Relationship between drug-induced interstitial lung diseases and cytochrome P450 polymorphisms

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Current Opinion in Pulmonary Medicine 2010, 16:496–502

Purpose of review

Interstitial lung disease and especially drug-induced interstitial lung disease can occur as a cause of drug(s) or drug–drug interactions. In this review we summarize the possible role of cytochrome P450 (CYP) enzymes in drug-induced interstitial lung disease.

Recent findings

The CYP enzyme family plays an important role in the metabolism of all sorts of ingested, injected or inhaled xenobiotic substances. Although the liver is considered to be the major metabolism site of CYP enzymes, in recent years more CYP isoforms have been detected in lung tissue. Polymorphisms in these *CYP* genes can influence the metabolic activity of the subsequent enzymes, which in turn may lead to localized (toxic) reactions and tissue damage.

Summary

Drug toxicity can be the consequence of no or very poor enzyme activity, especially if no other metabolic route is available. In the case of reduced enzyme activity, dose reduction or prescribing an alternative drug metabolized by a different, unaffected CYP enzyme is recommended to prevent toxic side effects. Therefore, knowing a patient's CYP profile before drug prescription could be a way to prevent drug-induced interstitial lung disease. Moreover, it might be helpful in explaining serious adverse effects from inhaled, injected or ingested xenobiotic substances.

Keywords

adverse drug reactions, cytochrome P450 polymorphisms, drug-induced pneumonitis, fenfluramine, lung, xenobiotics

Curr Opin Pulm Med 16:496–502

1070-5287

Introduction

The lungs are a target for a variety of xenobiotic and possible toxic substances, because of their large contact surface with both the outside world and circulating blood. Air can deliver (mineral) particles or (toxic) fumes and blood is the main supplier of most drugs, independent of the way of administration. Moreover, they form not only an important first point of contact or barrier, but also can act as a metabolism site for certain substances. Drugs can induce specific respiratory reactions or the lungs may be affected as part of a generalized response. The most common form of drug-induced respiratory disease is drug-induced interstitial lung disease (drug-induced ILD). The drugs involved not only include prescribed and over-the-counter-drugs, but also illicit drugs, herbs, alcohol, and dietary ingredients [1–4]. An ever increasing number of drugs can produce or reproduce various patterns of naturally occurring infiltrative lung disease, including most forms of interstitial pneumonias, alveolar involvement, and, rarely, vasculitis [1,3,5]. Although only in a limited number of cases have drugs unequivocally been identified as the cause, it is important to acknowledge the potential role of medication in the development of drug-induced ILD [1,6]. This is owing to the severity of the potentially irreversible damage to the lungs and the improvement that is often easily achieved by stopping administration of drugs. Rational treatment of drug toxicities in cases where the mechanism of toxicity is known is common clinical practice. However, often the connection with drug use and the development of related inflammatory damage or idiosyncratic toxicities is hard to recognize and objectify, especially in those cases using multiple drugs [7].

The aim of this review is to discuss drug-induced respiratory reactions and the possible mechanisms involved, focussing on the role of cytochrome P450 (*CYP*) polymorphisms.

Drugs and lungs

The diagnosis of drug-induced ILD primarily rests on the temporal association of exposure to drug(s) and the development of respiratory symptoms. It is also clinically challenging, especially when trying to find predictors for the possibility that an individual is at risk for developing such a reaction, and moreover, in avoiding rechallenge with the trigger. For an overview of drugs known to be able to damage the respiratory system see www.pneumotox.com. In some cases the evidence that reactions in the lungs are drug-induced is circumstantial [1]. A straightforward interpretation is hampered when the damage is irreversible or when the symptoms aggravate after stopping drug administration. Thus, the diagnosis of drug-induced ILD is mainly one of exclusion and requires the meticulous ruling out of all other possible causes.

