered toxic.
- if a dose increase is not wanted due to the potentially cardiotoxic hydroxy metabolites: avoid doxepin.
  Antidepressants that are not metabolised by CYP2D6, or to a lesser extent, include citalopram and sertraline.

**Literature:**


**Date 19-11-2018**

**CYP2D6 IM: duloxetine**

This is NOT a gene-drug interaction.

**Literature:**


**Date 30-01-2017**

**CYP2D6 PM: duloxetine**

This is NOT a gene-drug interaction.

**Literature:**

3. SPC Cymbalta.

**Date 30-01-2017**

**CYP2D6 UM: duloxetine**

This is NOT a gene-drug interaction.
Literature:


Date 30-01-2017

CYP2B6 IM: efavirenz

Genetic variations increase the efavirenz plasma concentration and therefore the risk of side effects. However, the efavirenz plasma concentration remains within the therapeutic range for the majority of patients.

Recommendation:

1. Determine the efavirenz plasma concentration if side effects occur and reduce the dose if needed.
   In 14 IM adults, a dose reduction to 400 mg/day (2/3rd of the standard dose) was sufficient to achieve therapeutic plasma concentrations and to reduce or resolve side effects.
   The therapeutic range established for efavirenz is 1000-4000 ng/ml.

Literature:

CYP2B6 PM: efavirenz

Genetic variations increase the risk of side effects. The standard dose leads to an efavirenz concentration in the toxic range in the majority of patients with this genotype.

Recommendation:

- **Efavirenz in MONOpreparation, adults and children FROM 40 KG:**
  - Body mass index LESS THAN or EQUAL to 25:
    1. The recommended initial dose is 400 mg/day and this dose should be titrated to plasma concentration if needed (further reduction to 200 mg/day or in rare cases an increase to 600 mg/day).
    - The therapeutic range established for efavirenz is 1000-4000 ng/ml.
  - Body mass index GREATER than 25:
    1. The recommended initial dose is 600 mg/day and this dose should be titrated to plasma concentration if needed (reduction to 400 or 200 mg/day).
    - The therapeutic range established for efavirenz is 1000-4000 ng/ml.

- **Efavirenz in MONOpreparation, children LIGHTER THAN 40 KG:**
  1. Start with the standard dose and titrate this dose to plasma concentration if needed. In adults, therapeutic plasma concentrations were achieved at either 2/3rd of the standard dose (1/3rd of the patients) or 1/3rd of the standard dose (2/3rd of the patients). In children younger than 3 years, therapeutic plasma concentrations were achieved at doses of approximately 10 mg/kg per day (as capsules) (100 mg/day for 7-14 kg and 150 mg/day for 14-17 kg; 50-75% of the standard dose).
    - The therapeutic range established for efavirenz is 1000-4000 ng/ml.

- **Efavirenz in COMBINATION preparation:**
  1. Initiate the combination preparation and titrate the efavirenz dose to plasma concentration if needed (reduction to 400 or 200 mg/day).
    - The therapeutic range established for efavirenz is 1000-4000 ng/ml.

Note: the dosing recommendations above are based on PM patients with the *6/*6 genotype. There is evidence that the *18/*18 genotype in PM patients (only present in negroid patients) may require greater dose reductions.

Considerations:

Detailed justification for the recommendation is contained in the risk analysis. The considerations used for adults are also given below. The median or mean plasma concentrations or AUC in PM patients are above the therapeutic range, except in 3 studies with low efavirenz plasma concentrations in EM patients (2 of the 3 studies performed in Africa and 1 study in the United States and Italy). A recent study showed a similar virological response for efavirenz 400 and 600 mg/day in patients not selected on genotype. The risk of underdose is therefore very small if the initial dose is reduced to 400 mg/day. Two small studies showed that dose reductions did not reduce the efficacy (HIV remained undetectable), but side effects did reduce in 24 PM patients. Compliance improves with administration of a combination preparation and the absence of unnecessary side effects due to excessive plasma concentrations.

Consideration to CYP2B6 inducers such as rifampicin is not needed in PM patients. The significantly low or absent metabolic capacity of CYP2B6 makes induction of little to no relevance. Moreover, the effects of enzyme induction by rifampicin and enzyme inhibition by isoniazid on efavirenz plasma concentrations seem to largely cancel each other out, independent of the CYP2B6 phenotype of the patient.

Literature:

20. SPC’s Efavirenz Mylan en Sustiva (VS).

Date 05-03-2018

CYP2D6 IM: eliglustat

This gene variation reduces the conversion of eliglustat to inactive metabolites. However, in the absence of CYP2D6 and CYP3A inhibitors, this does not result in a clinically significant increased risk of side effects.

Recommendation:

- Co-medication with BOTH a MODERATE to STRONG CYP2D6 INHIBITOR AND a MODERATE to STRONG CYP3A INHIBITOR:
  - Eliglustat is contra-indicated.
  1. choose an alternative if possible
  2. Strong CYP2D6 inhibitor: for example paroxetine, fluoxetine, quinidine, bupropione.
  3. Moderate CYP2D6 inhibitor: for example duloxetine, terbinafine, moclobemide, mirabegron, cinacalcet, dronedarone.
  4. Strong CYP3A inhibitor: for example ketoconazole, clarithromycin, itraconazole, cobicistat, indinavir, lopinavir, ritonavir, saquinavir, telaprevir, tipranavir, posaconazole, voriconazole, telithromycin, conivaptan, boceprevir.
  5. Moderate CYP3A inhibitor: for example erythromycin, ciprofloxacin, fluconazole, diltiazem, verapamil, aprepitant, atazanavir, darunavir, fosamprenavir, imatinib, cetitidine.

- Co-medication with a STRONG CYP2D6 INHIBITOR (e.g. paroxetine, fluoxetine, quinidine, bupropione):
  1. use a dose of 84 mg eliglustat 1x daily
  2. be alert to side effects

- Co-medication with a MODERATE CYP2D6 INHIBITOR (for example duloxetine, terbinafine, moclobemide, mirabegron, cinacalcet, dronedarone):
  1. consider a dose of 84 mg eliglustat 1x daily
  2. be alert to side effects

- Co-medication with a STRONG CYP3A INHIBITOR (for example ketoconazole, clarithromycin, itraconazole, cobicistat, indinavir, lopinavir, ritonavir, saquinavir, telaprevir, tipranavir, posaconazole, voriconazole, telithromycin, conivaptan, boceprevir):
  1. choose an alternative if possible
  2. if an alternative is not an option:
     - consider a dose of 84 mg eliglustat 1x daily
     - be alert to side effects

- Co-medication with a MODERATE CYP3A INHIBITOR (for example erythromycin, ciprofloxacin, fluconazole, diltiazem, verapamil, aprepitant, atazanavir, darunavir, fosamprenavir, imatinib, cetitidine):
  1. choose an alternative
  2. if an alternative is not an option:
     1. consider a dose of 84 mg eliglustat 1x daily
2. be alert to side effects

- Co-medication with a STRONG CYP3A INDUCTOR (for example rifampicin, carbamazepine, phenobarbital, phenytoin, rifabutine, hypericum):
  Eliglustat is not recommended. The plasma concentration may decrease so sharply that a therapeutic effect cannot be achieved.
  1. choose an alternative if possible

- NO co-medication with a moderate or strong CYP2D6 or CYP3A inhibitor or strong CYP3A inducer:
  1. use the standard dose of 84 mg 2x daily

Literature:
1. SPC’s Cerdelga (Nederland en VS).

Date 31-10-2016

**CYP2D6 PM: eliglustat**

This gene variation reduces the conversion of eliglustat to inactive metabolites. This increases the risk of side effects, such as a (small, dose-dependent) elongation of the QT interval. CYP3A inhibitors increase this risk even further.

Recommendation:

- Co-medication with a STRONG CYP3A INHIBITOR (for example ketoconazole, clarithromycin, itraconazole, cobicistat, indinavir, lopinavir, ritonavir, saquinavir, telaprevir, tipranavir, posaconazole, voriconazole, telithromycin, conivaptan, boceprevir):
  Eliglustat is contra-indicated.
  1. choose an alternative if possible

- Co-medication with a MODERATE CYP3A INHIBITOR (for example erythromycin, ciprofloxacin, fluconazole, diltiazem, verapamil, aprepitant, atazanavir, darunavir, fosamprenavir, imatinib, cimetidine):
  Eliglustat is not recommended.
  1. choose an alternative if possible

- Co-medication with a WEAK CYP3A INHIBITOR (for example amlopidine, cilostazole, fluvoxamine, goldenseal, isoniazide, ranitidine, ranolazine):
  1. choose an alternative for the weak CYP3A inhibitor if possible
  2. if an alternative is not an option:
     1. use a dose of 84 mg eliglustat 1x daily
     2. be alert to side effects

- Co-medication with a STRONG CYP3A INDUCTOR (for example rifampicin, carbamazepine, phenobarbital, phenytoin, rifabutine, hypericum):
  Eliglustat is not recommended. The plasma concentration may decrease so sharply that a therapeutic effect cannot be achieved.
  1. choose an alternative if possible

- NO co-medication with a CYP3A inhibitor or strong CYP3A inducer:
  1. use a dose of 84 mg 1x daily

Literature:
1. SPC’s Cerdelga (Nederland en VS).

Date 31-10-2016

**CYP2D6 UM: eliglustat**

This gene variation increases the conversion of eliglustat to inactive metabolites. As a result, a normal dose is not effective. There is not enough scientific substantiation to suggest an effective dose for all UM.

Recommendation:

Eliglustat is contra-indicated.
1. choose an alternative if possible
The risk of QT prolongation and torsades de pointes is theoretically increased because the gene variation leads to an increased escitalopram plasma concentration. If you follow the dose recommendation below, the increased plasma concentration and the theoretically increased risk of QT prolongation will be offset.

- Do not exceed the following doses (75% of the standard maximum dose):
  adults < 65 years 15 mg/day, ≥65 years 7.5 mg/day

The risk of conversion to another antidepressant is increased. In addition, the risk of QT prolongation and torsades de pointes is theoretically increased because the gene variation leads to an increased escitalopram plasma concentration. If you follow the dose recommendation below, the increased plasma concentration, the theoretically increased risk of QT prolongation and the increased risk of conversion to another antidepressant will be offset.

Literature:

- Do not exceed the following doses (50% of the standard maximum dose):
  adults < 65 years 10 mg/day, ≥65 years 5 mg/day

Literature:

17. SPC’s Lexapro (NL en VS).

Date 14-05-2018

**CYP2C19 UM: escitalopram**

The risk of conversion to another antidepressant is increased as the gene variation leads to a reduction in the escitalopram plasma concentration.

- avoid escitalopram
  Antidepressants that are not metabolised or that are metabolised to a lesser extent by CYP2C19 are, for example, paroxetine or fluvoxamine.

Literature:

4. Hodgson K et al. Genetic differences in cytochrome P450 enzymes and antidepressant treatment response. J Psychopharmacol

CYP2C19 IM: esomeprazol

NO action is needed for this gene-drug interaction.

Although the genetic variation leads to a higher plasma concentration of esomeprazole, there is insufficient evidence to support an effect on the therapeutic effectiveness and side effects.

Literature:

on the therapeutic effectiveness and side effects.

Literature:

14. SPC Nexium (Nederlands en Amerikaans).

Date 05-03-2018

**CYP2C19 UM: esomeprazol**

NO action is required for this gene-drug interaction.

