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SPECIAL ARTICLE

A clinical approach to pharmacogenetics

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ABSTRACT

Taking into account the high frequency of adverse drug reactions (ADRs) in the clinic and taking into account the growing knowledge of the genetic mechanisms underlying some of these ADRs, we believe that every clinician should know at least the basic principles of pharmacogenetics. However, our experience is that many clinicians are unaware of the potential contribution of pharmacogenetic testing and have not implemented this new modality in their daily practice.

We present a case of Stevens-Johnson syndrome in a patient treated with carbamazepine. Following the pathways of clinical reasoning, we describe the possibilities of pharmacogenetic testing in the clinic (HLA-B*1502 and HLA-A*3101 in our patient). We describe the pharmacological and pharmacogenetic aspects relevant for the clinician's daily practice (the existence of ADR subtypes, cytochrome P450, drug-drug interactions, genetic variations, CYP450 and HLA genotyping). Based on the Dutch top 100 of most prescribed drugs, we provide data on CYP450 and HLA genotypes relevant to those 100 most commonly used drugs. We discuss the availability and costs of pharmacogenetic testing, show a calculation of the 'number needed to genotype' and, based on these data, we propose a decision model for pharmacogenetic testing by clinicians.

KEYWORDS

Adverse drug reaction, clinical medicine, decision modelling, pharmacogenetics

We provide clinically relevant pharmacological and pharmacogenetic information for the most commonly used drugs and we propose a decision model for pharmacogenetic testing by clinicians.

Key messages

Medication-related emergencies are a frequent cause of unplanned hospital admissions and adverse drug reactions are common in the clinic.

Every clinician should know at least the basic principles of pharmacogenetics.

INTRODUCTION

Medication-related emergencies account for 5.6% of unplanned hospital admissions in the Netherlands,[1] with comparable frequencies found in other countries;[2-7] see reference 8 for a review. Almost 50% of these cases are potentially preventable. Drugs most often associated with potentially preventable medication-related hospital admissions are those that affect blood coagulation, such as antiplatelet drugs (8.7%), oral anticoagulants (6.3%), NSAIDs (5.1%), a combination of these (10.5%), antidiabetic drugs (12.3%) and drugs that act on the central nervous system (5.1%).[1]

These numbers implicate that all clinicians, from internal medicine residents through emergency physicians to cardiologists, are facing medication-related clinical problems and adverse drug reactions (ADRs) on a regular, if not daily, base.

Some patients are more prone to adverse drug reactions than others. Apart from the impact that comorbidity, comedication, nutrients or herbal supplements can have on the occurrence of ADRs, recent developments have revealed underlying genetic mechanisms for these inter-individual differences. Pharmacogenetics is the study of how the actions of and reactions to drugs vary with the patient's genes. Taking into account the high frequency of ADRs in the clinic (in-hospital adverse drug events occur in up to one fourth of the patients [9]) and taking into account the growing knowledge of the genetic mechanisms underlying

some of these ADRs, we believe that every clinician should know at least the basic principles of pharmacogenetics. However, our experience is that many clinicians are unaware of the potential contribution of pharmacogenetic testing and have not implemented this new modality in their daily practice. With this article, we aim to provide comprehensive basic pharmacogenetic information for the most frequently used drugs in the Netherlands (as a country representative of the Western world): drugs that every clinician meets in everyday practice.

Firstly, we present a case of Stevens-Johnson syndrome (SJS) in a patient treated with carbamazepine. Based on the Dutch drug top 100, we discuss the pharmacological and pharmacogenetic aspects relevant for these frequently prescribed drugs in the Netherlands. After discussing the non-genetic issues, we provide data on CYP450 and HLA genotyping relevant to those 100 drugs, we give information about the availability and costs of pharmacogenetic testing and, based on these data, we propose a decision model for pharmacogenetic testing by clinicians.