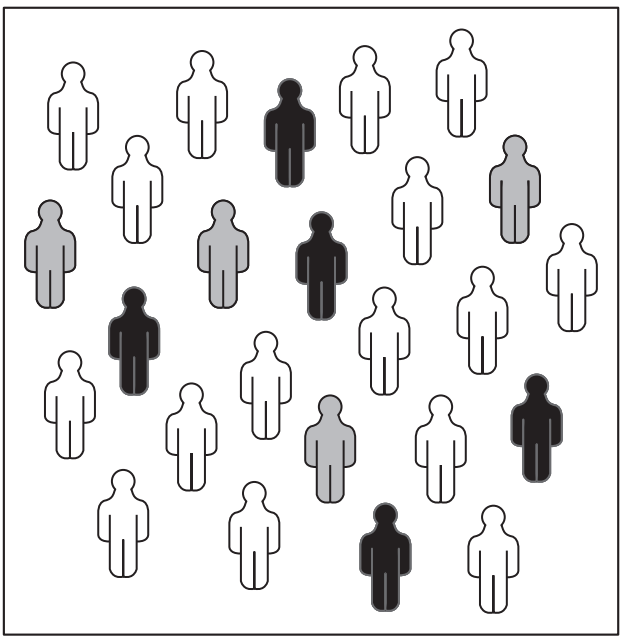
The variability in drug response among patients is multifactorial, including extrinsic factors such as environmental aspects, and also genetic and intrinsic factors that affect the disposition (absorption, distribution, metabolism and excretion) of a certain drug (Table 1). The existence of large population differences with small intra-individual variability is consistent with inheritance as a determinant of drug response; it is estimated that genetics can account for 20–95% of variability in drug disposition and effects, see also Fig. 1 [8].

Two metabolism routes (phase I and phase II reactions) are responsible for the transformation of the majority of xenobiotic substances, with the purpose of facilitating elimination from the body. Phase I reactions, performed mainly by CYP enzymes, involve hydroxylation, reduction and oxidation whereas in phase II reactions glucuronidation, sulfation, acetylation or methylation take place. The risk of developing drug-induced ILD and clinical patterns vary, depending on a variety of host and drug factors. Several different xenobiotic-metabolizing CYP and phase II enzymes are present in the human lung, possibly contributing to in-situ activation. Metabolism also affects the biological activity of the drug. Mostly, the biological activity of the parent drug is superior to that of the metabolite, but there are several exceptions. Sometimes CYP metabolism yields very toxic metabolites, for example acetaminophen, benzo[a]pyrene or carbamazepine [9]. Occasionally, drugs may cause the formation of reactive oxygen species by uncoupling of the electron transport of the CYP system. These metabolites or reactive oxygen species may damage vital cellular components, such as proteins, lipids or DNA.

Table 1 Factors influencing drug metabolism

Extrinsic factors	Environment	Smoking
		Diet
		Alcohol
		Inhalation of (toxic) fumes
	Drug use	Prescribed drugs
		Illicit drugs
		Over the counter drugs
		Herbal supplements
		Concomitant drugs
Intrinsic factors	Demographic	Gender
		Age
		Race
	Disease	Disturbed kidney excretion function
		Diminished liver blood perfusion
		Changed metabolic function
Genetic factors	Polymorphisms in genes encoding for metabolic enzymes	

Figure 1 Drug response in a population



Patients with the same diagnosis and treated with the same medication. Most patients react well (white), some of the patients do not respond to the therapy (grey), and some react with adverse reactions or toxicity (black).

Cytochrome P450 enzymes

The most common DNA variations in the human genome are called single nucleotide polymorphisms (SNPs). The presence of certain SNPs can result in a less functional enzyme and subsequently changed, that is slower, metabolism for certain drugs. SNPs in the *CYP* genes are one of the key factors known to cause variation in drug response between individuals [2,3,7–11]. In recent years more CYP enzymes were detected within lung tissue. Local metabolism, or rather the lack of metabolism in some cases, might explain adverse reactions and subsequent tissue damage in the lungs [2,10,12–14].

With the widespread possibility to determine the genetic profile of the CYP enzymes, their metabolic capacity can

Table 2 Cytochrome P450 distribution and metabolic activity in the liver and presence in lung tissue

CYP	Distribution (%)	Metabolic activity (%)	Presence in the lung
3A	30	55	+++
2C	20	10	++
1A2	13	2	+
2E1	7	1.5	+++
2A6	4	1.5	+++
2D6	2	30	++

CYP, cytochrome P450.

be determined. Patients can be divided into ultra-extensive, extensive, intermediate or poor metabolizers [15].