Although the genetic variation may lead to faster inactivation of esomeprazole, there is insufficient evidence to support an effect on the therapeutic effectiveness and side effects.

**Literature:**


Date 05-03-2018

**CYP2C9 IM: fenprocoumon**

NO action is required for this gene-drug interaction.

The genetic variation can result in a reduction in the required maintenance dose. However, there is not enough evidence to confirm that
this causes problems with normal initiation of the therapy (i.e. frequent INR monitoring).

Literature:


Date 14-05-2018

CYP2C9 PM: fenprocoumon

NO action is required for this gene-drug interaction.

The genetic variation can result in a reduction in the required maintenance dose. However, there is not enough evidence to confirm that this causes problems with normal initiation of the therapy (i.e. frequent INR monitoring).

Literature:


Date 14-05-2018

**CYP2C9*1/*2: fenprocoumon**

NO action is required for this gene-drug interaction.

The genetic variation can result in a reduction in the required maintenance dose. However, there is not enough evidence to confirm that this causes problems with normal initiation of the therapy (i.e. frequent INR monitoring).

Literature:


Date 14-05-2018

CYP2C9*1/*3: fenprocoumon

NO action is required for this gene-drug interaction.

The genetic variation can result in a reduction in the required maintenance dose. However, there is not enough evidence to confirm that this causes problems with normal initiation of the therapy (i.e. frequent INR monitoring).

Literature:
CYP2C9*2/*2: fenprocoumon

NO action is required for this gene-drug interaction.

The genetic variation can result in a reduction in the required maintenance dose and possibly in an extension of the time required to achieve a stable INR. However, there is not enough evidence to confirm that this causes problems with normal initiation of the therapy (i.e. frequent INR monitoring).

Literature:


Visser LE et al. The risk of overanticoagulation in patients with cytochrome P450 CYP2C9*2 or CYP2C9*3 alleles on acenocoumarol or phenprocoumon. Pharmacogenetics 2004;14:27-33.


Date 14-05-2018

**CYP2C9*2/*3: fenprocoumon**

NO action is required for this gene-drug interaction.

The genetic variation can result in a reduction in the required maintenance dose. However, there is not enough evidence to confirm that this causes problems with normal initiation of the therapy (i.e. frequent INR monitoring).

Literature:


Date 14-05-2018
NO action is required for this gene-drug interaction.

The genetic variation can result in a reduction in the required maintenance dose. However, there is not enough evidence to confirm that this causes problems with normal initiation of the therapy (i.e. frequent INR monitoring).

Literature:


Date 14-05-2018

VKORC1 -1639 AA: fenprocoumon

An INR ≥ 6, resulting in an increased risk of bleeding, occurs in 17% of these patients with standard regulation by the Anticoagulation Clinic. The genetic variation increases the sensitivity to phenprocoumon.

- Monitoring by a ANTICOAGULATION CLINIC:
  - recommend to use 50% of the standard initial dose
- NO monitoring by a anticoagulation clinic:
  - recommend to use 50% of the standard initial dose
  - recommend more frequent monitoring of the INR

For patients younger than 75 years, the initial dose and the maintenance dose can be calculated using an algorithm as found in EU-PACT: see https://www.knmp.nl/patientenzorg/medicatiebewaking/farmacogenetica for a calculation tool in the form of an Excel file. However, for patients aged 75 years and older, this algorithm increases the risk of an INR above the therapeutic range compared to an algorithm without gene variations. Therefore, use of this algorithm is not recommended for these patients.

Literature:

NO action is needed for this gene-drug interaction.

The gene variation leads to a lower dose requirement, but regular monitoring of patients ensures that this does not lead to a distinct increase in the risk of bleeding.

Literature:


Date 10-09-2018

CYP2C9 IM: fenytoine

Genetic variation reduces conversion of phenytoin to inactive metabolites. This increases the risk of side effects.

Recommendation:

1. The loading dose does not need to be adjusted.
2. For the other doses, use 75% of the standard dose and assess the dose based on effect and serum concentration after 7-10 days.
3. Advise the patient to get in touch if side effects (such as ataxia, nystagmus, slurred speech, sedation or rash) occur.

Literature:


Date 31-10-2016
CYP2C9 PM: fenytoine

Genetic variation reduces conversion of phenytoin to inactive metabolites. This increases the risk of side effects.

Recommendation:

1. The loading dose does not need to be adjusted.
2. For the other doses, use 40-50% of the standard dose and assess the dose based on effect and serum concentration after 7-10 days.
3. Advise the patient to get in touch if side effects (such as ataxia, nystagmus, slurred speech, sedation or rash) occur.

Literature:


Date 31-10-2016

CYP2C9*1/*2: fenytoine

Genetic variation reduces conversion of phenytoin to inactive metabolites. This increases the risk of side effects.

Recommendation:

1. The loading dose does not need to be adjusted.
2. For the other doses, use 75% of the standard dose and assess the dose based on effect and serum concentration after 7-10 days.
3. Advise the patient to get in touch if side effects (such as ataxia, nystagmus, slurred speech, sedation or rash) occur.

Literature:


Date 31-10-2016
CYP2C9*1/*3: fenytoine

Genetic variation reduces conversion of phenytoin to inactive metabolites. This increases the risk of side effects. The life-threatening cutaneous side effects Stevens-Johnson Syndrome and toxic epidermal necrolysis may occur, especially in Asian patients.

Recommendation:

1. The loading dose does not need to be adjusted.
2. For the other doses, use 75% of the standard dose and assess the dose based on effect and serum concentration after 7-10 days.
3. Advise the patient to get in touch if side effects (such as ataxia, nystagmus, slurred speech, sedation or, especially in Asian patients, rash) occur.

Literature:


Date 31-10-2016

CYP2C9*2/*2: fenytoine

Genetic variation reduces conversion of phenytoin to inactive metabolites. This increases the risk of side effects.

Recommendation:

1. The loading dose does not need to be adjusted.
2. For the other doses, use 50% of the standard dose and assess the dose based on effect and serum concentration after 7-10 days.
3. Advise the patient to get in touch if side effects (such as ataxia, nystagmus, slurred speech, sedation or rash) occur.

Literature:


Date 31-10-2016

CYP2C9*2/*3: fenytoine

Genetic variation reduces conversion of phenytoin to inactive metabolites. This increases the risk of side effects.

Recommendation:

1. The loading dose does not need to be adjusted.
2. For the other doses, use 50% of the standard dose and assess the dose based on effect and serum concentration after 7-10 days.
3. Advise the patient to get in touch if side effects (such as ataxia, nystagmus, slurred speech, sedation or rash) occur.

Literature:

5. www.nvza.nl, TDM monografie voor fenytoïne.

Date 31-10-2016

CYP2C9*3/*3: fenytoine

Genetic variation reduces conversion of phenytoin to inactive metabolites. This increases the risk of side effects. The life-threatening cutaneous side effects Stevens-Johnson Syndrome and toxic epidermal necrolysis may occur, especially in Asian patients.

Recommendation:

1. The loading dose does not need to be adjusted.
2. For the other doses, use 40% of the standard dose and assess the dose based on effect and serum concentration after 7-10 days.
3. Advise the patient to get in touch if side effects (such as ataxia, nystagmus, slurred speech, sedation or, especially in Asian patients, rash) occur.

Literature:

15. www.nvza.nl, TDM monografie voor fenytoïne.

Date 31-10-2016

**CYP2D6 IM: flecainide**

The genetic variation reduces conversion of flecainide to inactive metabolites. This may increase the risk of side effects.

**Recommendation:**

- Indications other than diagnosis of Brugada syndrome:
  1. reduce the dose to 75% of the standard dose and record an ECG and monitor the plasma concentration

- Provocation test for diagnosis of Brugada syndrome:
  No action required.
  At a dose of 2.0 mg/kg body weight to a maximum of 150 mg, the response is better for patients with alleles that result in reduced activity.
  All 5 patients with these alleles and 20% of the patients with two fully active alleles exhibited a response within 30 minutes.

**Literature:**

5. Doki K et al. Effect of CYP2D6 genotype on flecainide pharmacokinetics in Japanese patients with supraventricular
CYP2D6 PM: flecainide

The genetic variation reduces conversion of flecainide to inactive metabolites. This increases the risk of side effects.

Recommendation:

1. reduce the dose to 50% of the standard dose and record an ECG and monitor the plasma concentration

Literature:


CYP2D6 UM: flecainide

The genetic variation increases conversion of flecainide to inactive metabolites. A higher dose is possibly required as a result.

Recommendation:

There are no data about the pharmacokinetics and/or the effects of flecainide in UM.

1. monitor the plasma concentration as a precaution and record an ECG or select an alternative

Examples of anti-arrhythmic drugs that are not metabolised via CYP2D6 (or to a lesser extent) include sotalol, disopyramide, quinidine and amiodarone.

HLA-B*5701: flucloxacilline

HLA-B*5701-positive patients have an 80-fold elevated risk of flucloxacillin-induced liver injury. However, the incidence is low (1-2 per 1000 individuals).

Recommendation:
1. Regularly monitor the patient’s liver function
2. Choose an alternative if liver enzymes and/or bilirubin levels are elevated

Literature:

4. SmPC Floxapen.

Date 20-11-2017

**CYP2D6 IM: flufenazine**

This is NOT a gene-drug interaction.

Despite the fact that the SmPC for fluphenazine lists CYP2D6 as the metabolising enzyme, this cannot be substantiated by the available literature.

Literature:

1. SPC Anatensol decanoaat.

Date 26-05-2009

**CYP2D6 PM: flufenazine**

This is NOT a gene-drug interaction.

Despite the fact that the SmPC for fluphenazine lists CYP2D6 as the metabolising enzyme, this cannot be substantiated by the available literature.

Literature:

1. SPC Anatensol decanoaat.

Date 26-05-2009

**CYP2D6 UM: flufenazine**

This is NOT a gene-drug interaction.

Despite the fact that the SmPC for fluphenazine lists CYP2D6 as the metabolising enzyme, this cannot be substantiated by the available literature.
Genetic variation increases the risk of severe, potentially fatal toxicity. A reduced conversion of fluorouracil/capecitabine to inactive metabolites means that the normal dose is an overdose.

Recommendation:

- Choose an alternative

NOTE: If a patient has two different genetic variations that lead to a non-functional DPD enzyme (e.g. *2A and* 13), this recommendation only applies if the variations are on a different allele.

If both variations are on the same allele, this patient has gene activity score 1, for which no increased risk of severe, potentially fatal toxicity has been found with cutaneous use. These two situations can only be distinguished by determining the enzyme activity (phenotyping).

Literature:

15. SPC Efudix crème en Carac cream (VS).
Recommendation:

- Start with 25% of the standard dose or choose an alternative.
- Adjustment of the initial dose should be guided by toxicity and effectiveness.
- Tegafur is not an alternative, as this is also metabolised by DPD.

NOTE: This recommendation only applies if the two genetic variations are on a different allele.
If both variations are on the same allele, this patient has gene activity score 1 and the recommendation for that gene activity score should be followed. These two situations can only be distinguished by determining the enzyme activity (phenotyping).

Literature:

8. SPC’s Fluorouracil PCH, Xeloda, Efudix crème, Fluorouracil (VS), en Xeloda (VS).

Date 20-11-2017

**DPD genact 1.5: fluorouracil/capecitabine**

Genetic variation increases the risk of severe, potentially fatal toxicity. A reduced conversion of fluorouracil/capecitabine to inactive metabolites means that the normal dose is an overdose.