Figure 1. *Picture of our patient with SJS due to carbamazepine treatment. A) shows the normal situation, B) shows the patient during presentation at the emergency room*

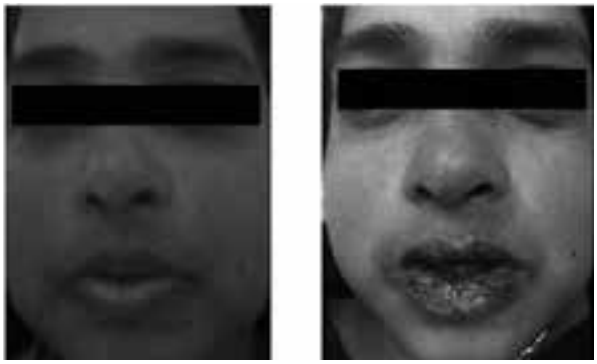
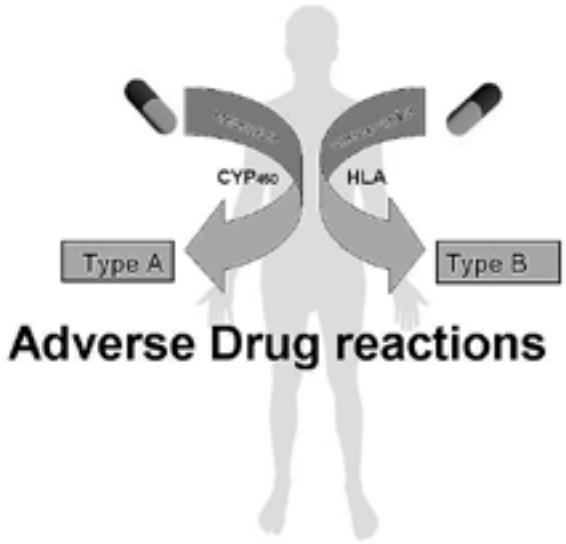


Figure 2. *Simplified model to provide basic understanding of the genetic causes underlying different types of ADR*



METHODS

From the database of the Dutch Health Care Insurance Board (College Voor Zorgverzekeringen, www.gipdatabank.nl), we downloaded the list of 100 most frequently used drugs in the Netherlands. In PubMed, we selected articles about the most clinically relevant cytochrome P450 enzymes (search strategy: "cytochrome P450 AND (1A2 OR 2B6 OR 2C8 OR 2C9 OR 2C19 OR 2D6 OR 2E1 OR 3A4) AND clinical (significance OR relevance OR implication)", limited to review articles).

We collected pharmacogenetic data of these 'top 100 drugs' on PubMed and from the cytochrome P450 Drug Interaction Table, which is a frequently updated table supplied by the Division of Clinical Pharmacology of the Indiana University School of Medicine, covering most of the clinically relevant CYP450 information from peer-reviewed biomedical journals cited by PubMed.[10] Finally, we summarise the information relevant for the drugs encountered daily in the clinic, in two 'white coat pocket size' figures *(figures 3 and 4)*.