The most important CYP enzymes for drug metabolism are CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5. This review will focus on clinical relevance and prevalence of *CYP* polymorphisms that are also important in relation to the lungs (Table 2).

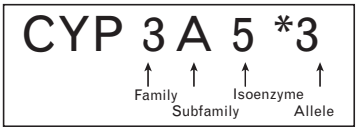
The completion of the sequence of the human genome revealed the presence of 115 human *CYP* genes: 57 active and 58 pseudo-genes [16]. The CYP enzymes are a superfamily of hemoproteins found in a wide range of different organs and tissues [9,17–21].

CYP proteins are conveniently arranged into families and subfamilies on the basis of percentage amino acid sequence identity [22]. Figure 2 illustrates an example of CYP enzyme nomenclature, see also www.cypalleles.ki.se for an overview of human CYP allele nomenclature. The CYP isoenzymes in families 1–3 are responsible for 70–80% of all phase I-dependent metabolism of clinically used drugs and also participate in the metabolism of a large number of xenobiotic substances [23–25].

Substances (medicines or other compounds) that are metabolized by CYP enzymes are called substrates. Inhibitors can reduce the action of a cytochrome, whereas so-called inducers can enhance the metabolism of a specific CYP enzyme.

The metabolic capacity of the different CYP enzymes is also defined as low affinity/high capacity or high affinity/low capacity. The CYP2D6 enzyme is, like CYP2C9 and CYP2C19, defined as a high affinity/low capacity, which implies that these CYP enzymes prefer to metabolize specific substrates at a low concentration. As the concentration of a medicine increases, the metabolism can possibly spill over to CYP3A4 and CYP1A2, which are low affinity/high capacity enzymes.

Figure 2 An example of the nomenclature of cytochrome P450 enzymes



The fully functional allele is indicated with *1, whereas the variant alleles are indicated with higher allele numbers and result in an aberrant functioning enzyme. CYP3A5*3, cytochrome P450 3A5*3.

Several CYP enzymes, important for metabolism in the liver, but also in the lungs, will be discussed in detail.

Cytochrome P450 1A2

Until recently, CYP1A2 was assumed to be present exclusively in the liver, but with more sensitive techniques available it has been detected in other tissues, including the lungs [9,12,13]. Sixteen variant alleles, not counting the 20 isotypes of the *1 allele, have been identified to date. The metabolic activity of CYP1A2 consists primarily of hydroxylating and demethylating compounds through oxidative metabolism. Substrates for CYP1A2 metabolism are, for example caffeine [26], theophylline, and naproxen [27]. Used in combination with an inhibitor, grapefruit juice for example, serum levels of substrates may increase, with toxicity and adverse drug reactions (ADRs) as a possible result [28]. Induction of CYP1A2 metabolism can be achieved by cruciferous vegetables such as Brussel sprouts, broccoli or cabbage, and charbroiled foods (burned meats). Another important inducer of CYP1A2 is tobacco smoke [29].

CYP1A2 is a low affinity/high capacity enzyme in contrast to CYP2D6, CYP2C9, and CYP2C19 in the metabolism of many drugs [30]. Gender differences have been found in the Chinese population, with men having more CYP1A2 activity compared with women [31].

Cytochrome P450 2C9

Of the CYP2C family, CYP2C9 is considered to be the most important isoform, being the largest contributor and responsible for the metabolic clearance of up to 15% of all drugs (among which a host of clinically important drugs such as nonsteroidal anti-inflammatory drugs, oral anticoagulants, and angiotensin II blockers) undergoing phase I metabolism [32]. Most of the CYP2C9 activity in terms of drug metabolism takes place in the liver, but it is also found in various other tissues [33]. To date, 34 variant alleles of the CYP2C9 enzymes have been identified and Lee *et al.* [34] determined that two of these *CYP2C9* variant alleles, *2 (430T) and *3 (1075C), were found in 35% of whites. These *CYP2C9* variant alleles are present much less frequently in African–Americans and Asians (about 2 and 5%, respectively) [35]. Patients with *CYP2C9*2* or *CYP2C9*3* variant alleles require lower doses of drugs metabolized by CYP2C9, because of the reduced activity of these common variants [36].

