

# **Metabolic Fate of Pharmaceuticals: A Focus on Slow Metabolizers**

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## Case Study 1

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- **CM is a 34-year-old Asian woman who emigrated to the United States six months ago, and recently tested PPD-positive on skin test**
- **Her physician initiates prophylactic therapy with isoniazid**
- **Shortly after she begins taking therapy, she experiences anorexia, vomiting, and jaundice**

Slide 1

### **Case Study 1**

CM is a 34-year-old Asian woman who emigrated to the United States six months ago. At her immigration physical, she had tested PPD-negative on skin test. However, during a more recent routine physical she tested PPD-positive on skin test. Her physician initiates a 6-month course of prophylactic therapy with isoniazid. Shortly after she begins her therapy, she experiences anorexia, vomiting, and jaundice.

## Case Study 1 cont'd

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- **Physical exam reveals mild hepatomegaly**
- **Laboratory studies show elevated liver enzymes**
- **Symptoms were determined to be associated with isoniazid-induced hepatotoxicity**
- **CM is immediately taken off isoniazid therapy and her symptoms improve**

Slide 2

### **Case Study 1**

CM returns to her physician to be evaluated for her symptoms. Physical examination reveals mild hepatomegaly. Laboratory studies are performed, and show serum AST elevations greater than 5 times over the upper limit of normal with mild elevated serum bilirubin levels. Her physician determines that symptoms may be associated with isoniazid-induced hepatotoxicity. CM is taken off of isoniazid. Shortly thereafter, her symptoms of hepatotoxicity subside.

## Overview

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- **Variability in drug metabolism affects clinical outcomes**
- **Drug metabolism is affected by numerous factors**
- **Genetic variation has been associated with variability in drug metabolism**
- **A portion of patients are slow metabolizers of drugs, including mephenytoin, hydralazine, isoniazid, and desloratadine**

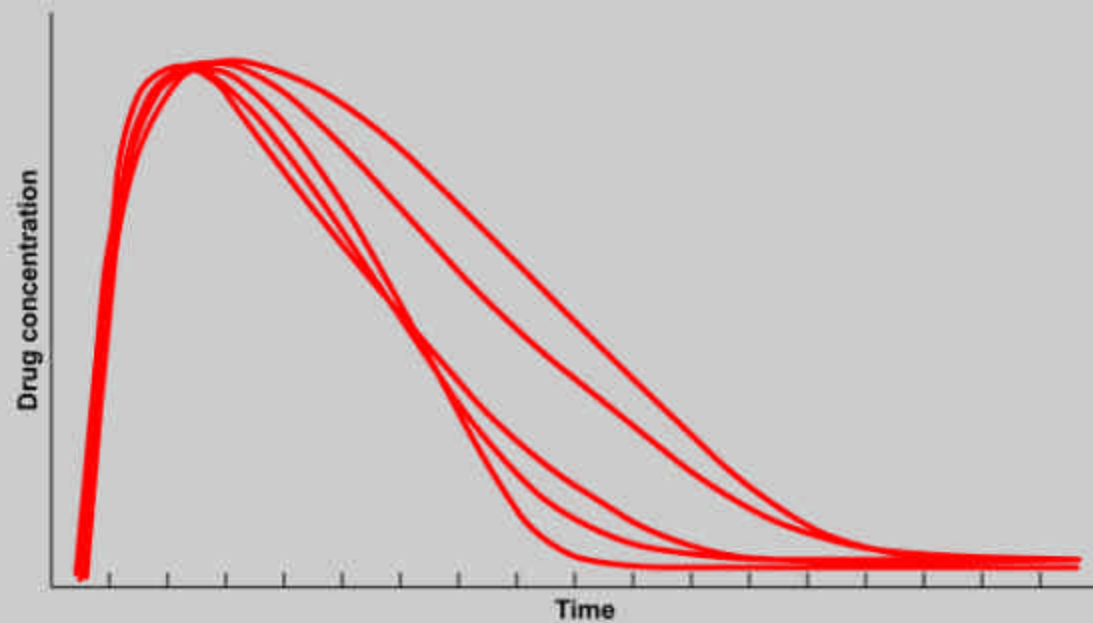
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### Overview

It has been shown that variability in drug metabolism can have a substantial effect on clinical outcomes in patients. The impact of such variability in inter-individual responsiveness to the same dose of a given drug has historically received considerable attention. Drug metabolism is affected by numerous factors of both environmental and genetic origin. Recently, increased attention has been given to the genetic factors that may affect drug metabolism. A substantial portion of the population may have altered drug metabolism due to genetic factors that substantially affects their ability to metabolize specific drugs. These individuals are identified as slow metabolizers. Such individuals tend to accumulate substantially higher drug concentrations than normal metabolizers, which increases their risk for drug-related adverse events. It is important that clinicians consider the influence of slow metabolizer status when confronted with an adverse drug reaction. This slide set will discuss the issue of slow metabolizers, and will review several drugs that have been associated with slow metabolizer populations, including mephenytoin, hydralazine, isoniazid, and the newly marketed antihistamine, desloratadine.

## Inter-Individual Variability in Drug Response

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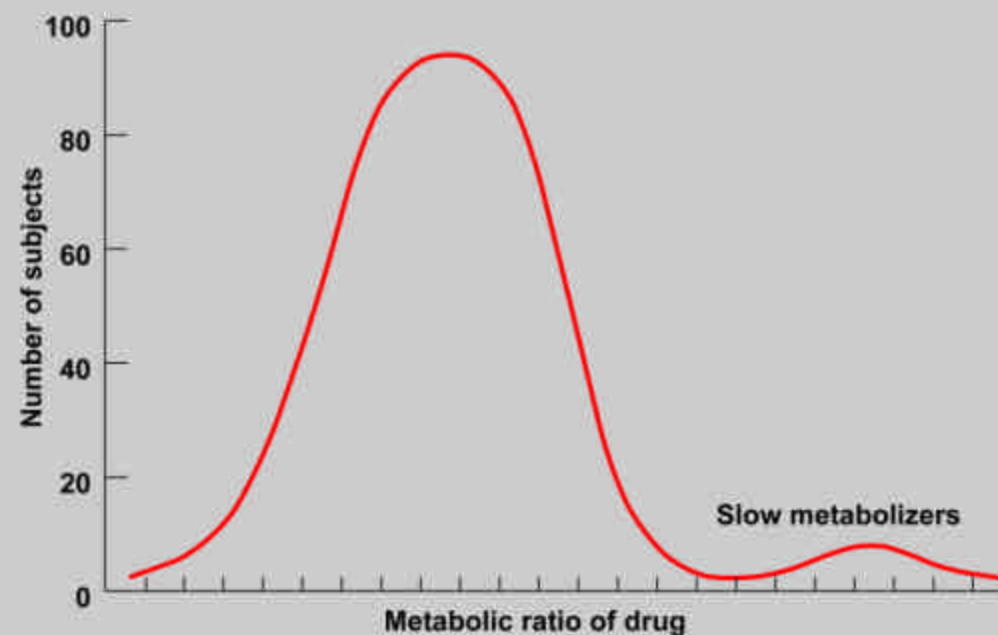
### Inter-Individual Variability in Drug Response

When prescribing therapy, it is important for physicians to recognize that each individual is genetically unique. Variability in drug efficacy may be up to 100-fold among individuals within the general population.<sup>1</sup> Inter-individual variability is also observed with regards to adverse effects following drug administration. Reductions in the rate of drug metabolism to inactive products may lead to an increased incidence of these undesirable effects. It has been shown that variability in responsiveness to the same dose of a given drug may result from both environmental and genetic factors that alter the metabolism of drugs.

### Reference

1. West W, Knight E, Pradhan S, et al. Interpatient variability: genetic predisposition and other genetic factors. *J Clin Pharmacol.* 1997;37:635-648.

## Normal and Slow Metabolizers



Metabolic ratio=ratio between parent drug concentration and a metabolite concentration in the urine

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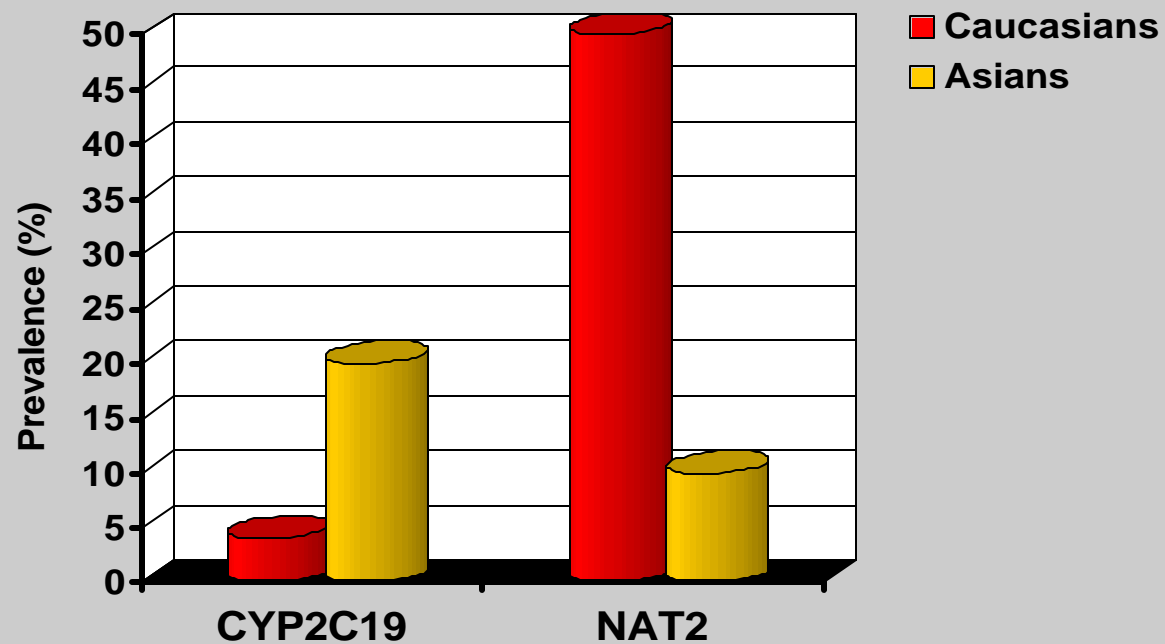
### Normal and Slow Metabolizers

Genetic polymorphisms are traits that occur within the population in at least two phenotypes.<sup>1,2</sup> Genetic polymorphisms of drug metabolism are relatively common occurrences. Mutations in the genes of drug-metabolizing enzymes may result in enzyme variants with reduced or altered activity, or may result in the partial or complete absence of an enzyme.<sup>3,4</sup> For certain drug-metabolizing enzymes, a subpopulation lacks or has greatly reduced enzyme activity, giving rise to distinct subgroups in the population which differ in their capacity to metabolize certain drugs. Based on these differences in drug metabolism, the general population may be subdivided into slow (poor) metabolizers and normal (extensive) metabolizers. Slow metabolizers are characterized by an increased metabolic ratio (the ratio between parent drug concentration and a metabolite concentration in the urine). Typically, the metabolic ratio between parent drug concentration and metabolite concentration for drugs with genetic polymorphism exhibits a bimodal or trimodal frequency of distribution in the general population. For some drugs, the difference between the center of distribution for the metabolic ratio of normal metabolizers and the center of distribution for the metabolic ratio of slow metabolizers may differ more than illustrated in the above graph. Genetic polymorphisms in drug metabolism explain why a small percentage of individuals are at increased risk of drug ineffectiveness or toxicity.<sup>5</sup>

### References

1. Meyer U, Zanger U. Molecular mechanisms of genetic polymorphisms of drug metabolism. *Annu Rev Pharmacol Toxicol.* 1997;37:269-296.
2. Alvan G. Clinical consequences of polymorphic drug oxidation. *Fundam Clin Pharmacol.* 1991;5:209-228.
3. Relling M. Polymorphic drug metabolism. *Clinical Pharmacy.* 1989;8:852-863.
4. Daly A. Molecular basis of polymorphic drug metabolism. *J Mol Med.* 1995;73:539-553.
5. Meyer U. Pharmacogenetics and adverse drug reactions. *Lancet.* 2000;356:1667-1671.

## Slow Metabolizers–Prevalence



Slide 6

### Slow Metabolizers–Prevalence

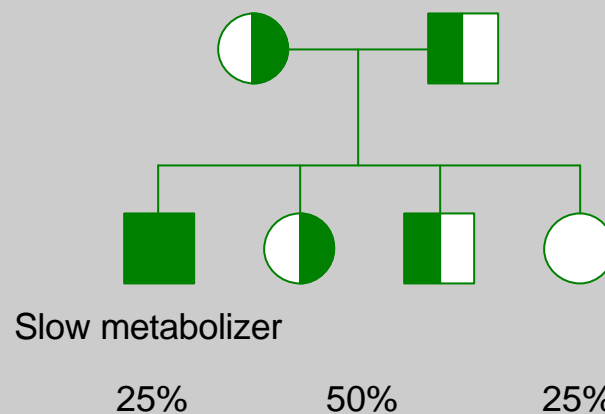
Some genetic polymorphisms of drug metabolism exist in a substantial portion of the population. Drugs metabolized by CYP2C19 and N-acetyltransferase 2 (NAT2) have been shown to exhibit differences in metabolism due to genetic polymorphism. Numerous population studies performed since the discovery of CYP2C19 and NAT2 polymorphisms have shown that the prevalence of these phenotypes vary substantially between various ethnic groups.<sup>1</sup> The slow metabolizer phenotype for the CYP2C19 enzyme has a prevalence of approximately 20% in Asian populations, compared with 2% to 6% in Caucasian populations.<sup>2</sup> Interethnic allelic frequencies of the slow metabolizer variant of NAT2 also vary. The prevalence of the NAT2 slow-metabolizer phenotype is much greater in Caucasian populations (50%) than in Asian populations (10%).