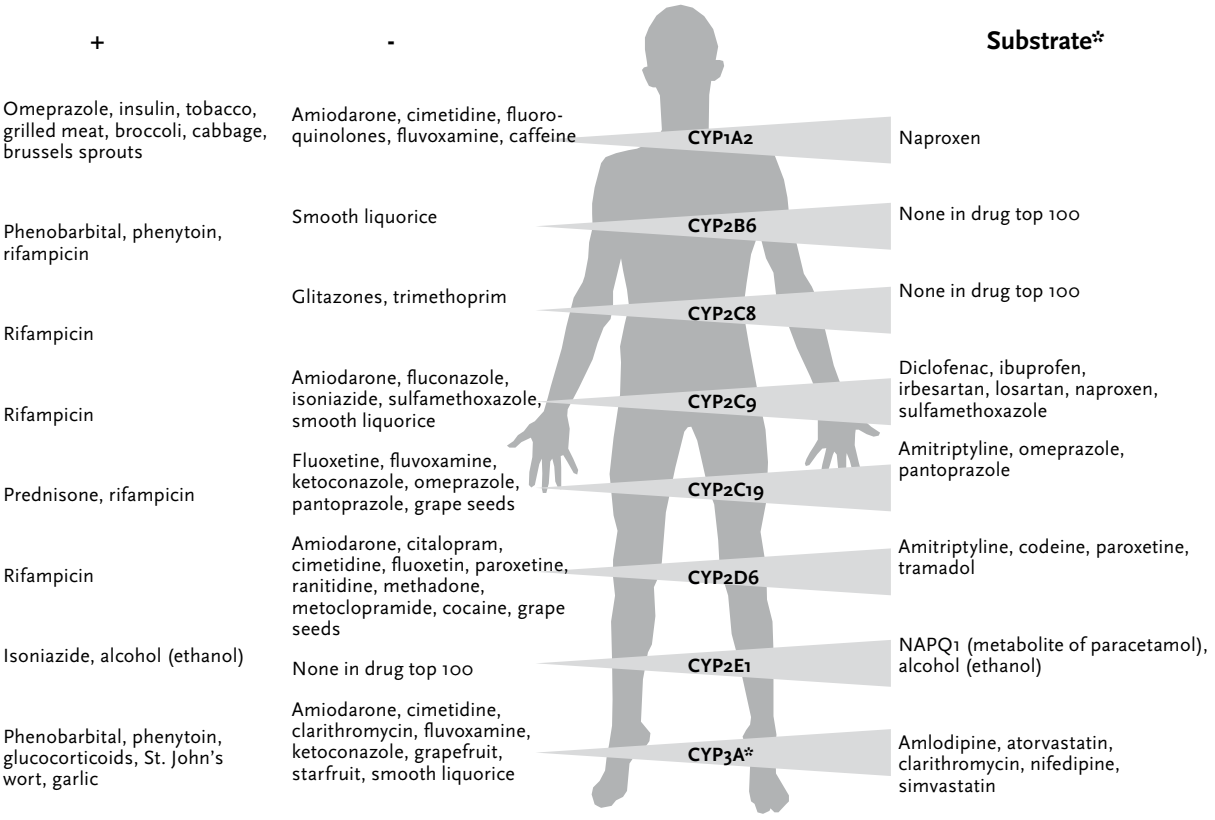
CLINICAL CASE

Our patient, a 47-year-old woman of Asian descent, presented to our emergency department with painful ulcers in her mouth. The ulcers had first appeared three days before. They were progressive and hindered her from eating and drinking. The patient's medical history was unremarkable, apart from epilepsy, diagnosed several months before presentation, for which she had been on carbamazepine 300 mg twice daily for one month. She was not on any other medication.

Physical examination revealed a blood pressure of 140/60 mmHg, a pulse of 100 beats/min and a body temperature of 38.7°C. The patient had confluent erosions on the lips and ulceration over the buccal mucosa *(figure 1)* as well as conjunctival inflammation of the left eye. She had a widespread erythematous bullous rash with target-shaped lesions over the upper trunk and the extremities. There was auricular erythema and swelling as well as tenderness of the plantar and palmar surfaces. There were no genital ulcers.

On admission, the C-reactive protein level was 61 mg/l (normal <10 mg/l) and the serum gamma-glutamyl

Figure 3. *CYP450 inhibitor, inducer and substrate data for drugs present in the Dutch drug top 100 and frequently used food components*



* P-450 3A4, 3A5, and 3A7 have overlapping catalytic specificities, although some selectivity exists

transpeptidase, aspartate transaminase and alanine transaminase were elevated: 478 U/l (normal <40 U/l), 85 U/l (normal <34 U/l) and 267 U/l (normal <44 U/l), respectively. The creatine kinase and lactate dehydrogenase were normal.

Based on the history and clinical findings, Stevens-Johnson's syndrome related to carbamazepine use was suspected. The carbamazepine was ceased and corticosteroids were started at a high dose (1 mg/kg), after which the patient's condition improved rapidly. She was released from hospital six days after presentation.

PHARMACOLOGICAL AND PHARMACOGENETIC ASPECTS INVOLVED IN MANAGEMENT OF PATIENTS WITH ADR'S

In the next paragraphs, we will discuss the basic pharmacological and pharmacogenetic principles each clinician needs to be aware of for the clinical management of patients with adverse drug reactions. We discuss the existence of different types of ADRs, cytochrome P450, drug-drug interactions, genetic variations involved in ADRs, CYP450 and HLA genotyping and the number needed to genotype.

Types of ADR

An adverse drug reaction is defined as 'harm associated with the use of given medications at a normal dosage during normal use'. Drug reactions can be divided into several subtypes, the major two being types A and B. Type A reactions are expected exaggerations of the drug's known effect. These are usually dose dependent and predictable and they account for the majority of ADRs. An example could be the occurrence of bleeding in a patient on anticoagulation therapy. Clinical factors contributing to the occurrence of type A reactions include: impaired metabolism or excretion and increased drug sensitivity. Type B reactions are idiosyncratic and usually unrelated to the drug's known pharmacology. Normally they are not related to the dose, are unpredictable, uncommon, and usually more serious than type A. Most of the type B reactions are mediated by the immune system and thus also termed drug-hypersensitivity reactions.[11] Our case history is an example of a type B reaction.