Recommendation:

- Start with 75% of the standard dose or choose an alternative.
- Adjustment of the initial dose should be guided by toxicity and effectiveness.
- Tegafur is not an alternative, as this is also metabolised by DPD.

Literature:


17. SPC’s Fluorouracil PCH, Xeloda, Efudix crème, Fluorouracil (VS) en Xeloda (VS).

Date 20-11-2017

DPD genact 1: fluorouracil/capecitabine

Genetic variation increases the risk of severe, potentially fatal toxicity. A reduced conversion of fluorouracil/capecitabine to inactive metabolites means that the normal dose is an overdose.

Recommendation:

- Start with 50% of the standard dose or choose an alternative.
- Adjustment of the initial dose should be guided by toxicity and effectiveness.
- Tegafur is not an alternative, as this is also metabolised by DPD.

NB1: The dose reduction described here is well substantiated for *1/*2A and 1236A/1236A.

The dose reduction for patients with 2846T (2846T/2846T or 1236A/2846T) is based on, among other factors, the dose reductions identified for *1/2846T.

NB2: If a patient has two different genetic variations that result in a partially functional DPD enzyme (e.g. 2846T and 1236A), this recommendation applies if the variations are on a different allele. If both variations are on the same allele, the gene activity score is between 1 and 1.5, depending on whether and how the two gene variations influence each other and on other factors that influence the DPD activity. Whether a gene activity score of 1 or 1.5 needs to be assigned in the case of two different genetic variations can only be determined by measuring the enzyme activity (phenotyping).

Literature:


33. SPC’s Fluorouracil PCH, Xeloda, Efudix crème, Fluorouracil (VS) en Xeloda (VS).

Date 20-11-2017

DPD genact 0: fluorouracil/capecitabine, systemisch

Genetic variation increases the risk of severe, potentially fatal toxicity. A reduced conversion of fluorouracil/capecitabine to inactive metabolites means that the standard dose is a more than 100-fold overdose.

Recommendation:
1. Choose an alternative
   Tegafur is not an alternative, as this is also metabolised by DPD.
2. If an alternative is not possible:
   • determine the residual DPD activity in mononuclear cells from peripheral blood and adjust the initial dose accordingly.
   A patient with 0.5% of the normal DPD activity tolerated 0.8% of the standard dose (150 mg capecitabine every 5 days). A patient with undetectable DPD activity tolerated 0.43% of the standard dose (150 mg capecitabine every 5 days with every third dose skipped). The average Caucasian DPD activity is 9.9 nmol/hour per mg protein.
   • adjust the initial dose based on toxicity and efficacy.
NOTE: If a patient has two different genetic variations that lead to a non-functional DPD enzyme (e.g. *2A and *13), this recommendation only applies if the variations are on a different allele. If both variations are on the same allele, this patient has gene activity score 1 and the recommendation for that gene activity score should be followed. These two situations can only be distinguished by determining the enzyme activity (phenotyping).

Literature:

16. SPC’s Fluorouracil PCH, Xeloda, Efudix crème, Fluorouracil (VS), Xeloda (VS) en Carac cream (VS).

Date 20-11-2017

CYP2D6 IM: fluoxetine 5997

NO action is needed for this gene-drug interaction.

The ratio of fluoxetine/norfloxetine increases as a result of the reduced activity of CYP2D6. However, this does not affect the sum of the plasma concentrations of the active substances (fluoxetine and norfluoxetine). There is no effect on adverse events or response.

Literature:

CYP2D6 PM: fluoxetine

NO action is needed for this gene-drug interaction.

The ratio of fluoxetine/norfluoxetine increases as a result of the reduced activity of CYP2D6. However, this does not affect the sum of the plasma concentrations of the active substances (fluoxetine and norfluoxetine). There is insufficient evidence to support an effect on adverse events or response.

Literature:

5. Roberts RL et al. No evidence of increased adverse drug reactions in cytochrome P450 CYP2D6 poor metabolizers treated with fluoxetine or nortriptyline. Hum Psychopharmacol 2004;19:17-23.
7. SPC Prozac, USA, 30-01-09.

CYP2D6 UM: fluoxetine

NO action is needed for this gene-drug interaction.

The ratio of fluoxetine/norfluoxetine decreases as a result of the increased activity of CYP2D6. However, this does not affect the sum of the plasma concentrations of the active substances (fluoxetine and norfluoxetine). There is no effect on adverse events or response.

Literature:


CYP2D6 IM: flupentixol

This is NOT a gene-drug interaction.

No studies have been published in which the kinetics and the effects of flupentixol were studied for this phenotype.
CYP2D6 PM: flupentixol

This is NOT a gene-drug interaction.

No studies have been published in which the kinetics and the effects of flupentixol were studied for this phenotype.

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CYP2D6 UM: flupentixol

This is NOT a gene-drug interaction.

No studies have been published in which the kinetics and the effects of flupentixol were studied for this phenotype.

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SLCO1B1 521CC: fluvastatine

This is NOT a gene-drug interaction.

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Literature:

SLCO1B1 521TC: fluvastatin

This is NOT a gene-drug interaction.

Literature:


CYP2C19 IM: fluvoxamine

This is NOT a gene-drug interaction.

Literature:


CYP2C19 PM: fluvoxamine

This is NOT a gene-drug interaction.

Literature:

CYP2C19 UM: fluvoxamine

This is NOT a gene-drug interaction.

Literature:


CYP2D6 IM: fluvoxamine

NO action is needed for this gene-drug interaction.

The plasma concentration of fluvoxamine can increase as a result of the reduced activity of CYP2D6. However, there is insufficient scientific substantiation of an increase in the risk of side effects.

Literature:


CYP2D6 PM: fluvoxamine

NO action is needed for this gene-drug interaction.

The plasma concentration of fluvoxamine can increase as a result of the reduced activity of CYP2D6. However, there is no evidence to substantiate an increase in the risk of adverse events.

Literature:

1. Christensen M et al. Low daily 10-mg and 20-mg doses of fluvoxamine inhibit the metabolism of both caffeine (cytochrome
Date 14-05-2018

**CYP2D6 UM: fluvoxamine**

NO action is needed for this gene-drug interaction.

The plasma concentration of fluvoxamine can decrease as a result of the increased activity of CYP2D6. However, there is no scientific substantiation of a reduced effectiveness.

**Literature:**


Date 14-05-2018

**CYP2D6 IM: gefitinib**

NO action is needed for this gene-drug interaction.

Side effects can occur more frequently, as the gene variation increases the gefitinib plasma concentration. However, the side effects are reversible and manageable, to an extent that adjustment of the therapy in advance is not necessary.

**Literature:**


Date 19-11-2018

**CYP2D6 PM: gefitinib**

NO action is needed for this gene-drug interaction.
The gefitinib plasma concentration may increase due to reduced CYP2D6 activity. However, there is no evidence to suggest that side effects increase to an extent that adjustment of therapy is needed.

Literature:

3. SPC Iressa.

Date 19-11-2018

**CYP2D6 UM: gefitinib**

NO action is needed for this gene-drug interaction.

The gene variation may lead to a decrease in the gefitinib plasma concentration. In practice, an alternative is only chosen if non-response to gefitinib has been proved. Moreover, dose adjustments guided by the gefitinib plasma concentration are rarely performed in clinical practice as the analytical method is not available in most hospitals.

Literature:

3. SPC Iressa.

Date 19-11-2018

**CYP2C9 IM: glibenclamide**

NO action is required for this gene-drug interaction.

The only relevant clinical consequence that was found is an increased effectiveness of glibenclamide without an increase in the frequency and severity of hypoglycaemia.

Literature:

CYP2C9 PM: glibenclamide

NO action is required for this gene-drug interaction.

No relevant clinical consequences have been found for the genetic variation.

Literature:


CYP2C9*1/*2: glibenclamide

NO action is required for this gene-drug interaction.

The only relevant clinical consequence that was found is an increased effectiveness of glibenclamide without an increase in frequency and severity of hypoglycaemia for a group of 1 *1/*2 and 15 *1/*3.

Literature:


CYP2C9*1/*3: glibenclamide

NO action is required for this gene-drug interaction.

The only relevant clinical consequence is an increased effectiveness of glibenclamide without an increase in frequency and severity of hypoglycaemia.

Literature:


Date 20-11-2017

CYP2C9*2/*2: glibenclamide

NO action is required for this gene-drug interaction.

No significant clinical consequences have been found for the genetic variation.

Literature:

Date 20-11-2017

CYP2C9*2/*3: glibenclamide

NO action is required for this gene-drug interaction.

No significant kinetic or clinical consequences have been found for this genetic variation.

Literature:

Date 20-11-2017

CYP2C9*3/*3: glibenclamide

NO action is required for this gene-drug interaction.

No relevant clinical consequences have been found for this genetic variation.
Literature:


Date 20-11-2017

**CYP2C9 IM: gliclazide**

NO action is required for this gene-drug interaction.

The genetic variation increases the effectiveness of gliclazide without significantly increasing the risk of hypoglycaemia.

Literature:


Date 20-11-2017

**CYP2C9 PM: gliclazide**

NO action is required for this gene-drug interaction.

The genetic variation increases the effectiveness of gliclazide without significantly increasing the risk of hypoglycaemia.

Literature:


Date 20-11-2017

**CYP2C9*1/*2: gliclazide**

NO action is required for this gene-drug interaction.

The genetic variation increases the effectiveness of gliclazide without significantly increasing the risk of hypoglycaemia.

Literature:

NO action is required for this gene-drug interaction.

The genetic variation increases the effectiveness of gliclazide.

Literature:


Date 20-11-2017

CYP2C9*1/*3: gliclazide

NO action is required for this gene-drug interaction.

The genetic variation increases the effectiveness of gliclazide without significantly increasing the risk of hypoglycaemia.

Literature:


Date 20-11-2017

CYP2C9*2/*2: gliclazide

NO action is required for this gene-drug interaction.

The genetic variation increases the effectiveness of gliclazide.

Literature:

Date 20-11-2017

**CYP2C9*2/*3: gliclazide**

NO action is required for this gene-drug interaction.

The genetic variation increases the effectiveness of gliclazide.

Literature:


Date 20-11-2017

**CYP2C9*3/*3: gliclazide**

NO action is required for this gene-drug interaction.

The genetic variation increases the effectiveness of gliclazide without significantly increasing the risk of hypoglycaemia.

Literature:


Date 20-11-2017

**CYP2C9 IM: glimepiride**

NO action is required for this gene-drug interaction.

The genetic variation increases the effectiveness of glimepiride.

Literature:


Date 20-11-2017

**CYP2C9 PM: glimepiride**

NO action is required for this gene-drug interaction.

Although the genetic variation increases the risk of hypoglycaemia, this risk remains low. This also means that the genetic variation increases the effectiveness. A lack of effectiveness is a much more common problem with sulphonylurea derivatives than the occurrence of hypoglycaemia.

**Literature:**


Date 20-11-2017

**CYP2C9*1/*2: glimepiride**

NO action is required for this gene-drug interaction.

No significant kinetic or clinical consequences have been found for the genetic variation.

**Literature:**


Date 20-11-2017

**CYP2C9*1/*3: glimepiride**

NO action is required for this gene-drug interaction.