### References

1. Weber W. Populations and genetic polymorphisms. *Mol Diag.*1999;4:299-307.
2. Tanaka E. Update: genetic polymorphism of drug metabolizing enzymes in humans. *J Clin Pharm Ther.* 1999;24:323-329.

## Genetic Polymorphism–Autosomal Recessive Inheritance

- Poor metabolizers inherit the characteristic as an autosomal recessive trait



Slide 7

### Genetic Polymorphism–Autosomal Recessive Inheritance

The less commonly expressed phenotype in the population does not typically result from a spontaneous mutation.<sup>1</sup> Rather, the distribution of enzyme metabolic activity within the general population is genetically controlled. At each gene locus, several different alleles may determine versions of an enzyme that are structurally distinct from those of the predominant phenotype. Although most of these structurally distinct versions are rare, some may be seen more frequently. When the gene controlling the less commonly expressed phenotype is found in at least 1% of the population, a genetic polymorphism exists and is maintained. Slow and normal metabolizer phenotypes each contain a distinct distribution of isoenzymes with different chemical and physical properties.<sup>2</sup>

Individuals who are poor metabolizers inherit this characteristic in an autosomal recessive fashion.<sup>1</sup> Both maternal and paternal alleles of the variant gene controlling poor-metabolizer enzyme activity must be present in the offspring for the poor-metabolizer phenotype to be present. Thus, the resulting genotype for the offspring is homozygous. Family pedigree studies have confirmed that the genotypes of traits inherited through genetic polymorphism are consistent with simple autosomal recessive inheritance, and are relatively resistant to environmental influence.

### References

1. Relling M. Polymorphic drug metabolism. Clin Pharm. 1989;8:852-863.
2. West W, Knight E, Pradhan S, et al. Interpatient variability: genetic predisposition and other genetic factors. J Clin Pharmacol. 1997;37:635-648.



## Pharmacogenetics

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- **Inter-individual variability in drug response may result in differences in clinical efficacy and toxicity**
- **Genetic variation in the genes for drug-metabolizing enzymes has been associated with inter-individual variability**
- **Pharmacogenetics is the study of the genetic basis for individuality in response to drugs**

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### **Pharmacogenetics**

The discipline of pharmacogenetics explores the hereditary basis for differences among individuals in responsiveness to therapeutic agents.<sup>1</sup> Pharmacogenetics attempts to identify those individuals within the population who are susceptible to possible alterations in drug metabolism so that this may be taken into account during development of a therapeutic regimen.<sup>2</sup> The ability to identify hereditary differences in metabolism would allow drugs to be prescribed in a more efficacious and safe manner without having to adjust the dosage based on undesired patient response.

### **References**

1. West W, Knight E, Pradhan S, et al. Interpatient variability: genetic predisposition and other genetic factors. *J Clin Pharmacol.* 1997;37:635-648.
2. Wolf C, Smith G. Pharmacogenetics. *Br Med Bul.* 1999;55(No. 2)366-386.

## Pharmacogenetics–History of the Field

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- **Pharmacogenetic research emerged following observations that some drug-related adverse events were associated with genetic differences in enzyme activity**
- **Early advances came from independent reports of serious drug-related adverse events**

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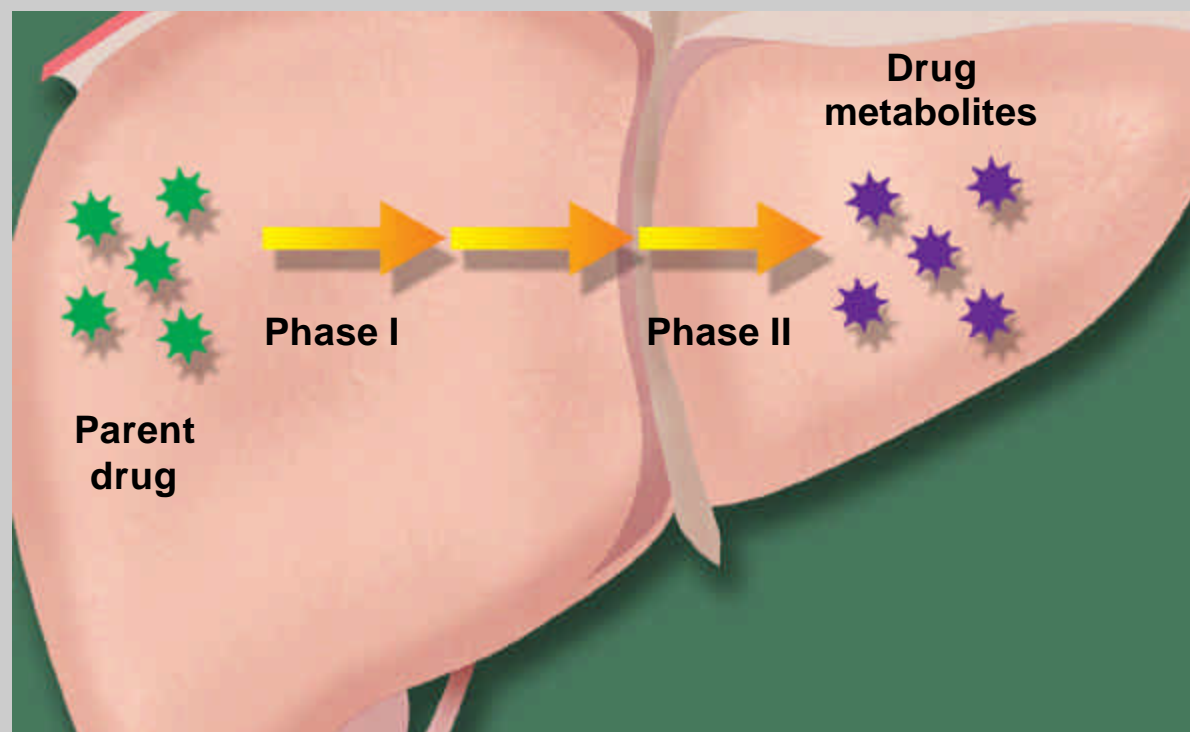
### Pharmacogenetics–History of the Field

As early as in the 1950s, it was observed that certain drug-related adverse events were caused by genetically determined variations in enzyme activity.<sup>1</sup> Many of these variations were first identified by incidental observations of these occurrences in patients receiving normal drug doses. For instance, there were reports that following the administration of the muscle relaxant succinylcholine, a number of individuals experienced prolonged muscle relaxation. It was subsequently shown that this variability in response was related to an inherited variant of cholinesterase.<sup>2</sup> Similarly, hemolysis caused by some antimalarial agents was determined to be related to inherited variants of the enzyme glucose-6-phosphate dehydrogenase. The existence of these polymorphisms within the population was confirmed by phenotypic methods and analysis of urinary metabolites.<sup>3</sup> Following these initial findings, the association between decreased drug clearance and decreased activity of metabolizing enzymes was evaluated for a wide variety of therapeutic agents.<sup>4</sup> The advent of molecular genetics and genomics has greatly influenced pharmacogenetics in the past decade. Substantial advances have been made with regards to the identification of the molecular basis of genetic polymorphisms and the ability to screen individuals for the presence of such genetically oriented alterations in drug metabolism.

### References

1. Meyer U. Pharmacogenetics and adverse drug reactions. *Lancet*. 2000;356:1667-1671.
2. Lockridge O. Genetic variants of human serum cholinesterase influence metabolism of the muscle relaxant succinylcholine. *Pharmacol Ther*. 1990;47(1):35-60.
3. Daly A. Molecular basis of polymorphic drug metabolism. *J Mol Med*. 1995;73:539-553.
4. Meyer U, Zanger U. Molecular mechanisms of genetic polymorphisms of drug metabolism. *Annu Rev Pharmacol Toxicol*. 1997;37:269-296.

## Drug Metabolism–Polymorphisms of Phase I and Phase II Reactions



Slide 10

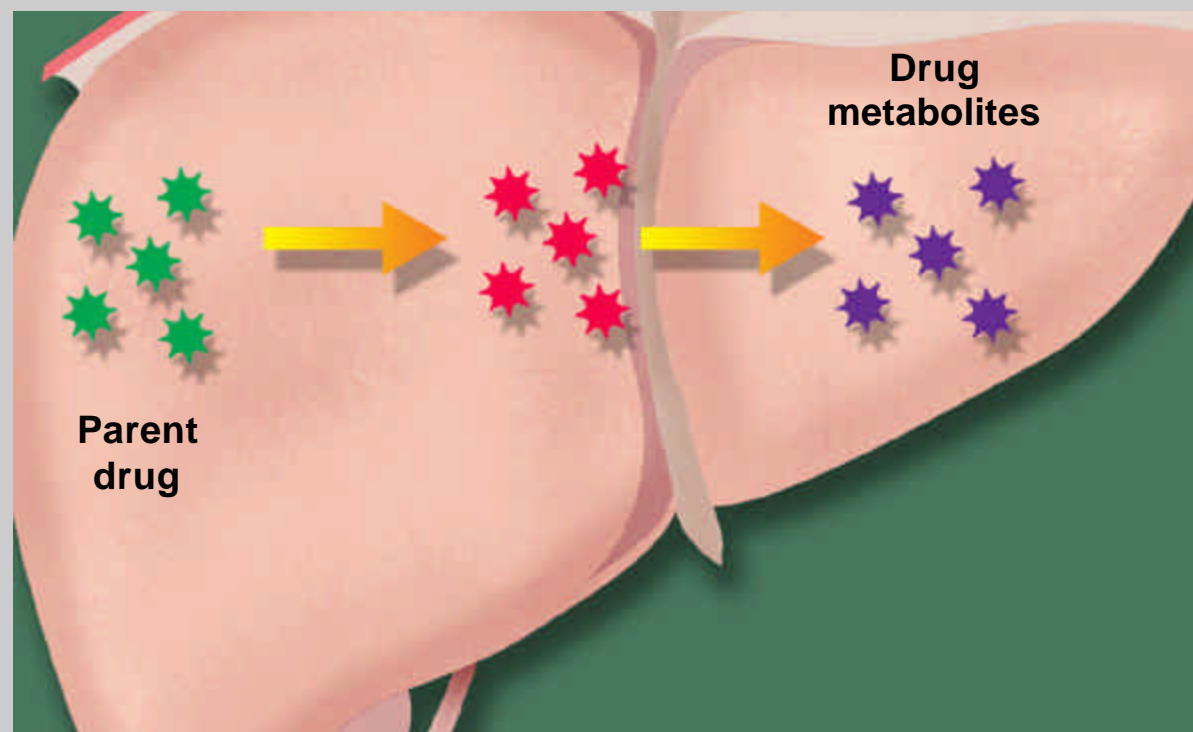
### Drug Metabolism–Polymorphisms of Phase I and Phase II Reactions

Drug metabolism in the liver typically consists of a sequence of enzymatic steps.<sup>1</sup> Two general sets of reactions occur, described as phase I and phase II reactions. Polymorphisms in genes associated with the enzymes involved in both phase I and phase II reactions have been identified.<sup>2</sup> In phase I metabolism, drugs are oxidized by cytochrome P450-dependent monooxygenases.<sup>3</sup> These oxidation-reduction reactions occur in the liver, the gastrointestinal tract, and other tissues. Drugs metabolized by cytochrome P450 CYP2C19 isoenzymes have been shown to exhibit differences in phase I metabolism due to genetic polymorphism. Those drugs that are not sufficiently polar following phase I reactions subsequently undergo phase II conjugation reactions. During phase II metabolism, drugs are conjugated through sulphation, glucuronidation, or acetylation. These conjugation reactions also occur mainly in the liver, and may involve a number of enzymes, such as glutathione S-transferase, N-acetyltransferase, and UDP-glucuronosyl transferase. Drugs metabolized by N-acetyltransferase 2 (NAT2) have been shown to exhibit differences in phase II metabolism due to genetic polymorphism.

### References

1. Wolf C, Smith G. Pharmacogenetics. *Br Med Bull.* 1999;55(No. 2):366-386.
2. Daly A. Molecular basis of polymorphic drug metabolism. *J Mol Med.* 1995;73: 539-553.
3. West W, Knight E, Pradhan S, et al. Interpatient variability: genetic predisposition and other genetic factors. *J Clin Pharmacol.* 1997;37:635-648.