There is increasing knowledge of the molecular basis underlying ADRs. Studies investigating type A ADRs have revealed associations with genetic variations in cytochrome P450 enzymes, among others. For type B drug hypersensitivity reactions, immunological studies have shown clear associations with HLA-class I alleles.[11] Although there is no 100% correlation between ADR subtypes (A or B) and the possible underlying genetic factors, one could make a general distinction as shown in *figure 2*.

Cytochrome P450

Cytochrome P450 (CYP450) enzymes are important for the oxidative metabolism of drugs. There are more than 50 CYP450 enzymes, but only six (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5) metabolise 90% of drugs (for a comprehensive overview, see reference 12). The majority of these enzymes are expressed in the liver.

Some drugs are inactivated by CYP450 enzymes, whereas other drugs, such as losartan, tamoxifen, codeine and tramadol, need to be activated by CYP450 enzymes.[13] These prodrugs may cause an increased effect or adverse effects when their corresponding CYP450 enzyme activity is increased. Conversely, therapeutic failure is likely due to little or no production of the active drug when CYP450 enzyme activity is decreased.

Drugs that alter CYP450 enzyme activity are referred to as either inhibitors or inducers. The extent to which an inhibitor affects the metabolism of a drug depends upon the dose and the ability of the inhibitor to bind to the enzyme. For instance, sertraline is considered a mild inhibitor of CYP2D6 at a dose of 50 mg, but if the dose is increased, it becomes a potent inhibitor.[14]

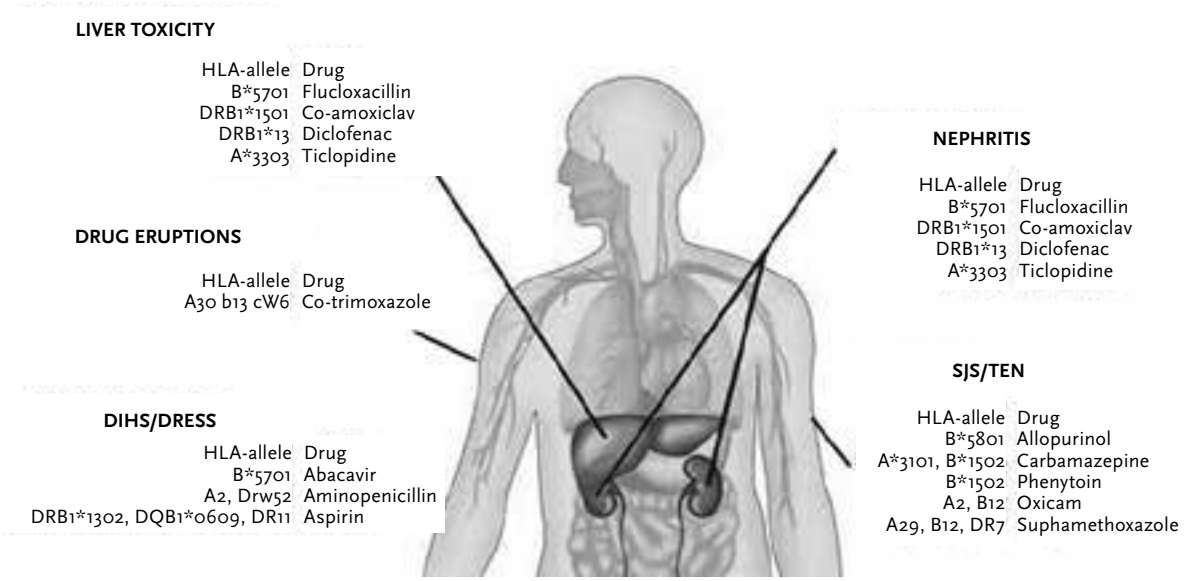
When patients are extremely sensitive or resistant to drug effects at normal doses, the clinician should exclude drug-drug interactions before searching for genetic variations in CYP450 metabolism as the underlying cause.