The only clearly recognized inducer of CYP2C9 is rifampicin. Moreover, in the case of concomitant rifampicin use, serum levels of drugs metabolized by CYP2C9 have been shown to reduce, by induction. In the case of for example warfarin use, this can lead to not enough anticoagulation and in turn could cause thrombotic events [37].

Cytochrome P450 2C19

CYP2C19 is found in many tissues, but predominantly in the liver were it accounts, together with CYP2C9, for approximately 20% of the total CYP activity. Until recently, 26 different variant alleles for CYP2C19 were identified [38].

The prevalence of CYP2C19 enzyme polymorphisms differs significantly between ethnic groups. For example, the poor metabolizer phenotype occurs in 2–6% of whites, 10–20% of Africans, and in 15–30% of Asians [39,40]. Variant alleles of *CYP2C19* lead to reduced or no enzyme function. Determining the metabolizer phenotype may also help in the case of treatment with drugs that rely on CYP2C19. Rifampicin has been identified as an inducer of both CYP2C19 and CYP2C9 [41]. Other drugs (anticonvulsants and steroids) that typically induce other CYP enzymes may also induce CYP2C19, but to a lesser extent than CYP2C9 and CYP3A4 [42].

Cytochrome P450 2D6

Although CYP2D6 represents only 1–2% of the liver CYP isoenzymes by weight, it takes care of some 30% of its metabolic activity (Table 2) [43,44]. Next to its important role in the liver's drug metabolism, CYP2D6 is also found in many other tissues, including the lungs [45,46]. For many drugs, especially psychotropic drugs, CYP2D6 is considered a high affinity/low capacity enzyme, which implies that CYP2D6 will preferentially metabolize drugs at lower concentrations [47].

Case

A 43-year-old female presented with a nonproductive cough and dyspnea. The chest radiograph and high-resolution computed tomography scan (Fig. 3) showed coarse reticular opacities indicative of ILD. She used metoprolol for her hypertension, flecainide as an antiarrhythmic, and fenfluramine for obesity. Bronchoalveolar lavage fluid (BALF) showed an increased number of cells, predominantly lymphocytes, and the presence of plasma cells and foamy alveolar macrophages (Fig. 4), indicative of hypersensitivity pneumonitis or drug-induced ILD. Lung biopsy specimens demonstrated nonspecific interstitial pneumonia of the cellular type. The patient's clinical condition deteriorated and artificial respiration was required for 6 weeks. She was treated with prednisone and fenfluramine was stopped. Hereafter, the clinical condition improved spectacularly and the chest radiograph abnormalities resolved completely. Four years later, the patient's initial complaints returned. Again, the chest radiograph showed the earlier reported reticular opacities and BALF analysis revealed the aforementioned signs of drug-induced ILD. Dexfenfluramine had been started 6 weeks prior to this admission. The first clinical deterioration was not recognized as drug-induced ILD related to fenfluramine. The second deterioration appeared after starting dexfenfluramine as adjuvant therapy for her obesity. At that time, a role for (dex)fenfluramine was assumed in the development of pneumonitis. In addition, genotyping revealed a *CYP2D6**1/*3 heterozygote variant. She used metoprolol and flecainide on a regular base. When another drug metabolized by the CYP2D6 system was added she deteriorated. Therefore, the use of various drugs metabolized by the same affected enzyme should be avoided, for this may result in significant accumulation of these