## Drug Metabolism–Normal Metabolizers



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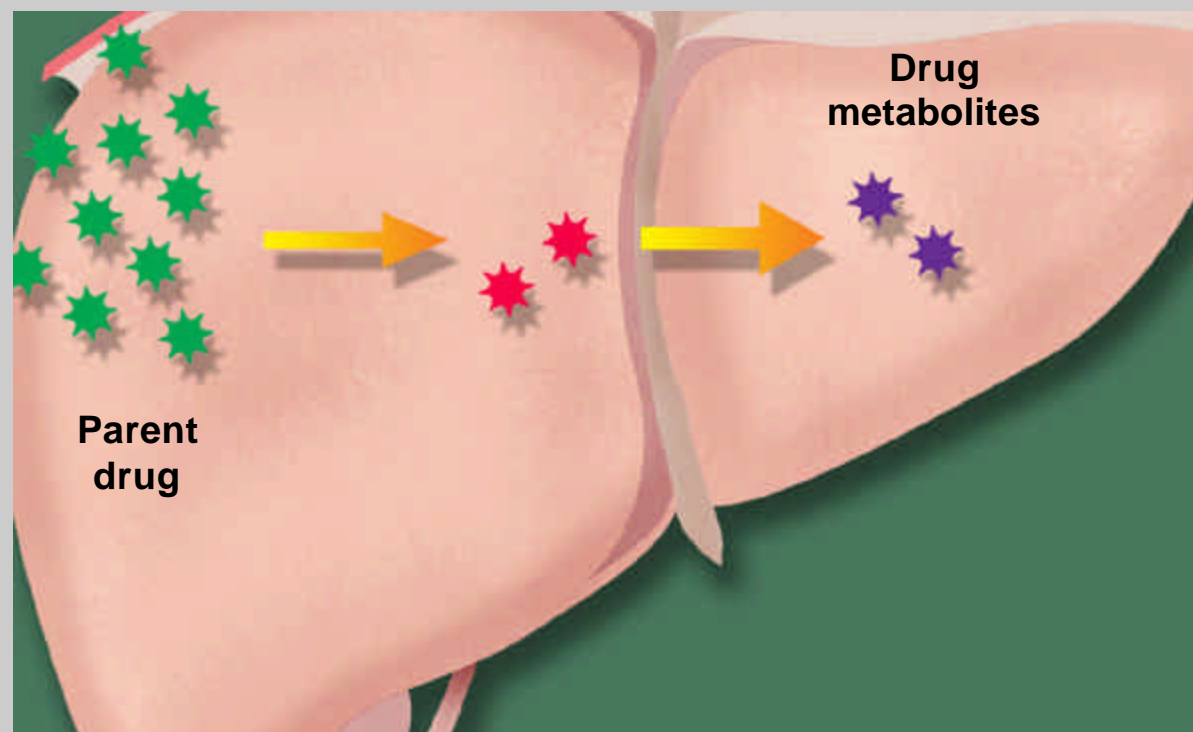
### Drug Metabolism–Normal Metabolizers

Most drugs are metabolized to more polar products through numerous metabolic pathways by microsomal enzymes located mainly in the liver and, to a lesser extent, in the small intestine.<sup>1,2</sup> The pharmacokinetic and clinical consequences of polymorphic enzyme activity depend on whether the enzyme mediates metabolism of the parent drug, primary metabolite, or both.<sup>3</sup> The consequences also depend on whether the parent drug, metabolites, or both are active, and the overall contribution of the polymorphic enzyme to clearance from the affected pathway. The efficacy and safety of active compound and the patency of the available pathways of elimination also impact the pharmacokinetic and clinical relevance of polymorphic enzyme activity.

### References

1. Ingelman-Sundberg M, Oscarson M, McLellan R. Polymorphic human cytochrome P450 enzymes: an opportunity for individualized drug treatment.
2. Wolf C, Smith G. Pharmacogenetics. *Br Med Bull.* 1999;55(No.2):366-386.
3. Tucker G. Clinical Implications of genetic polymorphism in drug metabolism. *J Pharm Pharmacol.* 1994;46(Suppl 1):417-424.

## Drug Metabolism–Slow Metabolizers



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### Drug Metabolism–Slow Metabolizers

When the parent drug is an active agent and most of its metabolism and clearance from the system are affected by a polymorphic enzyme, the affected individual is considered a slow metabolizer.<sup>1</sup>The reduction in, or lack of, a functional enzyme in such an individual results in decreased metabolism and accumulation of the active drug. This results in increased bioavailability of the active drug and prolongation of its half-life.

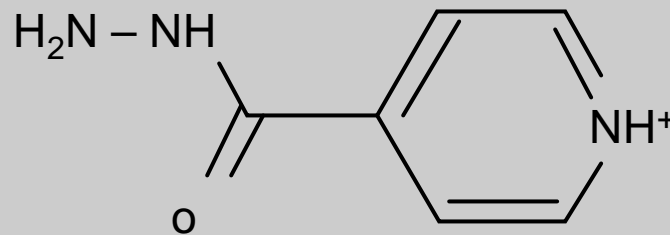
### Reference

1. Tucker G. Clinical implications of genetic polymorphism in drug metabolism. J Pharm Pharmacol. 1994;46(Suppl 1):417-424.

## Isoniazid

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- Genetic polymorphism occurs in phase II acetylation reactions



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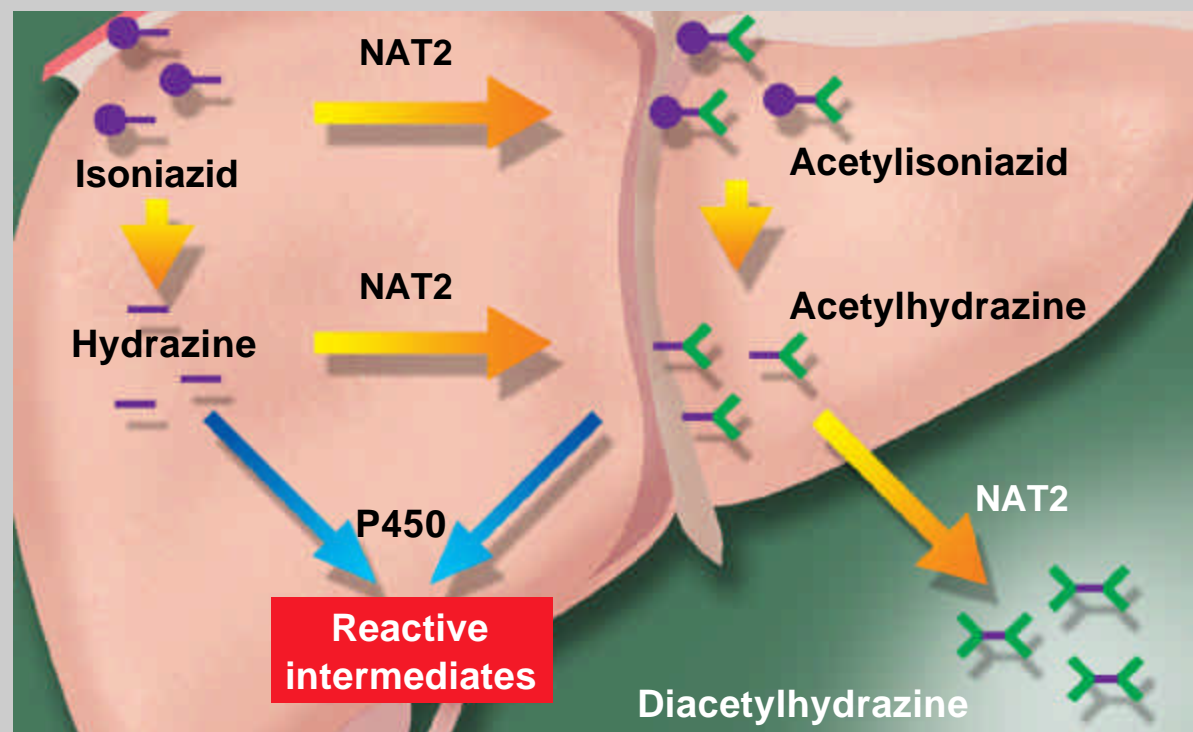
### Isoniazid

Isoniazid has been used for the treatment of tuberculosis since 1952 and is still widely used today.<sup>1,2</sup> Shortly after its introduction, high inter-individual variation in the urinary excretion of isoniazid was observed, and frequency histograms of plasma isoniazid concentrations showed a bimodal distribution of slow and fast acetylators in the general population.<sup>3</sup> It was observed that therapeutic failure rates for pulmonary tuberculosis were higher in rapid acetylators than in slow acetylators, presumably because the duration of action for isoniazid was shorter.<sup>4</sup> Similar to hydralazine, altered metabolism of isoniazid has been associated with a genetic polymorphism that occurs with the NAT2 enzyme in phase II acetylation reactions.

### References

1. Gross A, Kroemer H, Eichelbaum M. Genetic polymorphism of drug metabolism in humans. In: Witmer C, et al, eds. Biological Reactive Intermediates IV. New York: Plenum Press;1990:627-640.
2. Chaisson R. New developments in the treatment of latent tuberculosis. Int J Tuberc Lung Dis. 2000;4(Suppl 2):S176-S181.
3. Meyer U. Genetic polymorphisms of drug metabolism. Fundam Clin Pharmacol. 1990;4:595-615.
4. Clark D. Genetically determined variability in acetylation and oxidation: therapeutic implications. Drugs. 1985;29:342-375.

## Isoniazid–Normal Metabolizers



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### Isoniazid–Normal Metabolizers

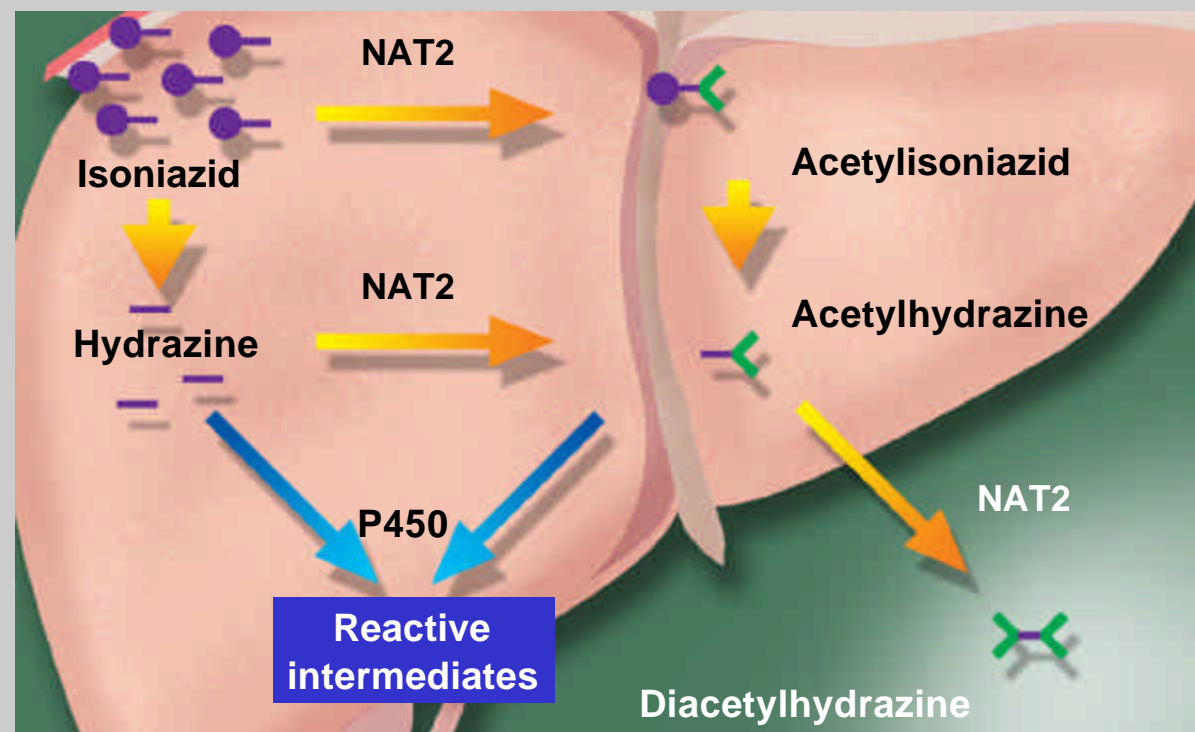
Isoniazid is metabolized in the liver by NAT2 to acetylisoniazid, which is subsequently hydrolyzed to acetylhydrazine.<sup>1</sup> Isoniazid is also metabolized to hydrazine, which is in turn metabolized to acetylhydrazine by NAT2. Acetylhydrazine is then further metabolized by two different routes. One pathway involves acetylation to the nontoxic metabolite, diacetylhydrazine. The alternate pathway involves oxidation by cytochrome P450 to form reactive intermediates that are responsible for its hepatotoxicity.

### Reference

1. Gross A, Kroemer H, Eichelbaum M. Genetic polymorphism of drug metabolism in humans. In: Witmer C, et al, eds. Biological Reactive Intermediates IV. New York: Plenum Press;1990:627-640.