The genetic variation increases the effectiveness of glimepiride.

**Literature:**


Date 20-11-2017

**CYP2C9*2/*2: glimepiride**

NO action is required for this gene-drug interaction.

No significant clinical effects were observed for this genetic variation.

**Literature:**

CYP2C9*2/*3: glimepiride

NO action is required for this gene-drug interaction.

Although the genetic variation increases the risk of hypoglycaemia, this risk remains low. This also means that the genetic variation increases the effectiveness. A lack of effectiveness is a much more common problem with sulphonyl urea derivatives than the occurrence of hypoglycaemia.

Literature:


Date 20-11-2017

CYP2C9*3/*3: glimepiride

NO action is required for this gene-drug interaction.

Although the genetic variation increases the risk of hypoglycaemia, this risk remains low. This also means that the genetic variation increases the effectiveness. A lack of effectiveness is a much more common problem with sulphonyl urea derivatives than the occurrence of hypoglycaemia.

Literature:


Date 20-11-2017

CYP2D6 IM: haloperidol

NO action is required for this gene-drug interaction.

Literature:


Date 22-03-2006

CYP2D6 PM: haloperidol

The genetic polymorphism leads to decreased metabolic capacity of CYP2D6, which may cause increased plasma concentrations of haloperidol and the active metabolite.

Recommendation:
1. Advise the prescriber to:
   1. decrease the initial dose to 50% of the standard initial dose and adjust the dose according to the effect,
   2. or prescribe an alternative.
Anti-psychotics that are not metabolised via CYP2D6 - or to a much lesser extent - include, for example, flupentixol, fluphenazine, quetiapine, olanzapine or clozapine.

Literature:

Date 22-03-2006

CYP2D6 UM: haloperidol

The genetic polymorphism leads to increased metabolic capacity of CYP2D6, which may cause decreased plasma concentrations of haloperidol and the active metabolite reduced haloperidol.

Recommendation:
It is not possible to offer substantiated advice for dose adjustment due to the limited amount of available literature.
1. Advise the prescriber to:
   1. be alert to possible reduced plasma concentrations of haloperidol and reduced haloperidol and increase the dose based on results of therapeutic drug monitoring,
   2. or prescribe an alternative according to the current guidelines.
   Anti-psychotics that are not metabolised via CYP2D6 - or to a much lesser extent - include, for example, flupentixol, fluphenazine, quetiapine, olanzapine or clozapine.
Date 22-03-2006

CYP2C19 IM: imipramine

NO action is required for this gene-drug interaction.

The genetic variation increases imipramine plasma concentrations, but not imipramine+desipramine plasma concentrations, which govern effectiveness and side effects.

Date 10-09-2018

CYP2C19 PM: imipramine

The risk of side effects is increased. The gene variation results in an increase in the plasma concentration of imipramine+desipramine.

- use 70% of the standard dose and monitor the effect and side effects, or the imipramine and desipramine plasma concentrations to determine the maintenance dose.
- or avoid imipramine

Antidepressants that are not or to a lesser extent metabolised by CYP2C19 include, for example, nortriptyline, fluvoxamine and mirtazapine.

Literature:


Date 10-09-2018

**CYP2C19 UM: imipramine**

NO action is required for this gene-drug interaction.

The genetic variation decreases imipramine plasma concentrations, but not imipramine+desipramine plasma concentrations, which govern effectiveness and side effects.

Literature:


Date 19-11-2018

**CYP2D6 IM: imipramine**

The risk of side effects may be increased, because the gene variation leads to increased plasma concentrations of imipramine and desipramine.

- use 70% of the standard dose and monitor the effect and side effects or the plasma concentrations of imipramine and desipramine in order to set the maintenance dose
  
  The therapeutic range is 150-300 ng/mL for the sum of the imipramine and desipramine plasma concentrations. Values exceeding 500 ng/mL are considered toxic.

Literature:


Date 19-11-2018
CYP2D6 PM: imipramine

The risk of side effects may be increased, because the gene variation leads to increased plasma concentrations of imipramine and the active metabolite desipramine.

- use 30% of the standard dose and monitor the effect and side effects or the plasma concentrations of imipramine and desipramine in order to set the maintenance dose.
  The therapeutic range is 150-300 ng/mL for the sum of the imipramine and desipramine plasma concentrations. Values exceeding 500 ng/mL are considered toxic.

Literature:

7. SmPC Tofranil-PM (VS).

Date 19-11-2018

CYP2D6 UM: imipramine

The risk of ineffectiveness and cardiotoxic side effects may be increased. The gene variation leads to reduced plasma concentrations of imipramine and the active metabolite desipramine and to increased plasma concentrations of the potentially cardiotoxic hydroxy metabolites.

- use 1.7 times the standard dose and monitor the effect and side effects or the plasma concentrations of imipramine and desipramine in order to set the maintenance dose.
- if a dose increase is not wanted due to the potentially cardiotoxic hydroxy metabolites: avoid imipramine.
  Antidepressants that are not metabolised by CYP2D6 - or to a lesser extent - include, for example, citalopram and sertraline.

Literature:


Date 19-11-2018

UGT1A1 *1/*28: irinotecan

NO action is needed for this gene-drug interaction.

This genetic variation (*1/*28) is more common in Western populations than the wild-type (*1/*1). This means that treatment is largely geared to patients with this genetic variation. Adjustment of the treatment is therefore not useful.
Literature:

UGT1A1*28/*28: irinotecan

Serious, life-threatening adverse events occur more often in patients with this genetic variation. The genetic variation reduces conversion of irinotecan to inactive metabolites.

- Start with 70% of the standard dose
- If the patient tolerates this initial dose, the dose can be increased, guided by the neutrophil count.

Literature:

41. SPC’s Campto en Camptosar (VS).
Serious, life-threatening adverse events occur more often in patients with this genetic variation. The genetic variation reduces conversion of irinotecan to inactive metabolites.

- Start with 70% of the standard dose
  - If the patient tolerates this initial dose, the dose can be increased, guided by the neutrophil count.

Literature:

CYP2D6 PM: kinidine 2533

This is NOT a gene-drug interaction.

Literature:


CYP2D6 UM: kinidine 2535

This is NOT a gene-drug interaction.

Literature:

-

CYP2C19 IM: lansoprazol 1831

NO action is needed for this gene-drug interaction.

The higher plasma concentration of lansoprazole results in an increase in the therapeutic effectiveness, without an increase in the incidence of side effects.

Literature:

8. Lee JH et al. The influence of CYP2C19 polymorphism on eradication of Helicobacter pylori: a prospective randomized study of
The higher plasma concentration of lansoprazole results in an increase in the therapeutic effectiveness, without an increase in the incidence of side effects.

Literature:

39. SPC Prezal.

Date 05-03-2018

CYP2C19 UM: lansoprazol

The genetic variation may reduce lansoprazole plasma concentrations and therefore lansoprazole effectiveness.

Recommendation:

- For Helicobacter pylori ERADICATION THERAPY:
  1. Use a 4-fold higher dose
  2. Advise the patient to contact their doctor if symptoms of dyspepsia persist
- OTHER INDICATIONS:
  1. Be alert to reduced effectiveness
  2. If necessary, use a 4-fold higher dose
  3. Advise the patient to report persisting symptoms of dyspepsia

Literature:

11. Furuta T et al. CYP2C19 genotype is associated with symptomatic recurrence of GERD during maintenance therapy with low-
41. SPC Prezal.

Date 05-03-2018

CYP2D6 IM: methylfenidaat 2528
This is NOT a gene-drug interaction.

Literature:

Date 24-08-2016

**CYP2D6 PM: methylfenidaat**

This is NOT a gene-drug interaction.

Literature:


Date 24-08-2016

**CYP2D6 UM: methylfenidaat**

This is NOT a gene-drug interaction.

Literature:

Date 24-08-2016

**CYP2D6 IM: metoprolol**

The gene variation reduces the conversion of metoprolol to inactive metabolites. However, the clinical consequences are limited mainly to the occurrence of asymptomatic bradycardia.

Recommendation:

- If a GRADUAL REDUCTION in HEART RATE is desired, or in the event of SYMPTOMATIC BRADYCARDIA:
  1. increase the dose in smaller steps and/or prescribe no more than 50% of the standard dose
- OTHER CASES:
  1. no action required

Literature:

5. Goryachkina K et al. CYP2D6 is a major determinant of metoprolol disposition and effects in hospitalized Russian patients treated for acute myocardial infarction. Eur J Clin Pharmacol 2008;64:1163-73.

Date 25-05-2016

**CYP2D6 PM: metoprolol**

The gene variation reduces the conversion of metoprolol to inactive metabolites. However, the clinical consequences are limited mainly to the occurrence of asymptomatic bradycardia.

Recommendation:

- **If a GRADUAL REDUCTION in HEART RATE is desired, or in the event of SYMPTOMATIC BRADYCARDIA:**
  1. increase the dose in smaller steps and/or prescribe no more than 25% of the standard dose
- **OTHER CASES:**
  1. no action required

Literature:

5. Goryachkina K et al. CYP2D6 is a major determinant of metoprolol disposition and effects in hospitalized Russian patients treated for acute myocardial infarction. Eur J Clin Pharmacol 2008;64:1163-73.
9. Terra SG et al. Beta1-adrenergic receptor polymorphisms and left ventricular remodeling changes in response to beta-blocker

Date 25-05-2016

**CYP2D6 UM: metoprolol**

The gene variation increases the conversion of metoprolol to inactive metabolites. This can increase the dose requirement. However, with a target dose of 200 mg/day, there was no effect on the blood pressure and hardly any effect on the reduction of the heart rate.

Recommendation:

1. use the maximum dose for the relevant indication as a target dose
2. if the effectiveness is still insufficient: increase the dose based on effectiveness and side effects to 2.5 times the standard dose or select an alternative
   Possible alternatives include:
   - HEART FAILURE: bisoprolol or carvedilol. Bisoprolol: advantage: not metabolised by CYP2D6; disadvantage: elimination depends on the kidney function. Carvedilol: advantage: elimination does not depend on the kidney function; disadvantage: is metabolised (to a lesser extent than metoprolol) by CYP2D6.
   - OTHER INDICATIONS: atenolol or bisoprolol. Neither is metabolised by CYP2D6.

Literature:

2. Goryachkina K et al. CYP2D6 is a major determinant of metoprolol disposition and effects in hospitalized Russian patients treated for acute myocardial infarction. Eur J Clin Pharmacol 2008;64:1163-73.

Date 25-05-2016

**CYP2C19 IM: mirtazapine**

This is NOT a gene-drug interaction.

**CYP2C19 PM: mirtazapine**

This is NOT a gene-drug interaction.


**CYP2C19 UM: mirtazapine**

This is NOT a gene-drug interaction.


**CYP2D6 IM: mirtazapine**

NO action is required for this gene-drug interaction.

The higher plasma concentration of mirtazapine does not result in an increase in the side effects.

CYP2D6 PM: mirtazapine

NO action is required for this gene-drug interaction.

The higher plasma concentration of mirtazapine does not result - or hardly results - in an increase in the side effects.

Literature:


CYP2D6 UM: mirtazapine

NO action is required for this gene-drug interaction.

The effect on the plasma concentration of mirtazapine is small. No effect has been demonstrated with regard to effectiveness or side effects.

Literature:


CYP2C19 IM: moclobemide

NO action is required for this gene-drug interaction.