Figure 3 High-resolution computed tomography scan

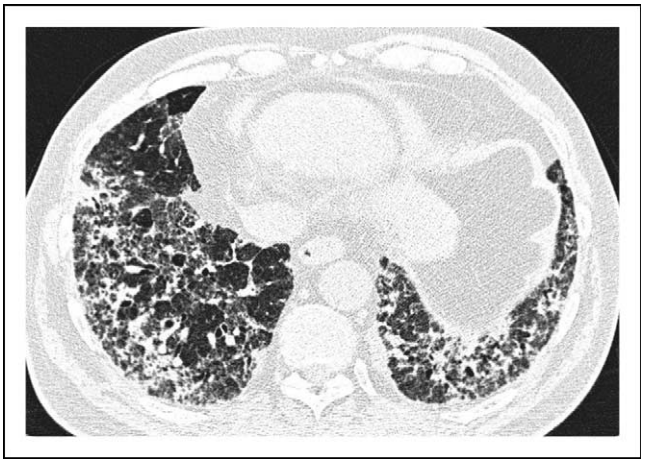
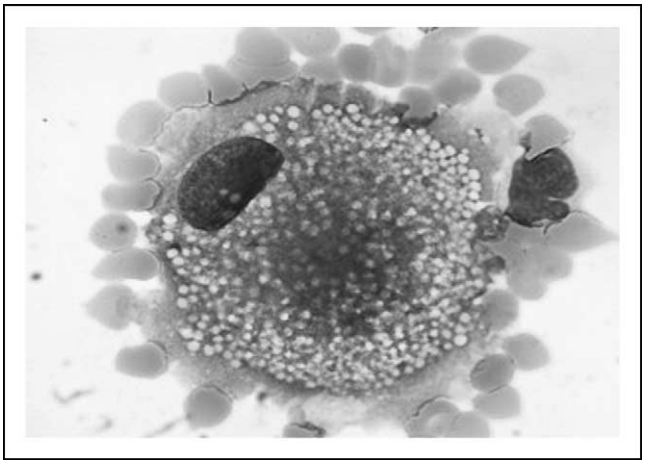


Figure 4 Foamy alveolar macrophage



drug(s), leading to toxic serum levels and severe side effects. Avoiding those drugs or dose reduction appeared to be beneficial in this patient and had protected her from similar adverse effects upto now.

Until recently, 75 different variant alleles for *CYP2D6* were identified. There are ethnic differences in the distribution of extensive, poor, and ultra-extensive metabolizers. Poor metabolizers are present in approximately 5–14% of whites [48,49]. Bradford [50] indicated that Asians, Pacific Islanders, Africans and African–Americans have a higher percentage of reduced-function or nonfunctional CYP2D6 (40–50%) than do whites (26%). Ultra-extensives carry a duplication of a fully functional *CYP2D6* allele, which results in higher CYP2D6 enzyme levels. Owing to these higher CYP2D6 enzyme levels, ultra-extensives require a higher daily dose to obtain a therapeutic drug blood level. Ultra-extensives are generally rare, representing 1–3% of the white population [51].

CYP2D6 is the main metabolic enzyme for a whole range of (psychotropic) drugs and the presence of a less functional enzyme can have serious treatment consequences or lead to severe ADRs [52•,53].

Cytochrome P450 3A4

To date, 20 *CYP3A4* allelic variants have been identified. CYP3A4 is considered to be one of the most contributing CYP enzymes in all phase I drug metabolism. In the liver the CYP3A enzymes make up about 30% of all CYPs present, but take care of about 55% of the metabolism. CYP3A4, together with CYP3A5, are considered to be the major forms present. Whenever the concentration of a substrate increases beyond the capacity of the main metabolizing CYP enzyme, the metabolism can spill over to CYP3A4, which is a low affinity/high capacity enzyme.

The most common variant in the 5′-untranslated region is *CYP3A4**1B, which is strongly associated with increased CYP3A5 expression in a study by Wojnowski *et al.* [54]. And also associated with enhanced CYP3A4 expression [55]. Allelic frequencies range from 0% in Asians to 4–10% in whites and 48–80% in African–Americans [56]. Inducers of CYP3A4 are, for example, rifampicin, carbamazepine, phenobarbital, and St John's Wort. Grapefruit juice, amiodarone and verapamil are some of the possible inhibitors of CYP3A4 [4].

Cytochrome P450 3A5

CYP3A5, together with CYP3A4, is one of the most contributing CYP enzymes, but not so much in the white population because the homozygous *CYP3A5**3/*3 variant, which is a less functional enzyme, is the more prevalent genotype in the white population. Moreover, in whites the frequency of the *CYP3A5**3 allele is about 90–95% and of the functional *CYP3A5**1 allele only about 10% [57,58]. In Asians the *CYP3A5**3 allelic frequency is about 75%, and about 35% in African–Americans [58]. In all CYPs the term 'wild type' stands for the most prevalent and fully functional (*1/*1) enzyme, CYP3A5 being the exception to the rule. As a consequence, an individual who possesses one or two *CYP3A5**1 alleles, needs a higher (two to threefold) maintenance dose of medicines metabolized by CYP3A5, such as the immune modulator tacrolimus [59].