## Isoniazid–Slow Metabolizers



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### Isoniazid–Slow Metabolizers

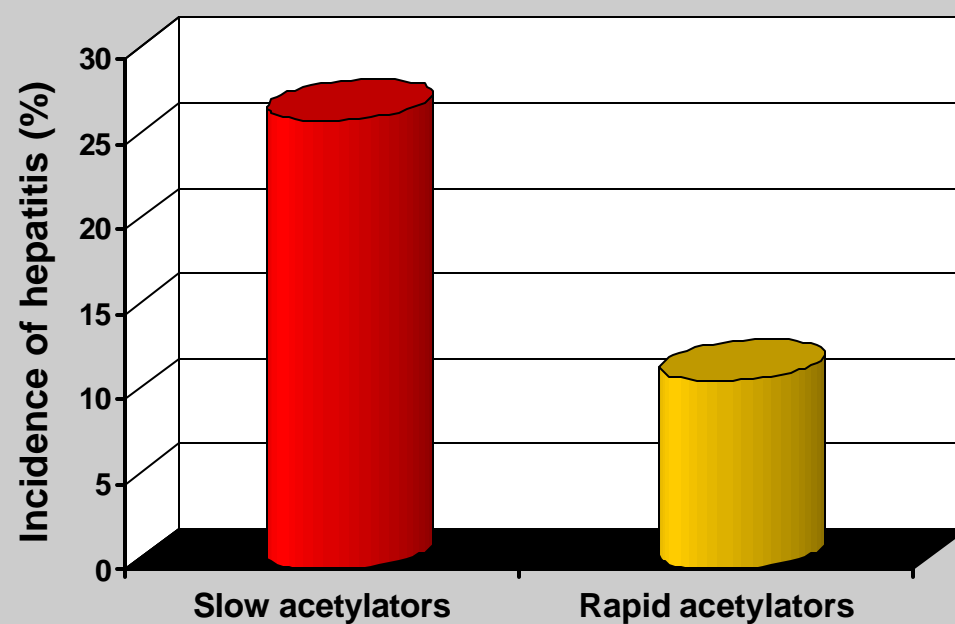
The slow acetylator phenotype of isoniazid is associated with a 10% to 20% reduction in the quantity of NAT2 in the liver.<sup>1</sup> Slow acetylators have reduced metabolism of isoniazid, which results in an accumulation of the parent compound. It is important to note that isoniazid itself is not hepatotoxic, but rather the products of its hydrolysis—acetylhydrazine and hydrazine—are toxic.<sup>2</sup> Rapid acetylators produce increased quantities of acetylhydrazine, compared with slow acetylators. However, rapid acetylators are able to further acetylate acetylhydrazine by NAT to form the nontoxic metabolite, diacetylhydrazine. Slow acetylators dispose of hydrazine and acetylhydrazine through the formation of reactive intermediates by cytochrome P450 pathways, and thus are at increased risk for the development of hepatotoxicity.

### References

1. Meyer U, Zanger U. Molecular mechanisms of genetic polymorphisms of drug metabolism. *Annu Rev Pharmacol Toxicol.* 1997;37:269-296.
2. Gross A, Kroemer H, Eichelbaum M. Genetic polymorphism of drug metabolism in humans. In: Witmer C, et al, eds. *Biological Reactive Intermediates IV.* New York: Plenum Press;1990:627-640.



## Isoniazid-Induced Hepatitis



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### Isoniazid-Induced Hepatitis

It has been observed that isoniazid-induced hepatitis occurs more frequently in slow acetylators than rapid acetylators.<sup>1</sup> The increased incidence of this disorder among rapid acetylators was confirmed in a recent study. In this study, 224 patients with tuberculosis who received isoniazid therapy were genotyped for NAT2. Thirty-three patients (14.7%) in total were diagnosed with isoniazid-induced hepatitis. Genotyping showed that the incidence of isoniazid-induced hepatitis was significantly higher among slow acetylators than rapid acetylators (26.4% vs 11.1%,  $P=.013$ ). Further, among those patients who developed isoniazid-induced hepatitis, serum aminotransferase levels were higher in slow acetylators, compared with rapid acetylators.

### Reference

1. Huang Y, Chern H, Su W, et al. Polymorphism of the N-acetyltransferase 2 gene as a susceptibility risk factor for antituberculosis drug-induced hepatitis. *Hepatology*. 2002;35:883-889.

## Isoniazid–Clinical Consequences in Slow Metabolizers

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- Hepatotoxicity
- Isoniazid-induced hepatitis
- Peripheral neuropathy
- Phenytoin CNS toxicity
- SLE

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### Isoniazid–Clinical Consequences in Slow Metabolizers

Slow acetylators are also more likely to develop peripheral neuropathy than rapid acetylators.<sup>1</sup> Approximately 20% of slow acetylator isoniazid-treated patients develop peripheral neuropathy, compared with 3% of rapid acetylators. Isoniazid-induced peripheral neuropathy develops following the depletion of vitamin B6 (pyridoxine) stores, which occurs as a result of the formation of isoniazid-pyridoxal phosphate complexes.<sup>2</sup> Since slow acetylators have decreased isoniazid metabolism, they tend to accumulate higher plasma concentrations of isoniazid than do rapid metabolizers receiving the same dosage. Thus, a greater depletion of vitamin B6 will tend to occur in slow acetylators. Phenytoin CNS toxicity is also more prevalent in isoniazid slow acetylators who are receiving both agents, compared with rapid acetylators.<sup>3</sup> It is caused by the increased plasma phenytoin concentrations that occur due to the increased binding of isoniazid to cytochrome P450 in slow acetylators. This results in inhibition of phenytoin oxidation and toxicity. Isoniazid-induced SLE is a fairly rare occurrence, and slow acetylators appear to be at only a slightly increased risk for the development of SLE following therapy with isoniazid.

### References

1. Clark D. Genetically determined variability in acetylation and oxidation: therapeutic implications. *Drugs*. 1985;29:342-375.
2. Gross A, Kroemer H, Eichelbaum M. Genetic polymorphism of drug metabolism in humans. In: Witmer C, et al, eds. *Biological Reactive Intermediates IV*. New York: Plenum Press;1990:627-640.
3. Relling M. Polymorphic drug metabolism. *Clin Pharm*. 1989;8:852-863.

## Drugs That Undergo Polymorphic N-Acetylation

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### Cardiac inotrope

- Amrinone

### Antiarrhythmic

- Procainamide

### Beta blocker

- Acebutolol

### Benzodiazepines

- Clonazepam metabolites
- Nitrazepam

### Antidepressant

- Phenezine

### Sulfonamides

- Sulfadiazine
- Sulfamerazine
- Sulfamethazine
- Sulfapyridine
- Sulfasalazine

### Other drugs

- Aminobenzolic acid
- Aminoglutethimide
- Aminosalicic acid
- 7-Amino nitrazepam
- Dapsone
- Dipyrone

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### Drugs That Undergo Polymorphic N-Acetylation

It has been shown that a wide variety of drugs may undergo polymorphic acetylation, including acebutolol, aminosalicic acid, aminoglutethimide, aminosalicic acid, 7-amino nitrazepam, amrinone, clonazepam metabolites, dapsone, dipyrone, nitrazepam, phenezine, procainamide, sulfadiazine, sulfamerazine, sulfamethazine, sulfapyridine, and sulfasalazine.<sup>1,2</sup>

### References

1. Meyer U. Genetic polymorphisms of drug metabolism. *Fundam Clin Pharmacol.* 1990;4:595-615.
2. Relling M. Polymorphic drug metabolism. *Clin Pharm.* 1989;8:852-863.

## Case Study 2

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- **JP is a 68-year-old man with CHF who recently experienced cardiogenic shock while receiving an ACE inhibitor**
- **Following this episode, he is initiated on therapy with a hydralazine/nitrate combination**
- **One year after he begins taking hydralazine, he experiences arthralgia, fever, extreme fatigue, and pleurisy**

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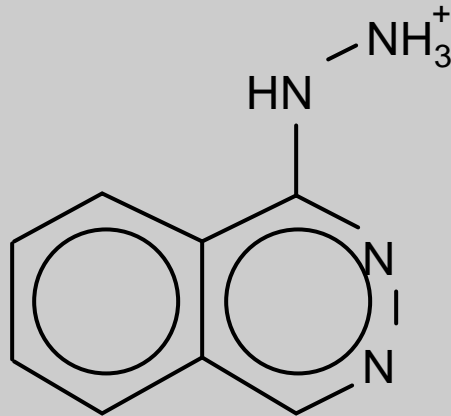
### **Case Study 2**

JP is a 68-year-old man with CHF who recently experienced cardiogenic shock while receiving an ACE inhibitor. Following this episode, he is initiated on therapy with a hydralazine/nitrate combination. One year after he begins taking hydralazine, he experiences arthralgia, fever, extreme fatigue, and pleurisy.

## Hydralazine

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- Genetic polymorphism occurs in phase II acetylation reactions



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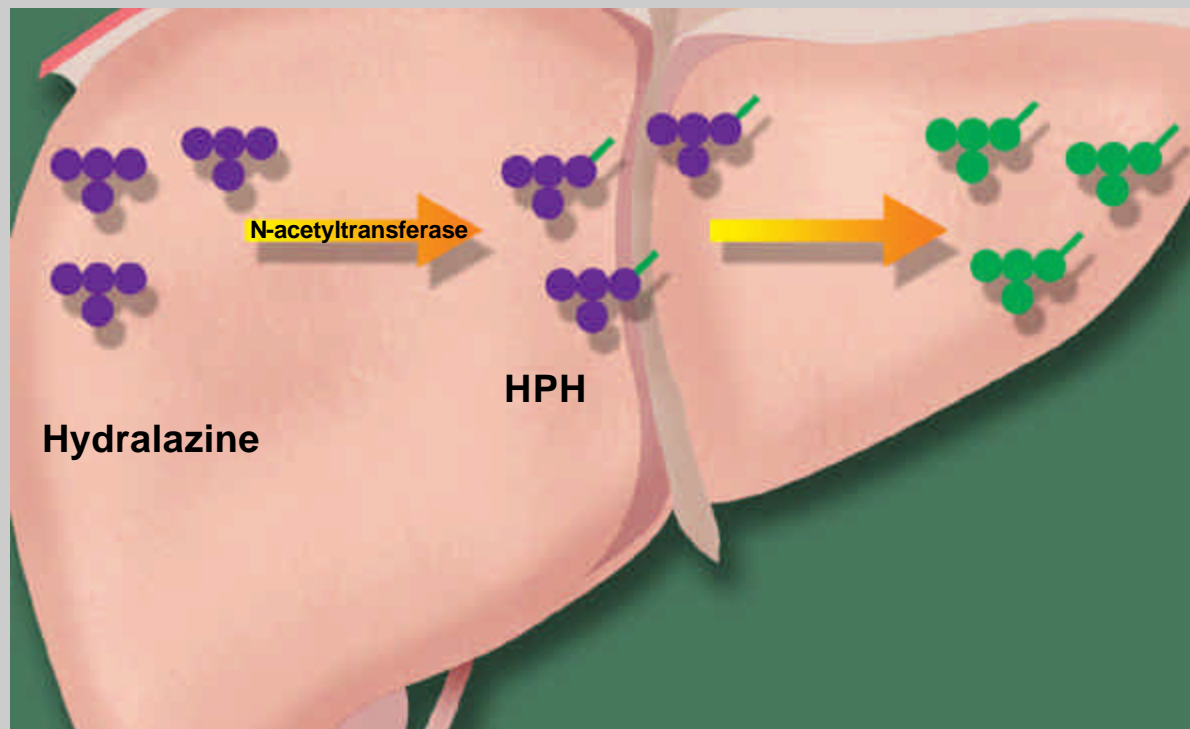
### Hydralazine

Hydralazine is an arterial vasodilator that was introduced in the early 1950s for the treatment of hypertension.<sup>1</sup> Hydralazine may be used to treat hypertension (primary, malignant, pulmonary, pre-eclampsia and eclampsia), congestive heart failure, pulmonary hypertension associated with chronic obstructive pulmonary disease, and aortic regurgitation.<sup>2-4</sup> Hydralazine undergoes first-pass metabolism in the liver. When administered orally, its bioavailability is variable, ranging from 50% to 90%.<sup>5</sup> Altered metabolism of hydralazine has been associated with a genetic polymorphism that occurs with the NAT2 enzyme in phase II acetylation reactions.

### References

1. Ram C, Ventaka S. Antihypertensive drugs: an overview. *Am J Cardiovasc Drugs*. 2002;2(2):77-89.
2. McFadden ER Jr, Braunwald E. Cor pulmonale. In: Braunwald E, ed. *Heart Diseases. A Textbook of Cardiovascular Medicine*, 4th ed. Philadelphia: Saunders, 1992:1581-1601.
3. Oates JA. Antihypertensives Agents and Drug Therapy of Hypertension. In: Hardman L, et al, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 9th ed. New York: McGraw-Hill, Health Professions Division; 1996: 809-838.
4. Gallagher MW, Repke JT, Goldstein PJ. Pharmacologic Approach to the Critically Ill Obstetric Patient. In: Chernow B, Brater C, et al, eds. *The Pharmacologic Approach to the Critically Ill Patient*, 3rd ed. Baltimore: Williams & Wilkins, 1994:847-862.
5. Clark D. Genetically determined variability in acetylation and oxidation: therapeutic implications. *Drugs*. 1985;29:342-375.