Although the moclobemide plasma concentration may increase as a result of the decreased CYP2C19 metabolic capacity, this does not lead to an increased incidence of side effects, in as far as is known.
Literature:

2. SPC Aurorix.

Date 23-05-2012

**CYP2C19 PM: moclobemide**

1992

NO action is needed for this gene-drug interaction.

Although the moclobemide plasma concentration may increase as a result of the decreased CYP2C19 metabolic capacity, this does not lead to an increased incidence of side effects, in as far as is known.

Literature:

3. SPC Aurorix.

Date 23-05-2012

**CYP2C19 UM: moclobemide**

1993

NO action is needed for this gene-drug interaction.

Although the moclobemide plasma concentration may decrease as a result of increased CYP2C19 metabolic capacity, this does not lead to increased effectiveness, in as far as is known.

Literature:

2. SPC Aurorix.

Date 23-05-2012

**CYP2D6 IM: nortriptyline**

1557

The risk of side effects may be increased, because the gene variation leads to an increased plasma concentration of nortriptyline.

- use 60% of the standard dose and monitor the effect and side effects or the plasma concentration of nortriptyline in order to set the maintenance dose
  - The therapeutic range of nortriptyline is 50-150 ng/mL. Values exceeding 250 ng/mL are considered toxic.
Literature:


Date 19-11-2018

CYP2D6 PM: nortriptyline

The risk of side effects may be increased, because the gene variation leads to an increased plasma concentration of nortriptyline.

- use 40% of the standard dose and monitor the effect and side effects or the plasma concentration of nortriptyline in order to set the maintenance dose The therapeutic range of nortriptyline is 50-150 ng/mL. Values exceeding 250 ng/mL are considered toxic.

Date 19-11-2018

CYP2D6 UM: nortriptyline

The risk of ineffectiveness and cardiotoxic effects may be increased. The gene variation leads to a decrease in the plasma concentration
of nortriptyline and an increase in the plasma concentration of the cardiotoxic metabolite Z-10-hydroxyimipramine.

- use 1.7 times the standard dose and monitor the effect and side effects or the plasma concentration of nortriptyline and be alert to an increase in the plasma concentration of the cardiotoxic metabolite Z-10-hydroxyimipramine.

Plasma concentrations of Z-hydroxyimipramine exceeding 40 ng/mL are considered toxic.

- if a dose increase is not wanted due to the cardiotoxic hydroxy metabolite: avoid nortriptyline.

Antidepressants that are not metabolised via CYP2D6 - or to a lesser extent - include, for example, citalopram and sertraline.

Literature:


Date 19-11-2018

CYP2D6 IM: olanzapine

This is NOT a gene-drug interaction.

Literature:


Date 22-03-2006

CYP2D6 PM: olanzapine

This is NOT a gene-drug interaction.

Literature:


Date 19-11-2018

CYP2D6 IM: olanzapine

This is NOT a gene-drug interaction.

Literature:

CYP2D6 UM: olanzapine

This is NOT a gene-drug interaction.

No studies have been published in which the pharmacokinetics and effects of the use of olanzapine on this phenotype were studied. Studies with PM and IM found no significant association between the genotype and clinical effects (clinical improvements, non-response and extrapyramidal side effects and changes in insulin levels).

Literature:

- 

Date 22-03-2006

CYP2C19 IM: omeprazol

NO action is required for this gene-drug interaction.

The higher plasma concentration of omeprazole results in an increase in the therapeutic effectiveness, without an increase in the side effects.

Literature:

29. SmPC Prilosec (VS).

Date 05-03-2018

CYP2C19 PM: omeprazol

NO action is required for this gene-drug interaction.

The higher plasma concentration of omeprazole results in an increase in the therapeutic effectiveness, without an increase in the side effects.

Literature:

28. SmPC’s Losec en Prilosec (VS).

Date 05-03-2018

**CYP2C19 UM: omeprazol**

The genetic variation may lead to a reduced omeprazole plasma concentration and therefore reduced effectiveness.

**Recommendation:**

- **For Helicobacter pylori ERADICATION THERAPY:**
  1. use a 3-fold higher dose
  2. advise the patient to contact their doctor if symptoms of dyspepsia persist

- **OTHER INDICATIONS:**
  1. be alert to reduced effectiveness
  2. if necessary, use a 3-fold higher dose
  3. advise the patient to report persisting symptoms of dyspepsia

**Literature:**

11. Roh HK et al. Omeprazole treatment of Korean patients: effects on gastric pH and gastrin release in relation to CYP2C19 geno-
13. Sagar M et al. Effects of omeprazole on intragastric pH and plasma gastrin are dependent on the CYP2C19 polymorphism.
15. Shimamori T et al. Effect of omeprazole 10 mg on intragastric pH in three different CYP2C19 genotypes, compared with ome-
16. Ando T et al. Endoscopic analysis of gastric ulcer after one week's treatment with omeprazole and rabeprazole in relation to
17. Sugimoto M et al. Initial 48-hour acid inhibition by intravenous infusion of omeprazole, famotidine, or both in relation to cyto-
18. Ji S et al. Comparison of the efficacy of rabeprazole 10 mg and omeprazole 20 mg for the healing rapidity of peptic ulcer diseases.
19. Ando T et al. A comparative study on endoscopic ulcer healing of omeprazole versus rabeprazole with respect to CYP2C19
20. Zhao F et al. Effect of CYP2C19 genetic polymorphisms on the efficacy of proton pump inhibitor-based triple therapy for
21. Sugimoto M et al. Influences of proinflammatory and anti-inflammatory cytokine polymorphisms on eradication rates of
22. Gawronska-Szklarz B et al. Effect of CYP2C19 and MDR1 polymorphisms on cure rate in patients with acid-related disorders
23. Sheu BS et al. Esomeprazole 40 mg twice daily in triple therapy and the efficacy of Helicobacter pylori eradication related to
26. Miwa H et al. Clarithromycin resistance, but not CYP2C-19 polymorphism, has a major impact on treatment success in 7-day
27. Dojo M et al. Effects of CYP2C19 gene polymorphism on cure rates for Helicobacter pylori infection by triple therapy with proton
pump inhibitor (omeprazole or rabeprazole), amoxicillin and clarithromycin in Japan. Dig Liver Dis 2001;33:671-5.
28. Furuta T et al. Effect of genotypic differences in CYP2C19 on cure rates for Helicobacter pylori infection by triple therapy with a
29. Tanigawara Y et al. CYP2C19 genotype-related efficacy of omeprazole for the treatment of infection caused by Helicobacter
30. Aoyama N et al. Sufficient effect of 1-week omeprazole and amoxicillin dual treatment for Helicobacter pylori eradication in
32. Rocha A et al. Investigation of the in vivo activity of CYP3A in Brazilian volunteers: comparison of midazolam and omeprazole
33. Baldwin RM et al. Increased omeprazole metabolism in carriers of the CYP2C19*17 allele; a pharmacokinetic study in healthy
34. Hu XP et al. Effects of CYP2C19 genetic polymorphism on the pharmacokinetics and pharmacodynamics of omeprazole in
35. Sim SC et al. A common novel CYP2C19 gene variant causes ultrarapid drug metabolism relevant for the drug response to proton
36. SmPC’s Losec en Prilosec (VS).

Date 05-03-2018

CYP2D6 IM: oxycod questions the need for this gene-drug interaction.

The reduced conversion of oxycodone to the more active metabolite oxymorphine does not result in reduced analgesia for patients.

Literature:

Pharmacol Ther 2017 Jun 23 [Epub ahead of print].

Date 20-11-2017

CYP2D6 UM: oxycodon

NO action is required for this gene-drug interaction.

The increased conversion of oxycodone to the more active metabolite oxymorphone does not result in an increase in side effects in patients.

Literature:

Date 20-11-2017

CYP2D6 PM: oxycodon

NO action is required for this gene-drug interaction.

The reduced conversion of oxycodone to the more active metabolite oxymorphone does not result in reduced analgesia in patients.

Literature:
breastfeeding mothers. Ther Drug Monit 2013;35:466-72.


Date 20-11-2017

CYP2C19 IM: pantoprazole

NO action is required for this gene-drug interaction.

The higher plasma concentration of pantoprazole results in an increase in the therapeutic effectiveness, without an increase in the side effects.

Literature:


NO action is required for this gene-drug interaction.

The higher plasma concentration of pantoprazole results in an increase in the therapeutic effectiveness, without an increase in the side effects.

Literature:

17. SPC’s Pantozol en Protonix I.V. (VS).
Literature:

20. SPC’s Pantozol en Protonix I.V. (VS).

Date 05-03-2018

**CYP2D6 IM: paroxetine**

NO action is needed for this gene-drug interaction.

The plasma concentration of paroxetine can increase as a result of the reduced activity of CYP2D6. However, studies did not find any clinical effects.

Literature:

3. Murata Y et al. Severe sleepiness and excess sleep duration induced by paroxetine treatment is a beneficial pharmacological effect, not an adverse reaction. J Affect Disord 2013;150:1209-12.

Date 14-05-2018

CYP2D6 PM: paroxetine

NO action is needed for this gene-drug interaction.

The plasma concentration of paroxetine can increase as a result of the reduced activity of CYP2D6. However, studies did not find any clinical effects.

Literature:


Date 14-05-2018
Efficacy will probably be lacking. The genetic variation increases the conversion of paroxetine.

It is not possible to offer substantiated advice for dose adjustment based on the literature.

- avoid paroxetine
  Antidepressants that are not metabolised by CYP2D6, or to a lesser extent, include for example citalopram or sertraline.

Literature:


Date 14-05-2018

CYP2D6 PM: pimozide

The risk of QT-prolongation – and thereby also the risk of torsade de points – is theoretically increased, because the genetic variation results in an increase in the plasma concentration of pimozide. The risk of an excessively high plasma concentration can be negated by following the dose recommendations provided below.

Recommendation:

- use no more than the following doses (50% of the standard maximum dose):
  - adults 10 mg/day
  - children 0.05 mg/kg per day to a maximum of 2 mg/day

Literature:

1. van der Weide K et al. The influence of the CYP3A4*22 polymorphism and CYP2D6 polymorphisms on serum concentrations of aripiprazole, haloperidol, pimozide, and risperidone in psychiatric patients. J Clin Psychopharmacol 2015;35:228-26 en persoonlijke communicatie (gemiddelde dosegecorrigeerde pimozidedalconcentraties).

Date 19-11-2018

CYP2D6 UM: paroxetine

The genetic variation increases the conversion of paroxetine.

It is not possible to offer substantiated advice for dose adjustment based on the literature.

- avoid paroxetine
  Antidepressants that are not metabolised by CYP2D6, or to a lesser extent, include for example citalopram or sertraline.

Literature:

Literature:

4. Pharmacogenetic changes to the FDA-approved Orap (pimozide) label include adult and pediatric dosing recommendations for CYP2D6 poor metabolizers. FDA-nieuwsbericht 27-09-11.
5. SPC Orap (NL en VS).

Date 19-11-2018

CYP2D6 UM: pimozide

NO action is required for this gene-drug interaction.
This gene variation can result in lower pimozide concentrations. However, there is no evidence of reduced effectiveness.

Literature:


Date 19-11-2018

CYP2C19 IM: prasugrel

This is NOT a gene-drug interaction.

Literature:

7. SPC Efient (NL en VS).
CYP2C19 PM: prasugrel

This is NOT a gene-drug interaction.