Drug-drug interactions

When a CYP450 enzyme inhibitor or inducer is added to drugs metabolised by one or more CYP450 enzymes, this can result in an increased or decreased effect of the drug in question. The following drugs are particularly known to cause clinically significant CYP450 drug interactions (*figure 3*): amiodarone, antiepileptic drugs such as carbamazepine, antidepressants as paroxetine, antitubercular drugs as rifampicin, macrolide antibiotics such as clarithromycin and protease inhibitors as ritonavir (the last-mentioned is not shown in *figure 3*: because the figure only shows drugs from the Dutch drug top 100).

A drug can either be both metabolised by and inhibit the same CYP450 enzyme (e.g., erythromycin,[15]) or it can be metabolised by one enzyme and inhibit another enzyme (e.g., terbinafine). Drugs may be combined on purpose, in order to take advantage of CYP450 inhibition. For example ritonavir, a protease inhibitor and potent CYP3A4 inhibitor, is added to lopinavir to increase serum levels in patients with an HIV infection.[16]

Figure 4. *HLA genotypes associated with ADR in reaction to drugs from the Dutch drug top 100, as well as specific drugs discussed in this article (underlined)*



SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis; DIHS/DRESS = drug-induced hypersensitivity syndrome/drug rash with eosinophilia and systemic symptoms (for a description of the differences between mild drug eruptions and the severe cutaneous adverse reactions SJS/TEN and DIHS/DRESS, see references 30 and 31).

Genetic variations

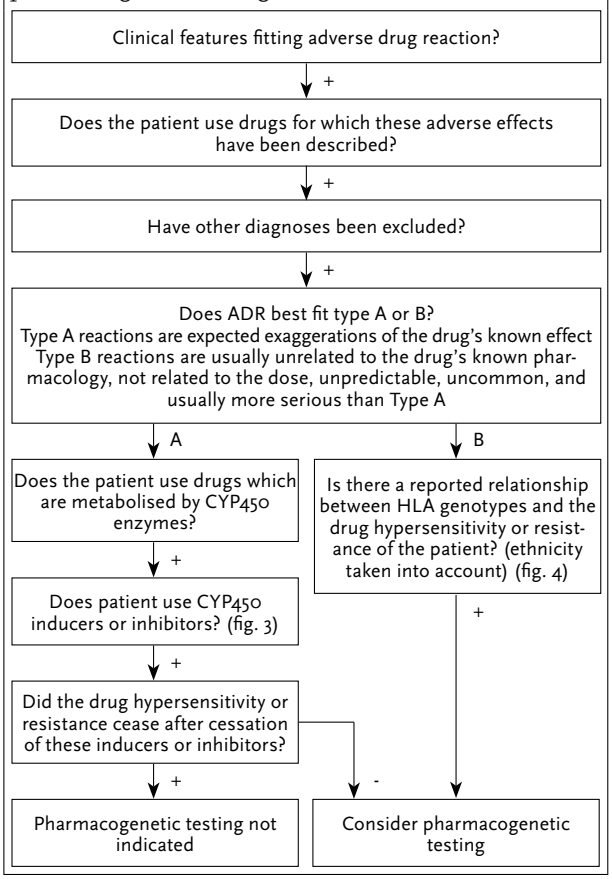
After excluding drug-drug interactions as the explanation for hypersensitivity or resistance to medication, the clinician should consider genetic variations as the underlying cause.

Variations in drug response among patients can be explained by polymorphisms in genes encoding CYP450 enzymes (for a recent review, see reference 17) as well as genetic variations in other drug-metabolising enzymes, drug transporters and drug receptors.[18] For this article, we focus on CYP450 and HLA genotyping because those are the genes most relevant for the drugs in the Dutch drug top 100.

Each CYP450 enzyme is encoded by a specific gene. Every person inherits one allele from the father and one from the mother. The wild-type allele is per definition the allele most commonly found in the general population, although in practice 'wild type' is interpreted as the most common allele encoding *active* enzyme. CYP3A5*3, for example, has an allele frequency of 90% in the Caucasian population,[19] but since it is a splice variant with a premature stop codon, which encodes a truncated *nonfunctional* protein, this allele is not referred to as 'wild type'.

A normal metaboliser has two copies of the wild-type allele. When a variant allele replaces one or both wild-type alleles, this may result in altered enzyme activity. Poor metabolisers are persons with two variant alleles, whereas slightly reduced enzyme activity is found in heterozygous individuals (those with one wild-type and one variant allele). Some persons have excess enzyme activity because they possess multiple copies of wild-type alleles. These individuals are called ultrarapid metabolisers.