Until recently, 11 different *CYP3A5* allelic variants have been found. Furthermore, contrary to the situation in the liver, in the lungs CYP3A5 is the main CYP3A form expressed [20].

Discussion

Many prescribed drugs are effective only in 25–60% of the patients (Fig. 1) [60]. Therefore, it is also important to determine cofactors in drug metabolism, as depicted in Table 1. A disadvantage of drug development is the fact that most drugs are tested in a standardized population, which rules out severe toxicity and will not always predict drug interaction(s). Also, in a lot of trials multiple drug prescription or intake is not taken into account. Moreover, in many cases genetic metabolic differences, like the presence of one or multiple polymorphisms in CYP enzymes, can make it difficult to predict therapeutic drug reactions.

Although in most cases the clinical consequences may be minor, the impact can be enormous for patients receiving medicines with a narrow therapeutic index, due to either subtherapeutic drug levels or (severe) ADRs, or increased mortality rates. For the latter this was established in a recent study about tamoxifen use and *CYP2D6* polymorphisms [52•]. An example of *CYP* polymorphisms and subsequent lung involvement is shown in another recent study, in which the link between *CYP2C9* and *VKORC1* SNPs, the prescription of oral anticoagulants and the occurrence of diffuse alveolar hemorrhage (DAH) was established [61]. Patients with *CYP2C9**2 and/or *CYP2C9**3 variant alleles require up to 61% lower maintenance doses of warfarin because of the reduced enzyme activity of these common variants [36]. A common serious ADR in these patients, therefore, can be overanticoagulation, resulting in (life threatening) bleeding complications, such as DAH.

Furthermore, in a case–control study it was found that 91.5% of patients with drug-induced ILD had at least one of the studied *CYP2D6*, *CYP2C9* or *CYP2C19* variant alleles compared with 70.5% ($P < 0.001$) of healthy volunteers. Drug-induced ILD appeared to be associated with the presence of at least one variant *CYP* allele [2]. These and other studies support the potential usefulness of

personalized medicine by genotyping aiming to improve efficacy, tolerability and drug safety [25,62].

Different patient categories should be tested for *CYP* polymorphisms: elderly patients with many drugs for different diseases, patients using drugs with a small therapeutic range and patients with unexplained side effects. Although the genotypic profile does not always predict the phenotypic expression, the interaction profile between different drugs can be estimated by computer models. Starting with a lower dose or using a medicine that is metabolized by another enzyme or route is often a way to prevent ADRs and reduce interactions. In addition, the best way to check the effect is to measure serum levels of the drug and its metabolites, the so-called therapeutic drug monitoring (TDM). However, therapeutic serum levels of many drugs are not available or expensive to ascertain. In organ transplantation medicine, TDM together with CYP genotyping is already daily practice and can be cost effective, because of the high costs and the small therapeutic range of the immunosuppressive medication used [59,63].

Nevertheless, genotyping should be considered to identify patients that might be at risk of severe toxic responses to environmental, pharmacological, herbal remedy and/or nutritional stimuli, in order to guide appropriate individual dosage(s) [25]. Nowadays, DNA material for genotyping can be easily obtained and patients do not even have to go to hospital for sample drawing [64]. Both clinical and genetic risk stratification (pharmacogenomics) may lead to more accurate prevention of drug-induced damage in the future [11,25]. However, further research is needed to explore the clinical relevance.

Conclusion

An ideal situation would be the introduction of a genetic medical passport for each patient to achieve a system in which therapeutic drug monitoring will be standard clinical practice. In this manner the incidence of ADRs and related medical consumption will decrease, which in the end will lead to a better pharmacotherapy for patients and reduced healthcare costs. To achieve this, a multidisciplinary approach will be necessary to individualize pharmacotherapy on the basis of the pharmcogenetic profile.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 526).

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