Literature:

8. SPC Efient (NL en VS).

CYP2C19 UM: prasugrel

This is NOT a gene-drug interaction.

Literature:

2. SPC Efient (NL en VS).

CYP2D6 IM: propafenon

Genetic variation increases the sum of the plasma concentrations of propafenone and the active metabolite 5-hydroxypropafenone. This may increase the risk of side effects.

Recommendation:

It is not possible to offer adequately substantiated recommendations for dose adjustment based on the literature.

1. Either guide the dose by therapeutic drug monitoring, perform an ECG and be alert to side effects
2. Or choose an alternative
   Antiarrhythmic drugs that are hardly if at all metabolised by CYP2D6 include, for example, sotalol, disopyramide, quinidine and amiodarone.
Literature:


Date 24-08-2016

CYP2D6 PM: propafenon

Genetic variation increases the sum of the plasma concentrations of propafenone and the active metabolite 5-hydroxypropafenone. This increases the risk of side effects.

Recommendation:

1. Reduce the dose to 30% of the standard dose, perform an ECG and monitor plasma concentrations

Date 24-08-2016

CYP2D6 UM: propafenon

Genetic variation decreases the sum of the plasma concentrations of propafenone and the active metabolite 5-hydroxypropafenone. This increases the risk of reduced or no efficacy.

Recommendation:

It is not possible to offer adequately substantiated recommendations for dose adjustment based on the literature.

1. Either monitor plasma concentrations, perform an ECG and be alert to reduced efficacy of the therapy.
2. Or choose an alternative

Antiarrhythmic drugs that are hardly if at all metabolised by CYP2D6 include, for example, sotalol, disopyramide, quinidine and amiodarone.

Literature:


Date 24-08-2016

**CYP2D6 IM: quetiapine**

This is NOT a gene-drug interaction.

Literature:


Date 26-05-2009

**CYP2D6 PM: quetiapine**

This is NOT a gene-drug interaction.

Literature:

- 

Date 26-05-2009

**CYP2D6 UM: quetiapine**

This is NOT a gene-drug interaction.

Literature:

- 

Date 26-05-2009
CYP2C19 IM: rabeprazole

NO action is required for this gene-drug interaction.

The higher plasma concentration of rabeprazole does not result in an increase in side effects.

Literature:

9. Ariizumi K et al. Therapeutic effects of 10 mg/day rabeprazole administration on reflux esophagitis was not influenced by the CYP2C19 polymorphism. J Gastroenterol Hepatol 2006;21:1428-34.
25. SPC Pariet.
The higher plasma concentration of rabeprazole does not result in an increase in side effects.

Literature:


10. Arizumi K et al. Therapeutic effects of 10 mg/day rabeprazole administration on reflux esophagitis was not influenced by the CYP2C19 polymorphism. J Gastroenterol Hepatol 2006;21:1428-34.


28. SPC’s Pariet and Aciphex (VS).
NO action is required for this gene-drug interaction.

There is currently insufficient information about this gene variation to recommend any action. Moreover, the fact that there are no differences in effectiveness between PM and EM patients also makes differences in effectiveness between UM and EM patients less likely.

Literature:

10. Arizumi K et al. Therapeutic effects of 10 mg/day rabeprazole administration on reflux esophagitis was not influenced by the CYP2C19 polymorphism. J Gastroenterol Hepatol 2006;21:1428-34.
28. SPC’s Pariet en Aciphex (VS).

Date 05-03-2018

**CYP2D6 IM: risperidon**

NO action is needed for this gene-drug interaction.

There is little evidence to support an increase in side effects caused by the genetic variation. The genetic variation may lead to a decrease in the required maintenance dose. However, as the effect on the dose is smaller than that of the normal biological variation, action is not useful.

Literature:

7. de Leon J et al. A study of genetic (CYP2D6 and ABCB1) and environmental (drug inhibitors and inducers) variables that may influence plasma risperidone levels. Pharmacopsychiatry 2007;40:93-102.

Date 27-05-2015

**CYP2D6 PM: risperidon**

NO action is needed for this gene-drug interaction.
The genetic variation can result in both an increase in side effects and a stronger decrease in schizophrenia symptoms. In addition to this, the genetic variation may lead to a decrease in the required maintenance dose. However, as the effect on the dose is smaller than that of the normal biological variation, action is not useful.

Literature:

5. de Leon J et al. A study of genetic (CYP2D6 and ABCB1) and environmental (drug inhibitors and inducers) variables that may influence plasma risperidone levels. Pharmacopsychiatry 2007;40:93-102.
12. SPC Risperdal.

Date 27-05-2015

CYP2D6 UM: risperidon

NO action is needed for this gene-drug interaction.

Genetic variation may lead to an increase in the required maintenance dose. However, as the effect is smaller than that of the normal biological variation, action is not useful.

Literature:

4. de Leon J et al. A study of genetic (CYP2D6 and ABCB1) and environmental (drug inhibitors and inducers) variables that may influence plasma risperidone levels. Pharmacopsychiatry 2007;40:93-102.
NO action is needed for this gene-drug interaction.

The gene variation has a minor effect on the sertraline plasma concentration. No effect on side effects was found.

Literature:


Date 14-05-2018

CYP2C19 PM: sertraline

The risk of side effects is increased. The gene variation leads to increased plasma concentrations of sertraline

- Do not give doses exceeding 75 mg/day
- Guide the dose by response and side effects and/or sertraline plasma concentration.

Literature:

7. SPC Zoloft.

Date 14-05-2018

CYP2C19 UM: sertraline

NO action is needed for this gene-drug interaction.
The gene variation has a negligible effect on the plasma concentration of sertraline. Moreover, no significant effect on response and side effects has been found.

Literature:

Date 14-05-2018

**CYP2D6 IM: sertraline**

This is NOT a gene-drug interaction.

Literature:

Date 14-05-2018

**CYP2D6 PM: sertraline**

This is NOT a gene-drug interaction.

Literature:

Date 14-05-2018

**CYP2D6 UM: sertraline**

This is NOT a gene-drug interaction.
Literature:


Date 14-05-2018

**SLCO1B1 521CC: simvastatine**

The genetic polymorphism leads to reduced simvastatin transport to the liver. This increases simvastatin plasma concentrations and therefore the risk of myopathy.

**Recommendation:**

1. Choose an alternative
   Consider any additional risk factors for statin-induced myopathy.
   Rosuvastatin and pravastatin are influenced to a lesser extent by SLCO1B1 polymorphisms. They are also not influenced by CYP3A4 inhibitors such as amiodarone, verapamil and diltiazem.
   Fluvastatin is not influenced by SLCO1B1 polymorphisms or CYP3A4 inhibitors.

Date 25-05-2016

**SLCO1B1 521TC: simvastatine**

The genetic polymorphism may lead to reduced simvastatin transport to the liver. This may increase simvastatin plasma concentrations and therefore the risk of myopathy.

**Recommendation:**

1. Choose an alternative
   Consider any additional risk factors for statin-induced myopathy.
   Rosuvastatin and pravastatin are influenced to a lesser extent by SLCO1B1 polymorphisms. They are also not influenced by CYP3A4 inhibitors such as amiodarone, verapamil and diltiazem.
Fluvastatin is not influenced by SLCO1B1 polymorphisms or CYP3A4 inhibitors.

2. If an alternative is not an option:
   1. Avoid simvastatin doses exceeding 40 mg/day
   2. Advise the patient to contact their doctor in the event of muscle symptoms.

Literature:

1. Hu M et al. Intronic variants in SLCO1B1 related to statin-induced myopathy are associated with the low-density lipoprotein cholesterol response to statins in Chinese patients with hyperlipidaemia. Pharmacogenet Genomics 2012 Jun 1 [Epub ahead of print].

Date 25-05-2016

**CYP2D6 IM: sotalol**

This is NOT a gene-drug interaction.

Literature:

Date 24-08-2016

**CYP2D6 PM: sotalol**

This is NOT a gene-drug interaction.

Literature:

Date 24-08-2016

**CYP2D6 UM: sotalol**

This is NOT a gene-drug interaction.
CYP3A5 heterozygote expressor: tacrolimus

Genetic variation results in an increased conversion of tacrolimus to inactive metabolites and as a result a higher dose is required. Adjustment of the initial dose results in an increased chance of reaching a tacrolimus concentration within the target range before the start of therapeutic drug monitoring on day three. However, there is no direct evidence that this results in improved clinical results.

Recommendation:

- Indications OTHER than liver transplantation:
  1. Start with 1.75 times of the standard initial dose that would yield the desired result in non-expressors
     Adjustment of the dose should then be based on therapeutic drug monitoring.
     NOTE: The initial dose that yields the desired result in non-expressors can be lower than the normal initial dose. In the example provided below, this dose was 75% of the standard initial dose. A 1.75 time dose increase corresponds in this case to a 1.3 time dose increase of the standard initial dose.

     For example: After three days, Thervet et al. found a median trough concentration for tacrolimus of 12.3 ng/mL at an initial dose of 0.15 mg/kg twice daily for heterozygous kidney transplant patients. Their target value was 10 - 15 ng/mL. This is lower than the target value that is used in the Netherlands in the first two - four weeks after kidney transplantation (15 - 20 ng/mL).

     For the reference group of non-expressors, a median trough concentration of 16.6 ng/mL and 12.0 ng/mL was achieved at a dosage of 0.1 mg/kg twice daily and 0.075 mg/kg twice daily respectively. In this hospital, the first dose is administered before the CYP3A5 genotype is known. The second dose is reduced according to the genotype.

- LIVER transplantation:

  In addition to the patient's genotype, the metabolism of tacrolimus is also determined by the genotype of the transplanted liver.
  - LIVER is also of the genotype HETEROZYGOUS EXPRESSOR:
    1. Start with 1.75 times the standard initial dose
       Adjustment of the dose should then be based on therapeutic drug monitoring.
  - LIVER has a DIFFERENT genotype:
    There is insufficient evidence in the literature to support a dose recommendation.

Literature:

11. Hesselink DA et al. CYP3A5 genotype is not associated with a higher risk of acute rejection in tacrolimus-treated renal transplant


Date 09-11-2015

CYP3A5 homozygote expressor: tacrolimus

Genetic variation results in an increased conversion of tacrolimus to inactive metabolites and as a result a higher dose is required. Adjustment of the initial dose results in an increased chance of reaching a tacrolimus concentration within the target range before the start of therapeutic drug monitoring on day three. However, there is no direct evidence that this results in improved clinical results.

Recommendation:

- Indications OTHER than liver transplantation:
  1. Start with 2.5 times the standard initial dose that would yield the desired result in non-expressors
     Adjustment of the dose should then be based on therapeutic drug monitoring.
     NOTE: The initial dose that yields the desired result in non-expressors can be lower than the standard initial dose. In the example provided below, this dose was 75 % of the standard initial dose. A 2.5 time dose increase corresponds in this case to a 2 time dose increase of the standard initial dose.

     For example: After three days, Thervet et al. found a median trough concentration for tacrolimus of 14.0 ng/mL at an initial dose of 0.15 mg/kg twice daily for four kidney transplant patients, who were homozygous expressors. This was 5.6 ng/mL (n = 6) for an initial dose of 0.1 mg/kg twice daily. Their target value was 10 - 15 ng/mL. This is lower than the target value that is used in the Netherlands in the first two - four weeks after kidney transplantation (15 - 20 ng/mL). For the reference group of non-expressors, a median trough concentration of 16.6 ng/mL and 12.0 ng/mL was achieved at a dosage of 0.1 mg/kg twice daily and 0.075 mg/kg twice daily respectively. In this hospital, the first dose is administered before the CYP3A5 genotype is known. The second dose is reduced according to the genotype.