Figure 5. *Proposed clinical decision model for the use of pharmacogenetic testing*



CYP450 genotyping

Several tests are available for genotyping CYP450 enzymes. The Amplichip® CYP450 test is an FDA-approved DNA microarray that can detect a large number of polymorphisms of CYP2D6, analysing 33 variant alleles in combination with two CYP2C19 variant alleles.[20] Costs of this analysis are €400 to €600. Costs of CYP450 genotyping in general vary between laboratories, and range from €50 to €700 per gene, mostly depending on the number of variant alleles being analysed and the analysing system used. Alternatively, CYP450 can be genotyped using Taqman®, LightCycler, PCR-RFLP, Luminex or DNA chip techniques such as Infiniti. At the moment, the results are usually available within one to two weeks after ordering, which depends more on the frequency of the analysis being carried out than on the testing time, which is one to four hours. Results are usually provided with a genotype to phenotype interpretation ('poor metaboliser', 'ultra-rapid metaboliser' etc.), based on the general observed activity of the enzyme studied on probe drugs. In the Netherlands, at least six hospitals offer pharmacogenetic testing for clinical use, mostly connected to psychiatric hospitals. The Erasmus MC offers pharmacogenetic testing for 19 genes involved in drug metabolism or drug effect on a regular (weekly) basis. In the US, the Mayo clinic performs CYP genotyping on a regular basis.

An international consensus or guideline for the use of pharmacogenetic testing has not yet been broadly established. Currently, pharmacogenetic testing is performed in individual cases, and mostly retrospectively, for example in patients who experience adverse effects. The indication depends on the ethnicity of the patient, since the frequency of the various genotypes differs between populations (see *figure 6,* reference 21 and paragraph 'number needed to genotype').

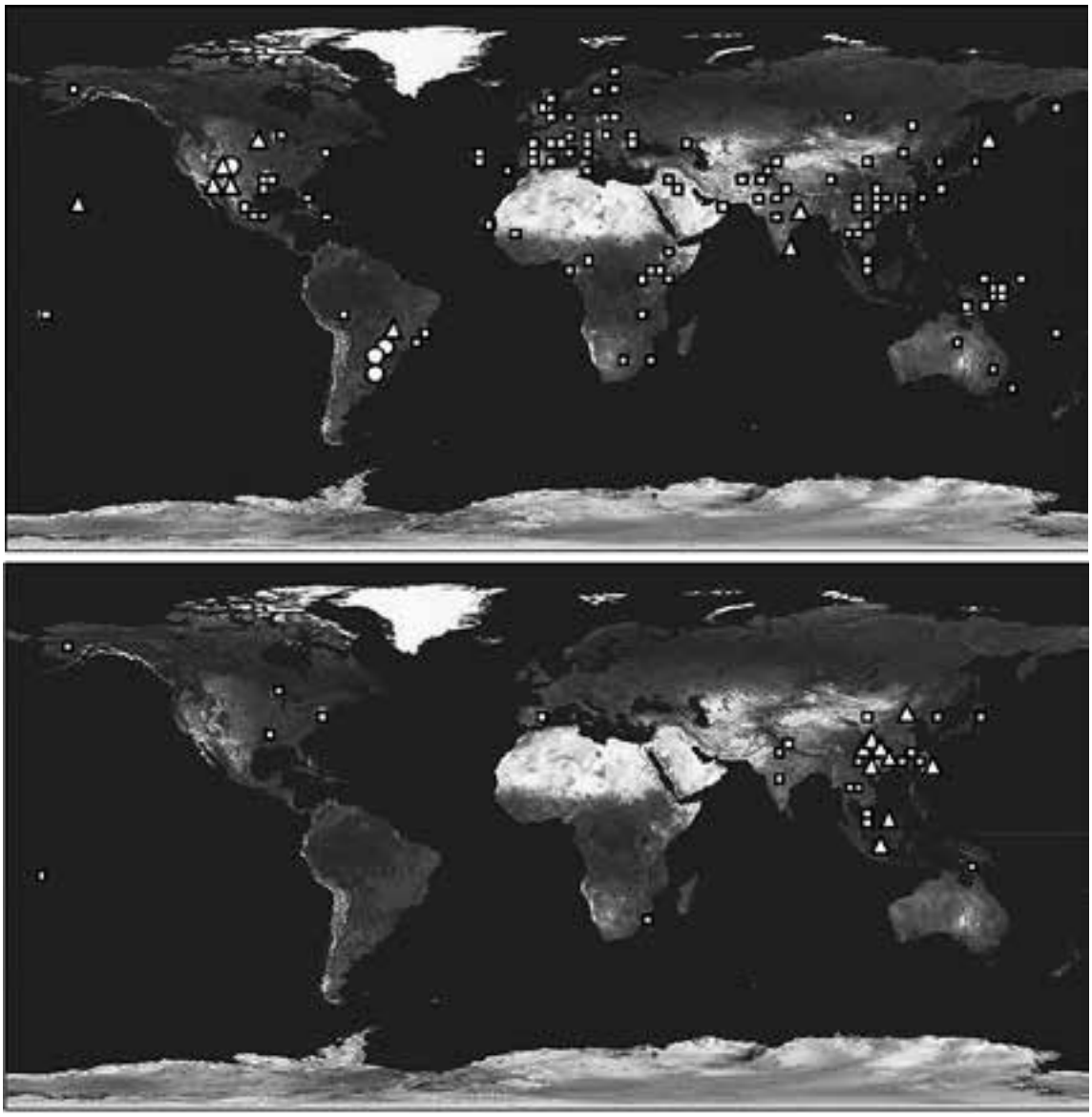
In 2011, Swen *et al*. published therapeutic (dose) recommendations for a large number of genotype/phenotype-drug combinations, including CYP2D6, CYP2C19 and CYP2C9.[22] From their list, we selected the drugs present in the Dutch drug top 100 (*table 1*). This table lists the most commonly used drugs for which therapeutic dose recommendations have been published.[22] The actual dose recommendations can be found on the website of the Royal Dutch Association for the Advancement of Pharmacy ('KNMP kennisbank') and on www.pharmgkb.com. The FDA has added pharmacogenetic information to the labels