## Hydralazine–Metabolism



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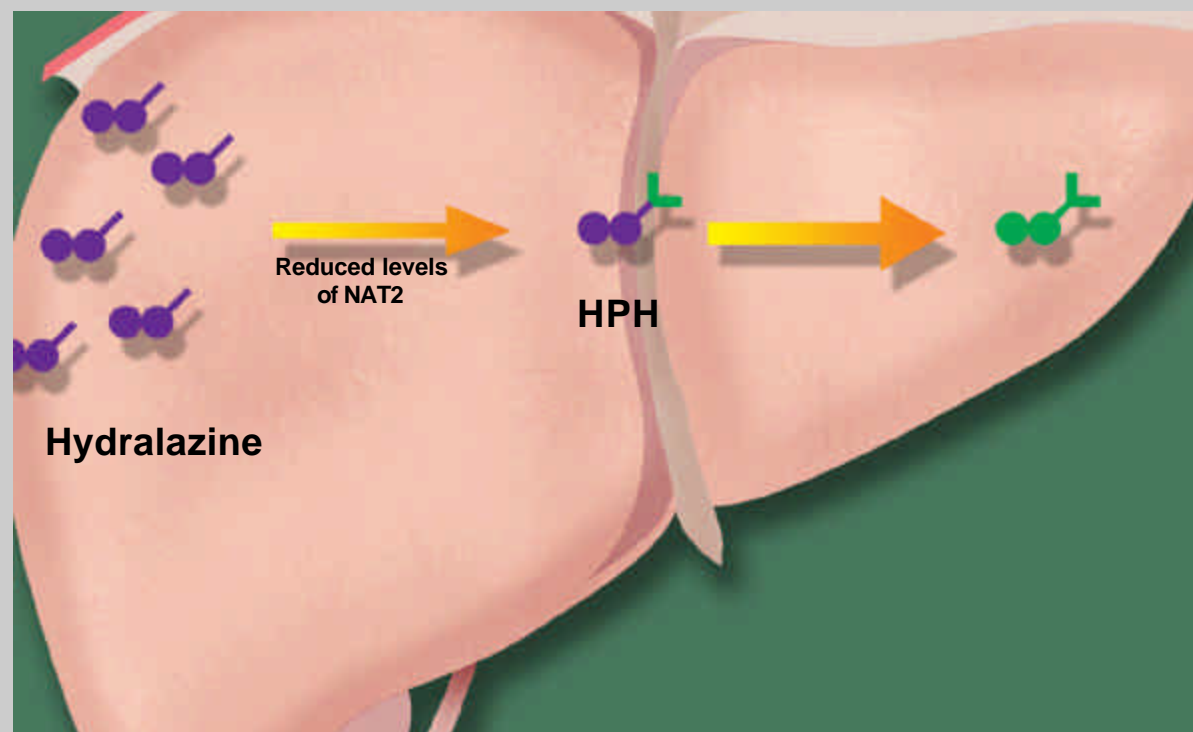
### Hydralazine–Metabolism

The gastrointestinal mucosa and the liver are the main sites of first-pass metabolism of hydralazine.<sup>1</sup> The major plasma metabolite of N-acetylation of hydralazine is hydralazine pyruvic acid hydrazone (HPH).

### Reference

1. Koch-Weser J. Hydralazine. N Engl J Med. 1976;295:320-323.

## Hydralazine–Slow Metabolizers



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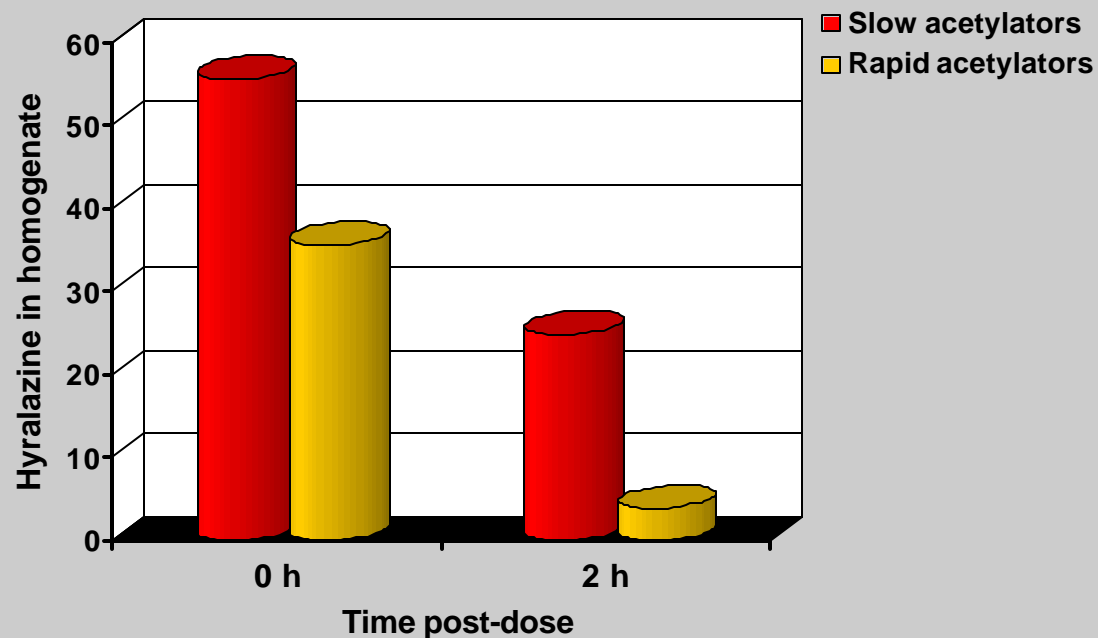
### Hydralazine–Slow Metabolizers

Two distinct enzymes found in the liver are N-acetylators, called N-acetyltransferase 1 and 2.<sup>1,2</sup> The enzyme NAT2 is involved in the genetic polymorphism associated with N-acetylation. In slow acetylators, NAT2 levels are reduced.<sup>3</sup> The slow acetylator phenotype has a 10% to 20% reduction in the quantity of NAT2 in the liver, resulting in accumulation of the parent drug.

### References

1. Meyer U. Genetic polymorphisms of drug metabolism. *Fundam Clin Pharmacol.* 1990;4:595-615.
2. West W, Knight E, Pradhan S, et al. Interpatient variability: genetic predisposition and other genetic factors. *J Clin Pharmacol.* 1997;37:635-648.
3. Meyer U, Zanger U. Molecular mechanisms of genetic polymorphisms of drug metabolism. *Annu Rev Pharmacol Toxicol.* 1997;37:269-296.

## Hydralazine–A Liver Study



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### Hydralazine–A Liver Study

In a study with hydralazine in human liver homogenate, it was demonstrated that the activity of the enzyme N-acetyltransferase was effected by acetylator phenotype.<sup>1</sup> It was shown that at two hours post-dose, slow acetylators excreted substantially greater amounts of hydralazine than rapid acetylators. Another study showed that hydralazine bioavailability was substantially higher in slow acetylators (31%) compared with fast acetylators (9.5%).<sup>2</sup> In general, serum concentrations of hydralazine in slow acetylators tend to be 1.7 times higher than those found in rapid acetylators. This fact has been used as a guide to hydralazine dosing.<sup>3</sup> It has been suggested that by limiting doses of hydralazine to 200 mg, blood pressure may be more safely controlled in slow acetylators. In rapid acetylators, hydralazine doses may be increased. The metabolic ratio of the serum concentration ratios of the acetyl metabolite and the parent compound of hydralazine exhibit a trimodal frequency of distribution in the general population.<sup>4</sup> This distribution may be divided into rapid acetylators, intermediate acetylators, and slow acetylators.

### References

1. Price Evans D, White T. Human acetylation polymorphism. *J Lab Clin Med.* 1964;63:394-403.
2. Shepherd A, Ludden T, McNay JL, et al. Hydralazine kinetics after single and repeated oral doses. *Clin Pharmacol Ther.* 1980;28:804-11.
3. Tanaka E. Update: genetic polymorphism of drug metabolizing enzymes in humans. *J Clin Pharm Ther.* 1999;24:323-329.
4. Clark D. Genetically determined variability in acetylation and oxidation: therapeutic implications. *Drugs.* 1985;29:342-375.



## Hydralazine–Clinical Consequences in Slow Metabolizers

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- Development of antinuclear antibodies and systemic lupus erythematosus (SLE)
- Facial flushing
- Coldness of the extremities
- Headache
- Peripheral neuropathy

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### Hydralazine–Clinical Consequences in Slow Metabolizers

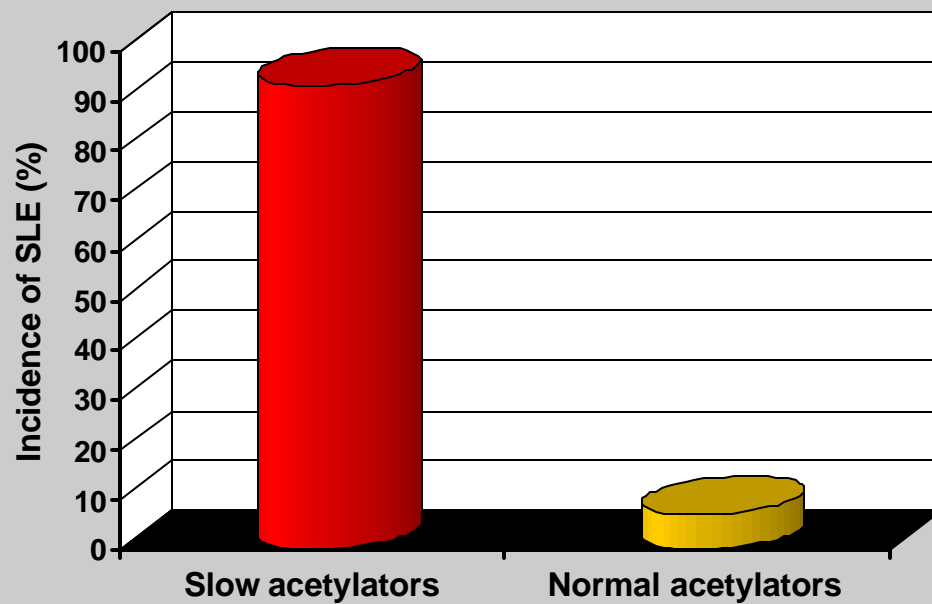
Because most of the drug toxicities associated with hydralazine therapy are presumed to be caused by the parent drug hydralazine, and not by the acetylated metabolite, an increased incidence of adverse events is to be expected in slow acetylators.<sup>1</sup> Adverse events that are observed more frequently in slow metabolizers of hydralazine include systemic lupus erythematosus (SLE), peripheral neuropathy, facial flushing, coldness of the extremities, and headache.

### Reference

1. Clark D. Genetically determined variability in acetylation and oxidation: therapeutic implications. *Drugs*. 1985;29:342-375.

## Hydralazine-Induced SLE

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### Hydralazine-Induced SLE

In addition to the increased incidence of drug-related adverse events in slow acetylators treated with hydralazine, there are associations of acetylator phenotype with drug-induced disease. Slow acetylators of hydralazine appear more likely than fast acetylators to develop antinuclear antibodies and SLE. In one study, 29 of 31 patients who developed SLE following hydralazine therapy were shown to be slow acetylators. The risk of developing hydralazine-induced lupus is proportional to the drug dosage, with long-term therapy at dosages greater than 200 mg/day enhancing the risk.<sup>1</sup>

### Reference

1. Clark D. Genetically determined variability in acetylation and oxidation: therapeutic implications. *Drugs*. 1985;29:342-375.

## Case Study 3

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- **GV is a 28-year-old man with a history of complex partial seizures who has been unresponsive to treatment with phenytoin and valproate**
- **His physician initiates therapy with mephenytoin**
- **Shortly after he begins taking mephenytoin, he experiences mental confusion, ataxia, and slurred speech**

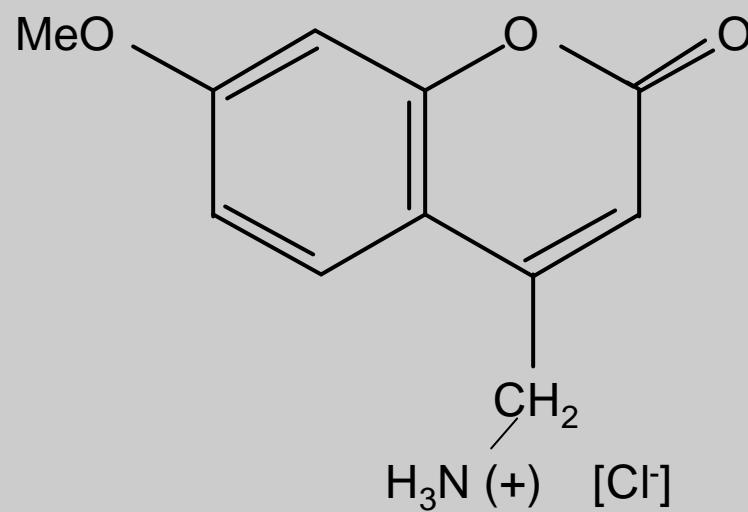
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### **Case Study 3**

GV is a 28-year-old man with a history of complex partial seizures who has been unresponsive to treatment with phenytoin and valproate. His physician initiates therapy with mephenytoin. Shortly after he begins taking mephenytoin, he experiences mental confusion, ataxia, and slurred speech.