- LIVER transplantation:
  In addition to the patient’s genotype, the metabolism of tacrolimus is also determined by the genotype of the transplanted liver.
  - LIVER is also of the genotype HOMOZYGOUS EXPRESSOR:
    1. Start with 2.5 times the standard initial dose Adjustment of the dose should then be based on therapeutic drug monitoring.
  - LIVER has a DIFFERENT genotype:
    There is insufficient evidence in the literature to support a dose recommendation.

Literature:


Date 09-11-2015

**CYP2D6 IM: tamoxifen**

This gene variation reduces the conversion of tamoxifen to the active metabolite endoxifen. This can result in reduced effectiveness.

**Recommendation:**

1. select an alternative or measure the endoxifen concentration and increase the dose if necessary by a factor of 1.5-2

   Aromatase inhibitors are a possible alternative for post-menopausal women.

2. if TAMOXIFEN is selected: avoid co-medication with CYP2D6 inhibitors such as paroxetine and fluoxetine

**Literature:**


5. Cronin-Fenton DP et al. Metabolism and transport of tamoxifen in relation to its effectiveness: new perspectives on an ongoing
Recommendation:

This gene variation reduces the conversion of tamoxifen to the active metabolite endoxifen. This can result in reduced effectiveness.

Recommendation:

1. select an alternative or increase the dose to 40 mg/day and monitor the endoxifen concentration.

   Studies have demonstrated that PM can achieve an adequate endoxifen concentration when the dose is increased to 40-60 mg/day.
Aromatase inhibitors are a possible alternative for post-menopausal women.

Literature:

CYP2D6 UM: tamoxifen

NO action is needed for this gene-drug interaction.

As a result of the genetic variation, the plasma concentration of the active metabolites 4-hydroxytamoxifen and endoxifen can increase. However, there is no evidence that this results in an increase in the side effects.

Literature:


DPD genact 0,5: tegafur

Genetic variation increases the risk of severe, possibly fatal toxicity. A reduced conversion of tegafur to inactive metabolites means that the normal dose is an overdose.

Recommendation:

- Choose an alternative or start with a low dose and adjust the initial dose based on toxicity and efficacy
  Fluorouracil and capecitabine are not alternatives, as these are also metabolised by DPD.
  It is not possible to offer substantiated advice for dose reduction based on the literature. For fluorouracil and capecitabine, starting with 25% of the standard dose is recommended.
  NOTE: This recommendation only applies if the two gene variations are on a different allele. If both variations are on the same allele, this patient has gene activity score 1 and the recommendation for that gene activity score should be followed. These two situations can only be distinguished by determining the enzyme activity (phenotyping).

Literature:

3. SPC Teysuno.
the normal dose is an overdose.

Recommendation:

- Choose an alternative
  - Do not choose fluorouracil or capecitabine, as these are also metabolised by DPD.
- If an alternative is not possible: start with a very low dose and adjust the initial dose based on toxicity and efficacy.
  - A substantiated recommendation for dose reduction cannot be made based on the literature.
  
  The recommendation for fluorouracil and capecitabine is to determine the residual DPD activity in mononuclear cells from peripheral blood and to adjust the initial dose accordingly. A patient with 0.5% of the normal DPD activity tolerated 0.8% of the standard capcitabine dose (150 mg every 5 days). A patient with undetectable DPD activity tolerated 0.43% of the standard capcitabine dose (150 mg every 5 days with every third dose skipped).
  
  The average Caucasian DPD activity is 9.9 nmol/hour per mg protein.

NOTE: If a patient has two different gene variations that lead to a non-functional DPD enzyme (e.g. *2A and *13), this recommendation only applies if the variations are on a different allele. If both variations are on the same allele, this patient has gene activity score 1 and the recommendation for that gene activity score should be followed. These two situations can only be distinguished by determining the enzyme activity (phenotyping).

Literature:

2. SPC Teysuno.

Date 20-11-2017

DPD genact 1,5: tegafur

Genetic variation increases the risk of severe, possibly fatal toxicity. A reduced conversion of tegafur into inactive metabolites means that the normal dose is an overdose.

Recommendation:

1. Choose an alternative or start with a low dose and adjust the initial dose based on toxicity and efficacy.
   - Fluorouracil and capecitabine are not alternatives, as these are also metabolised by DPD.
   - It is not possible to offer substantiated advice for dose reduction based on the literature. For fluorouracil and capecitabine, starting with 75% of the normal dose is recommended.

Literature:

3. SPC Teysuno.

Date 20-11-2017

DPD genact 1: tegafur

Genetic variation increases the risk of severe, possibly fatal toxicity. A reduced conversion of tegafur into inactive metabolites means that the normal dose is an overdose.

Recommendation:

1. Choose an alternative or start with a low dose and adjust the initial dose based on toxicity and efficacy
Fluorouracil and capecitabine are not alternatives, as these are also metabolised by DPD. It is not possible to offer substantiated advice for dose reduction based on the literature. For fluorouracil and capecitabine, starting with 50% of the standard dose is recommended.

NOTE: If a patient has two different gene variations that result in a partially functional DPD enzyme (e.g. 2846T and 1236A), this recommendation only applies if the variations are on a different allele. If both variations are on the same allele, the gene activity score is between 1 and 1.5, depending on whether and how the two gene variations influence each other and on other factors that influence the DPD activity. Whether a gene activity score of 1 or 1.5 needs to be assigned in the case of two different genetic variations can only be determined by measuring the enzyme activity (phenotyping).

Literature:


Date 20-11-2017

CYP2C19 IM: ticagrelor

This is NOT a gene-drug interaction.

Literature:


Date 19-11-2018

CYP2C19 PM: ticagrelor

This is NOT a gene-drug interaction.

Literature:

8. SPC’s Brilique (NL) en Brilinta (VS).

Date 19-11-2018

CYP2C19 UM: ticagrelor

This is NOT a gene-drug interaction.

Literature:


Date 19-11-2018

TPMT IM: tioguanine

Genetic variation reduces conversion of thioguanine to inactive metabolites. This increases the risk of serious adverse events such as myelosuppression.

Recommendation:

1. Start with 75% of the standard dose
   Adjustment of the initial dose should be guided by toxicity (monitoring of blood counts) and efficacy.
   The frequency of monitoring should be increased.

Literature:


Date 27-05-2015
**TPMT PM: thioguanine**

Genetic variation reduces conversion of thioguanine to inactive metabolites. This increases the risk of serious, life-threatening adverse events such as myelosuppression.

**Recommendation:**

1. Choose an alternative or start with 6-7% of the standard dose
   - Any adjustment of the initial dose should be guided by toxicity (monitoring of blood counts) and effectiveness.
   - The frequency of monitoring should be increased.
2. If the dose is decreased: advise patients to seek medical attention when symptoms of myelosuppression (such as severe sore throat in combination with fever, regular nosebleeds and tendency to bruising) develop

**Literature:**

5. SPC Lanvis.

**Date 27-05-2015**

**CYP2C9 IM: tolbutamide**

NO action is required for this gene-drug interaction.

There is insufficient evidence to state that the increased tolbutamide plasma concentration has any clinical consequences.

**Literature:**


**Date 20-11-2017**
CYP2C9 PM: tolbutamide

NO action is required for this gene-drug interaction.

No clinical consequences of the increased tolbutamide plasma concentration were observed.

Literature:


Date 20-11-2017

CYP2C9*1/*2: tolbutamide

NO action is required for this gene-drug interaction.

No clinical consequences of the increased tolbutamide plasma concentration were observed.

Literature:


Date 20-11-2017

CYP2C9*1/*3: tolbutamide

NO action is required for this gene-drug interaction.

There is insufficient evidence to state that the increased tolbutamide plasma concentration has any clinical consequences.
Literature:


Date 20-11-2017

CYP2C9*2/*2: tolbutamide

NO action is required for this gene-drug interaction.

No clinical consequences of the increased tolbutamide plasma concentration were observed.

Literature:


Date 20-11-2017

CYP2C9*2/*3: tolbutamide

NO action is required for this gene-drug interaction.

No clinical consequences of the increased tolbutamide plasma concentration were observed.

Literature:


Date 20-11-2017

CYP2C9*3/*3: tolbutamide

NO action is required for this gene-drug interaction.
No clinical consequences of the increased tolbutamide plasma concentration were observed.

Literature:


Date 20-11-2017

CYP2D6 IM: tramadol

The genetic variation reduces the conversion of tramadol to a metabolite with a higher activity. This can result in reduced analgesia.

Recommendation:
It is not possible to provide a recommendation for dose adjustment, because the total analgesic effect changes when the ratio between the mother compound and the active metabolite changes.

1. be alert to a reduced effectiveness
2. in the case of inadequate effectiveness:
   1. try a dose increase
   2. if this does not work: choose an alternative
      Do not select codeine, as this is also metabolised by CYP2D6.
      Morphine is not metabolised by CYP2D6.
      Oxycodone is metabolised by CYP2D6 to a limited extent, but this does not result in differences in analgesia in patients.
   3. if no alternative is selected: advise the patient to report inadequate analgesia

Literature:

The genetic variation reduces the conversion of tramadol to a metabolite with a higher activity. This can result in reduced analgesia.

Recommendation:
It is not possible to provide a recommendation for dose adjustment, because the total analgesic effect changes when the ratio between the mother compound and the active metabolite changes.

1. be alert to a reduced effectiveness
2. in the case of inadequate effectiveness:
   1. try a dose increase
   2. if this does not work: choose an alternative
      - Do not select codeine, as this is also metabolised by CYP2D6.
      - Morphine is not metabolised by CYP2D6.
      - Oxycodone is metabolised by CYP2D6 to a limited extent, but this does not result in differences in analgesia in patients.
3. if no alternative is selected: advise the patient to report inadequate analgesia

Literature:

CYP2D6 PM: tramadol

The genetic variation reduces the conversion of tramadol to a metabolite with a higher activity. This can result in reduced analgesia.

Recommendation:

It is not possible to provide a recommendation for dose adjustment, because the total analgesic effect changes when the ratio between the mother compound and the active metabolite changes.

1. be alert to a reduced effectiveness
2. in the case of inadequate effectiveness:
   1. try a dose increase.
   2. if this does not work: choose an alternative
      Do not select codeine, as this is also metabolised by CYP2D6.
      Morphine is not metabolised by CYP2D6.
      Oxycodone is metabolised by CYP2D6 to a limited extent, but this does not result in differences in analgesia in patients.
3. if no alternative is selected: advise the patient to report inadequate analgesia

Literature:

18. SPC Ultram (VS).
1. be alert to a reduced effectiveness
2. in the case of inadequate effectiveness:
   1. try a dose increase.
   2. if this does not work: choose an alternative
      Do not select codeine, as this is also metabolised by CYP2D6.
      Morphine is not metabolised by CYP2D6.
      Oxycodone is metabolised by CYP2D6 to a limited extent, but this does not result in differences in analgesia in patients.
3. if no alternative is selected: advise the patient to report inadequate analgesia

Literature:

18. SPC Ultram (VS).

Date 20-11-2017

CYP2D6 UM: tramadol

The genetic variation increases the conversion of tramadol to a metabolite with a stronger opioid effect. This can result in an increase in potentially life-threatening side effects.