of a number of drugs (for a list of these drugs, see http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm).

HLA

Apart from studies focusing on metabolic factors, predominantly involved in type A ADRs, recent immunological studies have revealed clear associations of certain type B drug hypersensitivity reactions with HLA-class I alleles (*figure 4*).[11] For example, in about 5% of treated patients, the antiviral drug abacavir causes a severe hypersensitivity reaction affecting multiple organs. The majority of these patients with drug hypersensitivity carries the HLA-B*5701 allele. This association is strongest in Caucasians[23] and the particular allele is present in 94.4% of patients who develop this drug hypersensitivity, but in only 1.7% of controls.[24] Partly based on these data, in 2008 an amendment was made to the product information of abacavir. Based on this change, before starting treatment with abacavir each HIV-infected patient should be screened for presence of the HLA-B*5701 allele, irrespective of race. Abacavir should not be used in patients who test positive for the HLA-B*5701 allele, unless there is no other therapeutic alternative available for these patients based on treatment history and resistance tests. To date, HLA-B*5701 testing

Figure 6. *Worldwide allele frequencies of two HLA alleles associated with carbamazepine hypersensitivity in Europeans and Han-Chinese, respectively A) HLA-A*3101, B) HLA-B*1502*[32]



Squares: 0-10%, triangles: 10-25%, circles: > 25%.

is the only pharmacogenetic HLA test that is performed on a regular basis in the Netherlands.

Another HLA allele which is clearly associated with severe type B ADRs is HLA-B*1502. This allele is strongly associated with the occurrence of Stevens-Johnson syndrome in Han-Chinese on carbamazepine treatment.[25] However, although the association with HLA alleles is very strong, many patients with HLA-B*1502 are exposed to carbamazepine without developing hypersensitivity.[23,24]

Another allele associated with type B ADRs in patients treated with carbamazepine, is HLA-A*3101. In subjects of Northern European ancestry, the HLA-A*3101 allele is associated with 'carbamazepine-induced hypersensitivity' being either the hypersensitivity syndrome (including rash, fever, eosinophilia, hepatitis and nephritis), maculopapular exanthema or SJS/TEN. The HLA-A*3101 allele has a prevalence of 2 to 5% in Northern European populations. The presence of the allele increases the risk of carbamazepine-induced hypersensitivity reactions from 5.0 to 26.0%, whereas its absence reduces the risk from 5.0 to 3.8%.[26]

Table 1. *Drugs from Dutch drug top 100 with therapeutic (dose) recommendations based on CYP450 genotype (adapted from reference 22)*