## Mephenytoin

- Genetic polymorphism occurs in phase I hydroxylation reactions



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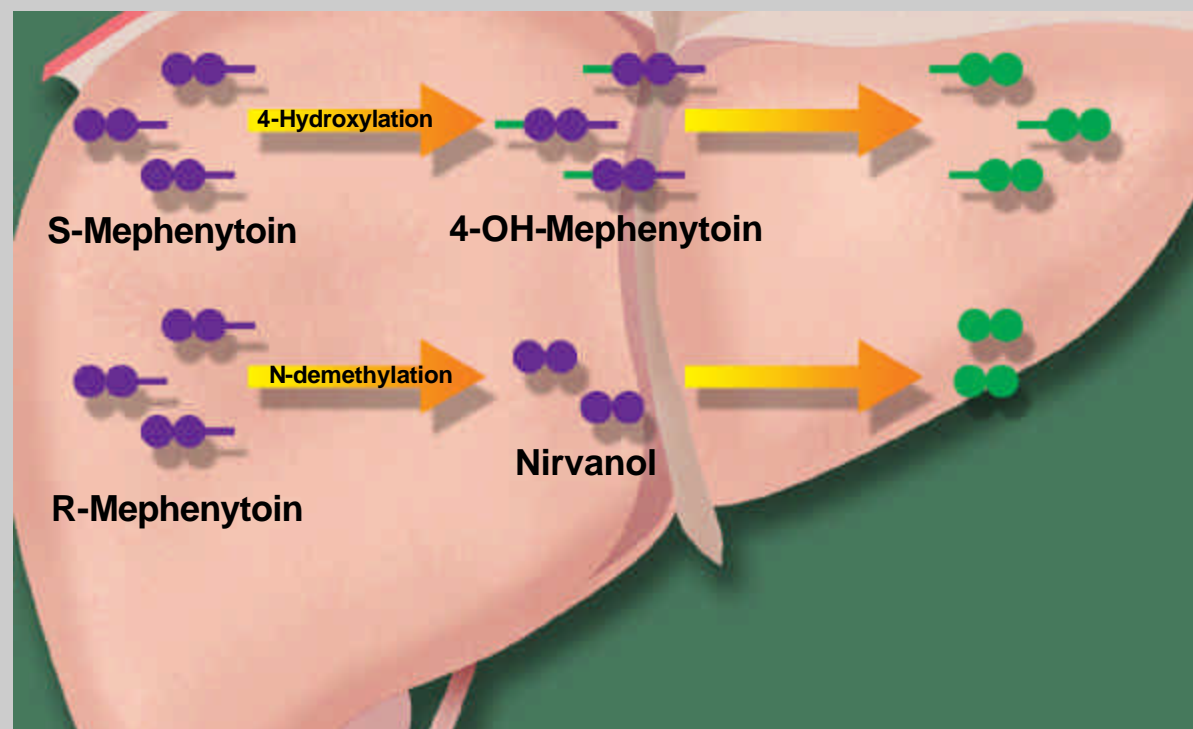
### Mephenytoin

Mephenytoin is an anticonvulsant that was introduced into clinical use in 1945 as an alternative to phenytoin. There is a reduced incidence of adverse events associated with long-term mephenytoin administration.<sup>1,2</sup> It may be used for the control of seizures of focal origin as well as major generalized seizures.<sup>3</sup> Currently, mephenytoin is mainly used for some types of refractory seizures.<sup>1,2</sup> Mephenytoin was one of the first drugs shown to display polymorphic drug metabolism. Altered metabolism of mephenytoin has been associated with a genetic polymorphism that occurs with the cytochrome P450 CYP2C19 enzyme in phase I hydroxylation reactions.

### References

1. Meyer U. Genetic polymorphisms of drug metabolism. *Fundam Clin Pharmacol.* 1990;4:595-615.
2. Relling M. Polymorphic drug metabolism. *Clin Pharm.* 1989;8:852-863.
3. Wilkinson G, Guengerich P, Branch R. Genetic polymorphism of S-mephenytoin hydroxylation. In: *Pharmacogenetics of Drug Metabolism.* Kalow W, ed. 1992: 657-685.

## Mephenytoin–Normal Metabolizers



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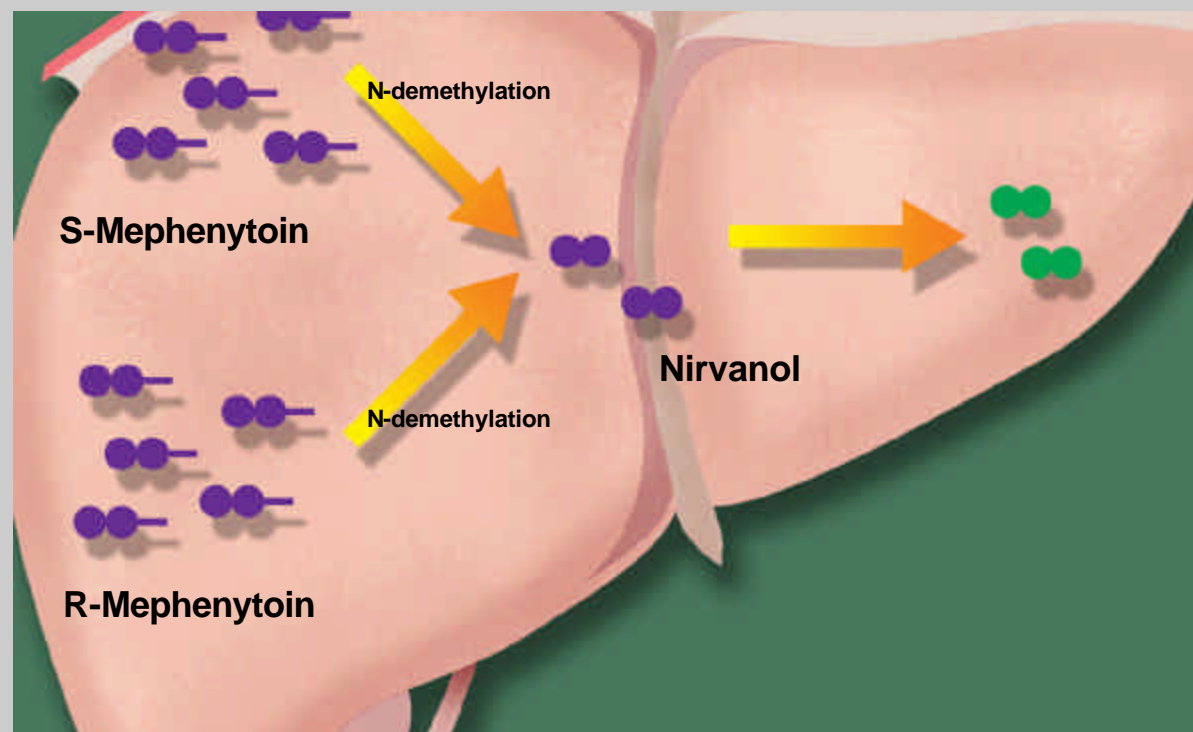
### Mephenytoin–Normal Metabolizers

Mephenytoin exists as a racemate of R and S isomers.<sup>1</sup> In normal (extensive) metabolizers, S-mephenytoin is oxidized to 4'-hydroxy-mephenytoin. S-mephenytoin is almost completely 4'-hydroxylated and rapidly eliminated, with a half-life of approximately 2 hours.<sup>2,3</sup> This is followed by glucuronidation, and the product is excreted over a 4-day period.<sup>1</sup> R-mephenytoin is demethylated to 5-phenyl-5-ethylhydantoin (Nirvanol) and is metabolized more slowly than is the S-enantiomer, with a half-life of approximately 75 hours.<sup>2,3</sup> Nirvanol has anticonvulsant activity that is similar to that of the parent drug. It has been suggested that the presence of this metabolite is contributory to the overall clinical effect of mephenytoin.<sup>4</sup> Nirvanol itself is hydroxylated very slowly, with a half-life of at least several days.<sup>1</sup> Normal metabolizers stereoselectively hydroxylate S-mephenytoin to inactive 4'-hydroxymephenytoin and nonstereoselectively demethylate R-mephenytoin to Nirvanol.<sup>5</sup> The hydroxylation and demethylation of mephenytoin is mediated by separate cytochrome P450 enzymes.

### Reference

1. West W, Knight E, Pradhan S, et al. Interpatient variability: genetic predisposition and other genetic factors. *J Clin Pharmacol.* 1997;37:635-648.
2. Wilkinson G, Guengerich P, Branch R. Genetic polymorphism of S-mephenytoin hydroxylation. In: *Pharmacogenetics of Drug Metabolism.* Kalow W, ed. 1992:657-685.
3. Wedlund P, Aslanian W, Jacqz E. Phenotypic differences in mephenytoin pharmacokinetics in normal subjects. *J Pharmacol Exp Ther.* 1985;23:662-669.
4. Relling M. Polymorphic drug metabolism. *Clin Pharm.* 1989;8:852-863.
5. Meyer U, Zanger U. Molecular mechanisms of genetic polymorphisms of drug metabolism. *Annu Rev Pharmacol Toxicol.* 1997;37:269-296.

## Mephenytoin–Slow Metabolizers



Slide 29

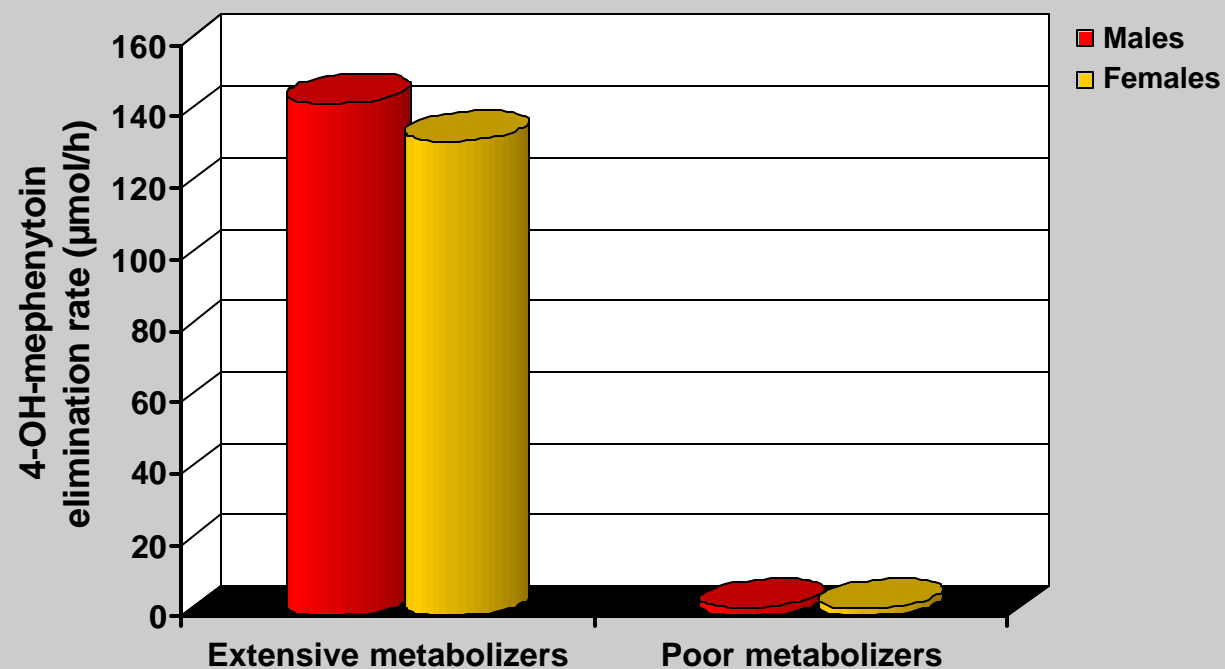
### Mephenytoin–Slow Metabolizers

It has been shown that poor metabolizers of mephenytoin are deficient in 4'-hydroxylation of S-mephenytoin.<sup>1</sup> Individuals exhibiting slow metabolism of mephenytoin are not able to differentiate between the metabolism of S- and R-enantiomers of the drug. In these individuals, both enantiomers of the drug undergo demethylation, and excretion of the Nirvanol metabolite is slow. Total mephenytoin levels are almost twice as high in slow metabolizers compared with normal metabolizers given the same amount of a drug.<sup>2</sup>

### References

1. Fromm M, Kroemer H, Eichelbaum M. Impact of P450 genetic polymorphism on the first-pass extraction of cardiovascular and neuroactive drugs. *Adv Drug Del Rev.* 1997;27:171-199.
2. Wilkinson G, Guengerich P, Branch R. Genetic polymorphism of S-mephenytoin hydroxylation. In: *Pharmacogenetics of Drug Metabolism.* Kalow W, ed. 1992:657-685.

## Mephenytoin–A Population Study



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### Mephenytoin–A Population Study

Kupfer et al conducted a landmark population study of mephenytoin hydroxylation in 221 subjects. In the larger population of 209 mephenytoin metabolizers, the elimination rate for 4-OH-mephenytoin was 137 µmol per 8 hours.<sup>1</sup> However, in a distinct group of 12 individuals, the 4-OH-mephenytoin elimination rate was much slower, at approximately 2.4 µmol per 8 hours or about 2% of the normal metabolizers. From this data it was estimated that there was a prevalence of about 5% for slow metabolizers.<sup>2</sup>

### References

1. Kupfer A, Preisig R. Pharmacogenetics of mephenytoin: a new drug hydroxylation polymorphism in man. *Eur J Clin Pharmacol.* 1984;36:753-759.
2. Relling M. Polymorphic drug metabolism. *Clin Pharm.* 1989;8:852-863.

## Mephenytoin–Clinical Consequences in Slow Metabolizers

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- Increased mephenytoin toxicity
- Sedation
- Scleroderma

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### **Mephenytoin–Clinical Consequences in Slow Metabolizers**

Slow metabolizers of mephenytoin experience an increased incidence of concentration-related adverse events, presumably because of the increased levels of mephenytoin as well as the accumulation of Nirvanol to concentrations approximately twice as high as those observed in extensive metabolizers.<sup>1</sup> Slow metabolizers have an increased incidence of the central adverse effects associated with mephenytoin, particularly sedation.<sup>2,3</sup> One study also demonstrated an increased incidence of scleroderma among the slow- metabolizer phenotype.<sup>4</sup>

### **References**

1. Wilkinson G, Guengerich P, Branch R. Genetic polymorphism of S-mephenytoin hydroxylation. In: Pharmacogenetics of Drug Metabolism. Kalow W, ed. 1992:657-685.
2. Fromm M, Kroemer H, Eichelbaum M. Impact of P450 genetic polymorphism on the first-pass extraction of cardiovascular and neuroactive drugs. *Adv Drug Del Rev.* 1997;27: 171-199.
3. Meyer U, Zanger U. Molecular mechanisms of genetic polymorphisms of drug metabolism. *Annu Rev Pharmacol Toxicol.* 1997;37:269-296.
4. May D, Black C, Olsen N. Scleroderma is associated with differences in individual routes of drug metabolism: a study with dapsone, debrisoquin, and mephenytoin. *Clin Pharmacol Ther.* 1990;48:286-295.