Recommendation:

As the total analgesic effect changes when the ratio between the mother compound and the active metabolite changes, the effect of a dose reduction cannot be predicted with certainty.

- select an alternative
  Do not choose codeine, as it is contra-indicated for CYP2D6 UM.
  Morphine is not metabolised by CYP2D6.
  Oxycodone is metabolised by CYP2D6 to a limited extent, but this does not result in differences in side effects in patients.
- if an alternative is not possible:
  - use 40% of the standard dose
  - advise the patient to report side effects (such as drowsiness, confusion, constipation, nausea and vomiting, respiratory depression or urine retention)
The genetic polymorphism leads to decreased metabolic capacity of CYP2D6. This can cause an increase in the plasma concentration of venlafaxine and a decrease in the plasma concentration of the active metabolite O-desmethylvenlafaxine.

Recommendation:

It is not possible to offer adequately substantiated advice for dose reduction based on the literature.

1. Choose an alternative
   Antidepressants that are not metabolised by CYP2D6 - or to a lesser extent - include, for example, citalopram and sertraline.
2. If an alternative is not an option and side effects occur:
   1. reduce the dose
   2. check the plasma concentrations of venlafaxine and O-desmethylvenlafaxine
      It is not known whether it is possible to reduce the dose to such an extent that the side effects disappear, while the effectiveness is maintained. In general, it is assumed that the effectiveness is determined by the sum of the plasma concentrations of venlafaxine and O-desmethylvenlafaxine. However, the side effects do not appear to be related to this sum.

Literature:

The genetic polymorphism leads to decreased metabolic capacity of CYP2D6. This can cause an increase in the plasma concentration of venlafaxine and a decrease in the plasma concentration of the active metabolite O-desmethylvenlafaxine. There are indications that the effectiveness of venlafaxine is reduced in depression patients with this genetic polymorphism.

Recommendation:

It is not possible to offer adequately substantiated advice for dose reduction based on the literature.

1. Choose an alternative
   Antidepressants that are not metabolised by CYP2D6 - or to a lesser extent - include, for example, citalopram and sertraline.

2. If an alternative is not an option and side effects occur:
   1. reduce the dose
   2. check the plasma concentrations of venlafaxine and O-desmethylvenlafaxine

   It is not known whether it is possible to reduce the dose to such an extent that the side effects disappear, while the effectiveness is maintained. In general, it is assumed that the effectiveness is determined by the sum of the plasma concentrations of venlafaxine and O-desmethylvenlafaxine. However, the side effects do not appear to be related to this sum. Furthermore, a reduced effectiveness of venlafaxine has been observed in depression patients with this genetic polymorphism.

Literature:


The genetic polymorphism leads to increased metabolic capacity of CYP2D6. This can cause a decrease in the plasma concentration of venlafaxine and an increase in the plasma concentration of the active metabolite O-desmethylvenlafaxine.

Recommendation:

1. be alert to a possible decrease in the sum of the plasma concentrations of venlafaxine and the active metabolite O-desmethylvenlafaxine
2. if necessary, increase the dose to 150% of the standard dose
3. if dose adjustment based on therapeutic drug monitoring is not possible, an alternative should be selected
   Antidepressants that are not metabolised by CYP2D6 - or to a lesser extent - include, for example, citalopram and sertraline.

Literature:

Date 23-05-2012

CYP2C19 IM: voriconazol

The gene variation can reduce the conversion of voriconazole and consequently increase the plasma concentration. This could result in improved efficacy or an increase in the risk of side effects.

Recommendation:

- Monitor the plasma concentration

Literature:

The gene variation can reduce the conversion of voriconazole and consequently increase the plasma concentration. This could result in improved efficacy or an increase in the risk of side effects. Initially, the risk of side effects is of particular interest.

**Recommendation:**

- Use 50% of the standard dose and monitor the plasma concentration

**Literature:**

22. SPC Vfend.
**CYP2C19 UM: voriconazol**

The gene variation increases the conversion of voriconazole, which increases the risk of ineffectiveness.

**Recommendation:**

- Use an initial dose that is 1.5x higher and monitor the plasma concentration

**Literature:**


**CYP2C9 IM: warfarine**

This gene variation reduces the conversion of warfarin to inactive metabolites. This can increase the risk of bleeding.

**Recommendation:**

1. use 65% of the standard initial dose

The genotype-specific initial dose and maintenance dose can be calculated using an algorithm. Algorithms for Caucasian patients usually contain only the *2 and *3 allele. If the activity of the reduced-activity alleles is comparable to the activity of *2 or *3, then the algorithm can be completed as if *1/*2 or *1/*3 is present. See https://www.knmp.nl/producten-en-diensten/gebruiksrecht-g-standaard/medicatiebewaking-g-standaard/background-information-pharmacogenetics for Excel files containing calculation modules for oral and equivalent intravenous doses. From day 6 on the standard algorithm without genotype information can be used to calculate the dose. Modified dose algorithms have been developed for patients of African or (East) Asian heritage.

**Literature:**

9. SPC Coumadin (VS).

Date 24-08-2016

**CYP2C9 PM: warfarine** 6234

This gene variation reduces the conversion of warfarin to inactive metabolites. This can increase the risk of bleeding.

Recommendation:

1. use 20% of the standard initial dose

The genotype-specific initial dose and maintenance dose can be calculated using an algorithm. Algorithms for Caucasian patients usually contain only the *2 and *3 allele. If the activity of the reduced-activity alleles is comparable to the activity of *2 or *3, then the algorithm can be completed as if *2 or *3 is present. See https://www.knmp.nl/producten-en-diensten/gebruiksrecht-g-standaard/medicatiebewaking-g-standaard/background-information-pharmacogenetics for Excel files containing calculation modules for oral and equivalent intravenous doses. From day 6 on the standard algorithm without genotype information can be used to calculate the dose.

Modified dose algorithms have been developed for patients of African or (East) Asian heritage.

Literature:

9. SPC Coumadin (VS).

Date 24-08-2016

**CYP2C9*1/*2: warfarine** 6228

NO action is required for this gene-drug interaction.
Genetic variation may lead to a decrease in the required maintenance dose. However, there is insufficient evidence that this causes problems when therapy is initiated as usual.

Literature:
9. SPC Coumadin (VS).

Date 24-08-2016

CYP2C9*1/*3: warfarine

This gene variation reduces the conversion of warfarin to inactive metabolites. This can increase the risk of bleeding.

Recommendation:
1. use 65% of the standard initial dose

The genotype-specific initial dose and maintenance dose can be calculated using an algorithm, as used in EU-PACT: see https://www.knmp.nl/producten-en-diensten/gebruiksrecht-g-standaard/medicatiebewaking-g-standaard/background-information-pharmacogenetics.

From day 6 on the standard algorithm without genotype information can be used to calculate the dose.

Literature:
9. SPC Coumadin (VS).
CYP2C9*2/*2: warfarine

This gene variation reduces the conversion of warfarin to inactive metabolites. This can increase the risk of bleeding.

Recommendation:

1. use 65% of the standard initial dose

The genotype-specific initial dose and maintenance dose can be calculated using an algorithm, as used in EU-PACT: see https://www.knmp.nl/producten-en-diensten/gebruiksrecht-g-standaard/medicatiebewaking-g-standaard/background-information-pharmacogenetics.

From day 6 on the standard algorithm without genotype information can be used to calculate the dose.

Literature:

9. SPC Coumadin (VS).

CYP2C9*2/*3: warfarine

This gene variation reduces the conversion of warfarin to inactive metabolites. This can increase the risk of bleeding.

Recommendation:

1. use 45% of the standard initial dose

The genotype-specific initial dose and maintenance dose can be calculated using an algorithm, as used in EU-PACT: see https://www.knmp.nl/producten-en-diensten/gebruiksrecht-g-standaard/medicatiebewaking-g-standaard/background-information-pharmacogenetics.

From day 6 on the standard algorithm without genotype information can be used to calculate the dose.

Literature:

3. Franchini M et al. Effects on bleeding complications of pharmacogenetic testing for initial dosing of vitamin K antagonists: a
CYP2C9*3/*3: warfarine

This gene variation reduces the conversion of warfarin to inactive metabolites. This can increase the risk of bleeding.

Recommendation:

1. use 20% of the standard initial dose

The genotype-specific initial dose and maintenance dose can be calculated using an algorithm, as used in EU-PACT: see https://www.knmp.nl/producten-en-diensten/gebruiksrecht-g-standaard/medicatiebewaking-g-standaard/background-information-pharmacogenetics. From day 6 on the standard algorithm without genotype information can be used to calculate the dose.

Literature:

9. SPC Coumadin (VS).

Date 24-08-2016

VKORC1 -1639 AA: warfarine

The genetic variation results in increased sensitivity to warfarin. This results in an increase in the risk of excessively severe inhibition of blood clotting (INR > 4) during the first month of the treatment.

Recommendation:

1. use 60% of the standard initial dose

The genotype-specific initial dose and maintenance dose can be calculated using an algorithm, as used in EU-PACT: see
From day 6 on the standard algorithm without genotype information can be used to calculate the dose.

Literature:

10. SPC Coumadin (VS).

Date 24-08-2016

VKORC1 -1639 GA: warfarine

NO action is required for this gene-drug interaction.

The genetic variation results in a reduction in the required dose and an increase in the risk of excessively severe inhibition of blood clotting during the first month of the treatment. However, the effect is small and GA is also the most common genotype, meaning that the standard treatment will primarily be based on patients with this genotype.

Literature:

9. SPC Coumadin (VS).

Date 24-08-2016
CYP2D6 IM: zuclopentixol

The genetic polymorphism leads to decreased metabolic capacity of CYP2D6, which may cause increased zuclopentixol plasma concentrations.

Recommendation:

1. Advise the prescriber to start with 75% of the standard dose or to choose an alternative according to the current guidelines. Antipsychotics that are not metabolised via CYP2D6 - or to a lesser extent - include, for example, flupentixol, quetiapine, olanzapine and clozapine.

Literature:


Date 14-12-2005

CYP2D6 PM: zuclopentixol

The genetic polymorphism leads to decreased metabolic capacity of CYP2D6, which may cause increased zuclopentixol plasma concentrations.

Recommendation:

1. Advise the prescriber to start with 50% of the standard dose or to choose an alternative according to the current guidelines. Antipsychotics that are not metabolised via CYP2D6 - or to a lesser extent - include, for example, flupentixol, quetiapine, olanzapine and clozapine.

Literature:


Date 14-12-2005

CYP2D6 UM: zuclopentixol

The genetic polymorphism leads to increased metabolic capacity of CYP2D6, which may cause decreased zuclopentixol plasma concentrations.

Recommendation:

No data have been published from studies into the pharmacokinetics and effects of zuclopentixol for this phenotype.

1. As a precaution, the prescriber should advised to be alert to a decreased zuclopentixol plasma concentration and - if necessary - the
dose should be increased on the basis of the clinical effect, or an alternative should be prescribed according to the current guidelines.
Antipsychotics that are not metabolised via CYP2D6 - or to a lesser extent - include, for example, flupentixol, quetiapine, olanzapine and clozapine.

Literature:

Date 14-12-2005