Amitriptyline	AD	2C19, 2D6
Aripiprazole	AP	2D6, 3A
Clomipramine	AD	2C19, 2D6
Clopidogrel	PAI	2C19
Clozapine	AP	1A2
Codeine	Opium alkaloid	2D6
Doxepin	AD	2D6
Duloxetine	AD	1A2, 2D6
Felodipine	Calcium antagonist	3A
Flecainide	AA	2D6
Haloperidol	AP	1A2, 2D6, 3A4
Imipramine	AD	1A2, 2D6
Lansoprazole	PPI	2C19
Olanzapine	AP	1A2
Omeprazole	PPI	2C19
Ondansetron	Aem	2D6
Pantoprazole	PPI	2C19
Paroxetine	AD	2D6
Phenytoin	Aep	2B6, 2C9, 2C19, 3A
Propafenone	AA	2D6
Rabeprazole	PPI	2C19
Risperidone	AP	2D6
Tolbutamide	SUd	2C9
Tramadol	Opioid	2D6
Venlafaxine	AD	2D6

See the website of the Royal Dutch Association for the Advancement of Pharmacy ('KNMP kennisbank') for the actual dose recommendations for these drugs. AD = antidepressant; AP = antipsychotic drug; PAI = platelet aggregation inhibitor; AA= antiarrhythmic drug, PPI = proton pomp inhibitor; Aep=antiepileptic drug; Aem = antiemetic drug, SUd = sulphonylurea derivative.

Number needed to genotype

To assess the clinical value of pharmacogenetic testing, one should consider the 'number needed to genotype' (NNG), which is an equivalent to the well-known 'number needed to treat'. The NNG is the average number of patients who need to be genotyped to prevent one additional ADR.

Ferrell *et al.*[27] recently calculated this NNG for carbamazepine in the Han-Chinese population. Assuming a 0.25% incidence of carbamazepine SJS/TEN in newly prescribed carbamazepine patients in Taiwan, one in every 400 newly treated patients would develop SJS/TEN. Since the sensitivity of genotyping of the HLA-B*1502 allele is 98.3%, this test would detect 98.3% of this one (out of 400) patients, being one in every 407 (400/0.983) patients. This means the number needed to screen is 407 people, with subsequent carbamazepine avoidance, to prevent one case of SJS/TEN.

For other ethnic groups, the situation is different: in Caucasians, at least two studies have failed to show a correlation between HLA-B*1502 status and carbamazepine SJS/TEN.[28,29] Based on the lack of evidence and relative infrequency of HLA-B*1502 in those with non-Asian ancestry, genotypic screening for HLA-B*1502 in non-Asian patients is of little value.

Based on the figures reported by McCormack,[26] who studied the association between carbamazepine-induced hypersensitivity and the HLA-A*3101 allele in Europeans, the NNG for the HLA-A*3101 allele would be 83.[26] This would mean that genotyping and carbamazepine avoidance of 83 individuals would prevent one case of carbamazepine-induced hypersensitivity. However, this calculation is based on carbamazepine-induced hypersensitivity in general (including milder forms), whereas the calculation by Ferrell strictly considers severe SJS/TEN. To date, HLA-A*3101 screening before starting carbamazepine treatment is not common in the Netherlands.[22]

CLINICAL DECISION MODEL

In order to assess whether pharmacogenetic testing is useful for a given patient presenting with an adverse drug reaction, we propose the decision model for clinicians, as shown in *figure 5*. Following our own clinical decision model, we performed HLA genetic testing in our patient, and found she was HLA-B*1502 positive. HLA-A*3101 was also tested, and was negative.

In summary, in this article we have provided basic pharmacological and pharmacogenetic information for the 100 most commonly prescribed drugs in the Netherlands, which are relevant in the daily clinical practice of every clinician. Based on the clinical case of Stevens-Johnson syndrome (SJS) in a patient treated with carbamazepine, we have described the basic principles of pharmacogenetic

testing, relevant for clinicians. We have provided clinically important CYP450 and HLA data for the drugs present in the Dutch drug top 100, we have given information about the availability and costs of pharmacogenetic testing and, based on these data, we have proposed a decision model for pharmacogenetic testing in order to apply pharmacogenetics to daily clinical practice. Finally, we have summarised this information in two 'white coat pocket size' figures.

Conflict of interests: None declared.

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