## Mephenytoin–Drug Interactions in Slow Metabolizers

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### Barbiturates

- Mephobarbital
- Hexobarbital

### Benzodiazepines

- Diazepam
- Desmethyldiazepam

### Antidepressants

- Imipramine
- Clomipramine
- Citalopram
- Moclobemide

### Proton pump inhibitors

- Omeprazole
- Lansoprazole
- Pantoprazole

### Beta blocker

- Propranolol

### Antimalarials

- Proguanil
- Chlorproguanil

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### Mephenytoin–Drug Interactions in Slow Metabolizers

The mephenytoin polymorphism affects a variety of drugs that are metabolized by CYP2C19.<sup>1</sup> The metabolism of mephobarbital and hexobarbital are impaired in slow metabolizers of mephenytoin.<sup>2,3</sup> The metabolism and clearance of diazepam and desmethyldiazepam are also reduced in slow metabolizers of mephenytoin. The tricyclic antidepressants imipramine and clomipramine, and the serotonin uptake inhibitor citalopram also appear to be dependent on S-mephenytoin hydroxylase activity. The metabolism of omeprazole, pantoprazole, lansoprazole, propranolol, proguanil, and chlorproguanil are affected by altered mephenytoin metabolism.<sup>4</sup>

### References

1. Gross A, Kroemer H, and Eichelbaum M. Genetic polymorphism of drug metabolism in humans. In: Biological Reactive Intermediates IV. Witmer et al, ed. 1990:627-640.
2. Fromm M, Kroemer H, Eichelbaum M. Impact of P450 genetic polymorphism on the first-pass extraction of cardiovascular and neuroactive drugs. *Adv Drug Del Rev.* 1997;27: 171-199.
3. Dahl M, Bertilsson L, Ingelman-Sundberg M. Molecular basis of drug oxidation polymorphisms. *Nord J Psychiatry.* 1993;47(Suppl 30):27-31.
4. Meyer U, Zanger U. Molecular mechanisms of genetic polymorphisms of drug metabolism. *Annu Rev Pharmacol Toxicol.* 1997;37:269-296.

## Case Study 4

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- **DK is a 25-year-old woman with seasonal allergic rhinitis**
- **Her physician initiates therapy with desloratadine for symptom relief**
- **Shortly after she begins taking therapy, she experiences drowsiness**

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### **Case Study 4**

DK is a 25-year-old woman with seasonal allergic rhinitis. Her physician initiates therapy with desloratadine for symptom relief. Shortly after she begins taking therapy, she experiences drowsiness.

## Second-Generation Antihistamines

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- **Competitively inhibit histamine by binding to H<sub>1</sub> receptors**
- **Used for the treatment of allergic rhinitis and chronic idiopathic urticaria**
- **Nonsedating antihistamines do not cross the blood-brain barrier and are generally considered safer than early generation antihistamines**
- **Metabolic properties of antihistamines also affect therapeutic efficacy and safety**

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### **Nonsedating Antihistamines**

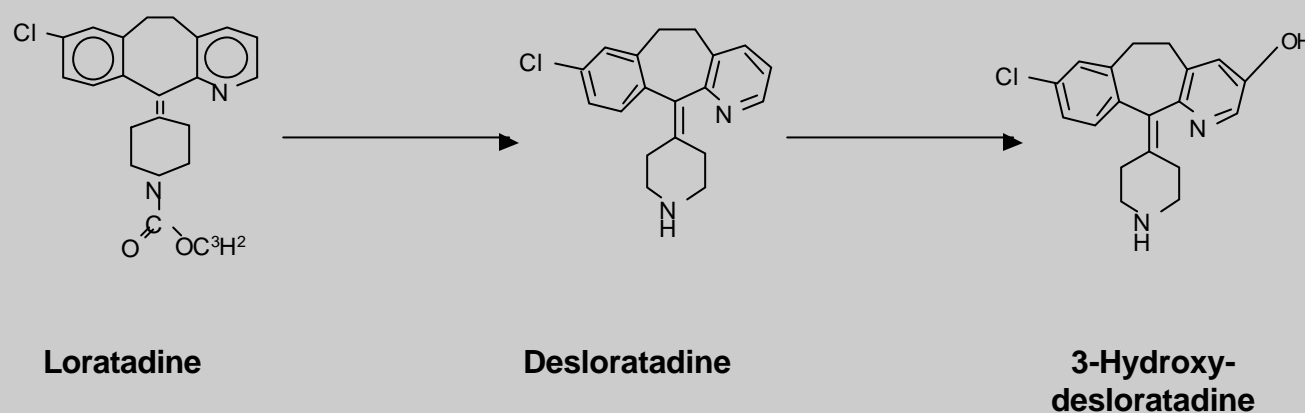
Antihistamines block the histamine-induced intracellular signaling cascade by competitively binding to H<sub>1</sub> receptors.<sup>1</sup> Antihistamines have been available for the treatment of allergies since the 1940s. Currently most available antihistamines may be used for the treatment of allergic rhinitis (AR) and chronic idiopathic urticaria. Early antihistamines were effective for the reduction of many of the symptoms associated with AR. However they were not selective for the H<sub>1</sub> receptor, and would also bind with various other receptor types including cholinergic, serotonin, and adrenergic receptors. These early generation antihistamines readily penetrated the blood-brain barrier, resulting in drowsiness and cognitive impairment. Second-generation antihistamines, including fexofenadine, cetirizine, and loratadine and its metabolite, desloratadine, have increased receptor specificity compared with first-generation agents.<sup>2,3</sup> This results in stronger selective peripheral

H<sub>1</sub>-blocking activity, and reduced sedating and anticholinergic side effects. While these new antihistamines are generally considered safer than early generation antihistamines, it is important to consider the effect that metabolic properties of antihistamines may have on therapeutic efficacy and safety.

### **References**

1. Grant JA. Molecular pharmacology of second-generation antihistamines. *Allergy Asthma Proc.* 2000;21:135-140.
2. Slater JW, Zechnich AD, Haxby DG. Second generation antihistamines: a comparative review. *Drugs.* 1999;57:31-46.
3. Ten Eick AP, Blumer JL, Reed MD. Safety of antihistamines in children. *Drug Saf.* 2001;24:119-147.

## Desloratadine



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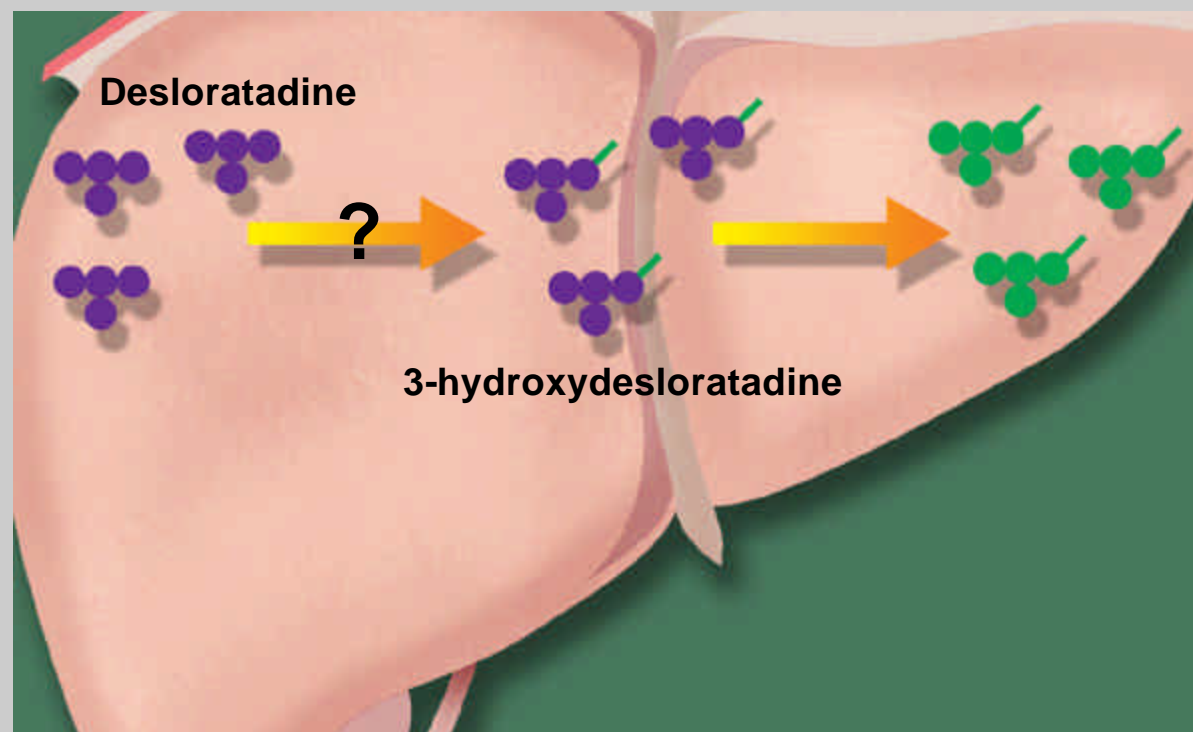
### Desloratadine

Desloratadine was recently introduced as a selective antihistamine ( $H_1$ -receptor antagonist).<sup>1</sup> Desloratadine is a major metabolite of loratadine. It undergoes extensive metabolism to 3-hydroxydesloratadine, and has exhibited polymorphic metabolism.<sup>2</sup> The enzyme responsible for the polymorphism associated with desloratadine is currently unknown.

### References

1. Agrawal D. Pharmacology and clinical efficacy of desloratadine as an anti-allergic and anti-inflammatory drug. *Expert Opin Investig Drugs*. 2001;10:547-60.
2. Clarinex [package insert]. Kenilworth, NJ: Schering Corporation; 2000. Available at: <http://www.clarinex.com/clarinex/productinfo.html>. Accessed July 18, 2002.

## Desloratadine–Metabolism



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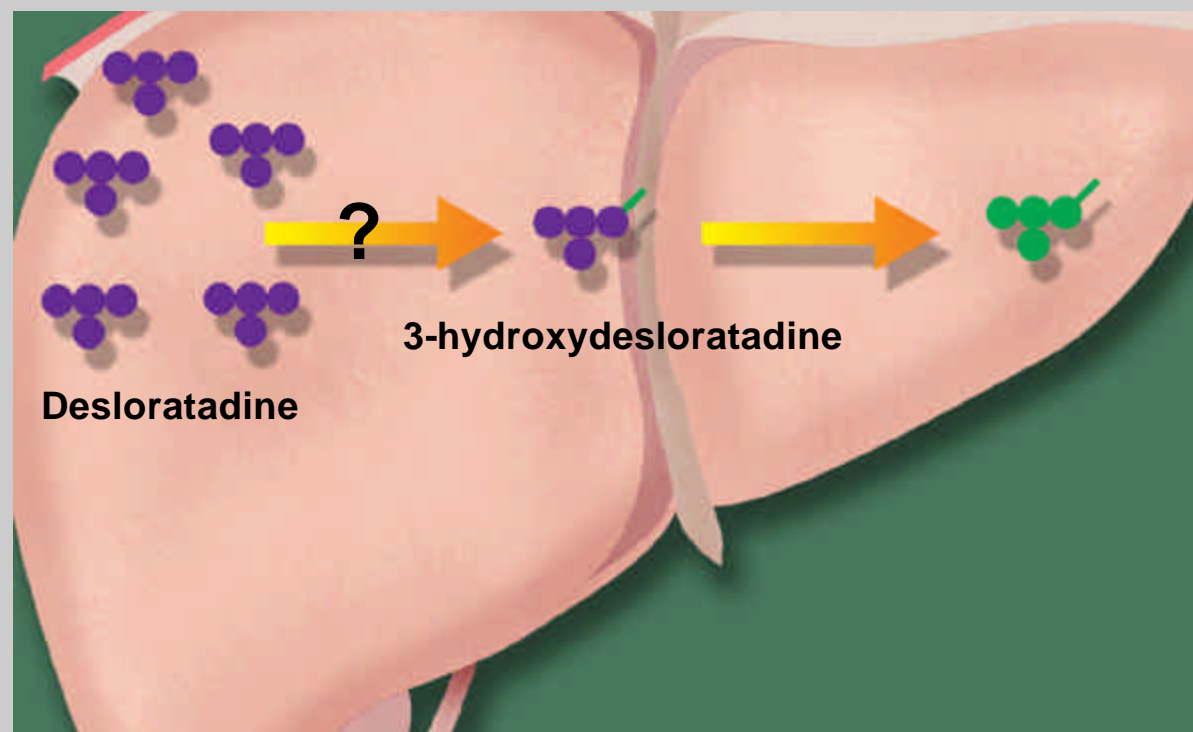
### Desloratadine–Metabolism

In the liver, desloratadine is extensively metabolized to 3-hydroxydesloratadine.<sup>1</sup> This metabolite is subsequently glucuronidated prior to excretion. The enzyme or enzymes that are responsible for the formation of 3-hydroxydesloratadine are currently unknown.

### Reference

1. Clarinex [package insert]. Kenilworth, NJ: Schering Corporation; 2000. Available at: <http://www.clarinex.com/clarinex/productinfo.html>. Accessed July 18, 2002.

## Desloratadine–Slow Metabolizers



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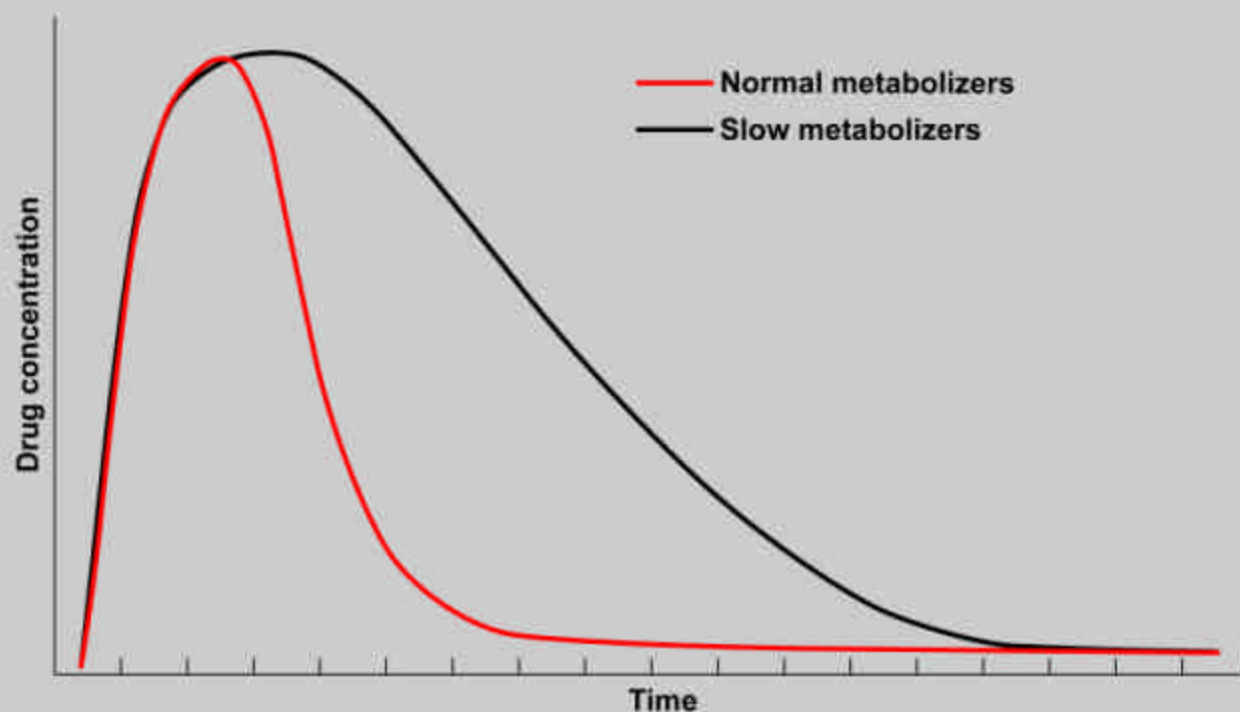
### Desloratadine–Slow Metabolizers

Slow metabolizers of desloratadine appear to have a decreased ability to form the metabolite 3-hydroxydesloratadine.<sup>1</sup>

### Reference

1. Clarinex [package insert]. Kenilworth, NJ: Schering Corporation; 2000. Available at: <http://www.clarinex.com/clarinex/productinfo.html>. Accessed July 18, 2002.

## Desloratadine—Slow Metabolizers Have a 6-Fold Increase in Bioavailability



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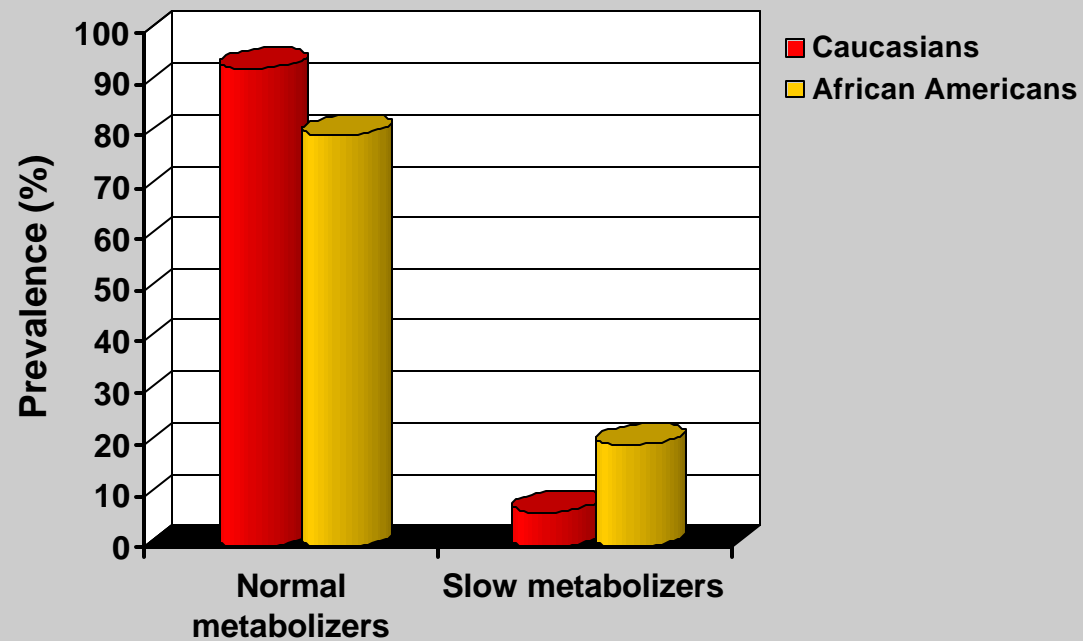
### Desloratadine—Slow Metabolizers and Bioavailability

Based on pharmacokinetic studies conducted with desloratadine, the median exposure area under the curve (AUC) to desloratadine is approximately 6-fold higher in slow metabolizers than in individuals who are not slow metabolizers. This compares with some of the previous examples in which slow metabolizers had 1.7- to 2.0-fold increases in parent compound levels.

### Reference

1. Clarinex [package insert]. Kenilworth, NJ: Schering Corporation; 2000. Available at: <http://www.clarinex.com/clarinex/productinfo.html>. Accessed July 18, 2002.

## Desloratadine–Slow Metabolizers by Ethnicity



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### Desloratadine–Slow Metabolizers by Ethnicity

In pharmacokinetic studies of 1087 individuals, it was shown that approximately 7% of the population are slow metabolizers of desloratadine.<sup>1</sup> In these studies, slow metabolizer status was defined as individuals with an AUC ratio of 3-hydroxydesloratadine to desloratadine of less than 0.1, or individuals with a desloratadine half-life of more than 50 hours. The frequency of slow metabolizers was shown to be higher among African Americans. In these studies, approximately 20% of African Americans were slow metabolizers. Data from other ethnic groups, such as Hispanics and Asians, are unknown.

### Reference

1. Clarinex [package insert]. Kenilworth, NJ: Schering Corporation; 2000. Available at: <http://www.clarinex.com/clarinex/productinfo.html>. Accessed July 18, 2002.



## Desloratadine–Slow Metabolizers

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- **Slow metabolizers of desloratadine cannot be prospectively identified**
- **Individuals who are slow metabolizers of desloratadine may be more susceptible to dose-related adverse events**

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### **Desloratadine–Slow Metabolizers**

Subjects who are slow metabolizers of desloratadine cannot be prospectively identified.<sup>1</sup> Such subjects will be exposed to higher levels of desloratadine when treated with the recommended dosage. Individuals who are slow metabolizers of desloratadine may be more susceptible to dose-related adverse events.

### **Reference**

1. Clarinex [package insert]. Kenilworth, NJ: Schering Corporation; 2000. Available at: <http://www.clarinex.com/clarinex/productinfo.html>. Accessed July 18, 2002.

## Desloratadine–Adverse Events

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- **Reported during initial clinical trials: somnolence, myalgia, fatigue, pharyngitis, dry mouth, and dysmenorrhea**
- **Adverse events reported during marketing phase**
  - tachycardia
  - hypersensitivity reactions (rash, pruritus, urticaria, edema, dyspnea, and anaphylaxis)
  - elevated liver enzymes, including bilirubin

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### **Desloratadine–Adverse Events**

Adverse events that were associated with therapeutic doses of desloratadine in clinical trials of patients with allergic rhinitis included somnolence, myalgia, fatigue, pharyngitis, dry mouth, and dysmenorrhea.<sup>1</sup> Other reported spontaneous adverse events include tachycardia, hypersensitivity reactions (rash, pruritus, urticaria, edema, dyspnea, and anaphylaxis), and elevated liver enzymes. Studies with its parent compound, loratadine, have shown that increased doses may be associated with sedation and cognitive impairment.<sup>2</sup>

### **References**

1. Clarinex [package insert]. Kenilworth, NJ: Schering Corporation; 2000. Available at: <http://www.clarinex.com/clarinex/productinfo.html>. Accessed July 18, 2002.
2. Hindmarch I, Shamsi Z. Antihistamines: models to assess sedative properties, assessment of sedation, safety and other side effects. *Clin Exp Allergy*. 1999;29:133-142.

## Drug-Related Adverse Events

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- **Drug-related adverse events remain a serious problem in the clinical setting**
- **Rare adverse drug reactions tend to be identified only when drugs are used in large patient populations, and not during drug development**
- **When confronted with an adverse drug reaction, it is important that physicians consider the possible influence of genetic polymorphism**

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### **Drug-Related Adverse Events**

The incidence of adverse events in association with available therapeutic agents remains a serious problem.<sup>1</sup> A recent meta-analysis found that 6.7% of inpatients experience serious adverse drug reactions. Although large numbers of individuals are typically enrolled in pivotal clinical trials for new therapies, rare adverse drug reactions that occur at a rate of less than 1 in 1000, are usually only identified after a drug has been used in much larger patient populations, such as during the initial marketing phase.<sup>2</sup> When confronted with an adverse drug reaction, it is important that physicians consider the possible influence of genetic polymorphism.

### **References**

1. Lazarou J, Pomeranz B and Corey P. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA*. 1998;279:1200-1205.
2. Roses A. Pharmacogenetics and future drug development and delivery. *Lancet*. 2000;355:1358-1361.

## **Genetic Polymorphisms–Clinical Relevance**

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- **Clinical significance of genetic polymorphisms of drug metabolism is related to whether:**
  - **the metabolic pathway subject to polymorphism is a major route of elimination for the drug**
  - **the drug has a narrow therapeutic index**
  - **the drug must be activated to produce pharmacologically active metabolites**
  - **the variability in drug response can easily be clinically determined**

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### **Genetic Polymorphisms–Clinical Relevance**

It has been suggested that the clinical significance of genetic polymorphisms of drug metabolism is related to a variety of factors.<sup>1,2</sup> These include whether the metabolic pathway subject to polymorphism is a major route of elimination for the drug, whether the drug has a narrow therapeutic index, whether the drug must be activated to produce the pharmacologically active metabolite or metabolites, and whether the variability in drug response can easily be clinically determined.

### **References**

1. Ensom M, Chang T, Patel P. Pharmacogenetics: the therapeutic drug monitoring of the future? *Clin Pharm.* 2001;40:783-802.
2. Meyer UA. Pharmacogenetics. In: Carruthers SG, Hoffman BB, Melmon KL, et al., eds. 4th ed. *Melmon and Morrelli's Clinical Pharmacology: Basic Principles in Therapeutics.* 4th ed. New York, NY: McGraw-Hill; 2000:

## Genetic Polymorphisms–Implications for Drug Development

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- For drugs in clinical trials that have known polymorphisms in metabolism, dosage and clinical effectiveness should be determined in individuals of known phenotypes
- Individuals participating in clinical trials should be characterized with respect to metabolizer phenotype
- Emphasis should be placed on determining the different dose requirements for all known phenotypes

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### Genetic Polymorphisms–Implications for Drug Development

There are important implications for drugs that have known polymorphisms in drug metabolism prior to marketing.<sup>1</sup> In regards to clinical trial design, sources of variation between groups should be removed to ensure valid statistical comparisons of drug effect among various treatments. Further, patients participating in these trials should be characterized with respect to their metabolizer phenotype.<sup>2</sup> For drugs that undergo polymorphic metabolism, appropriate drug dosage and clinical effectiveness in individuals of known phenotypes should be determined.<sup>1</sup> Any modifications to drug dosage that may be necessary should be determined prior to widespread use.

### References

1. Clark D. Genetically determined variability in acetylation and oxidation: therapeutic implications. *Drugs*. 1985;29:342-375.
2. Eichelbaum M. Defective oxidation of drugs: pharmacokinetic and therapeutic implications. *Clin Pharm*. 1982;7:1-22.

## Summary

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- **Adverse drug reactions are a serious clinical problem**
- **Genetic polymorphism in metabolism may result in drug responses that are outside the therapeutic range**
- **Slow metabolizers may be at increased risk for drug-related adverse events**
- **When confronted with an agent known to be subject to polymorphic metabolism, physicians should consider whether additional monitoring for efficacy and safety is appropriate**