Acenocoumarol and Phenytoin Toxicity in the Presence of CYP2C9 Mutation

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Abstract
This case report describes a rare interaction between therapeutic doses of phenytoin and acenocoumarol resulting in both acute phenytoin toxicity and increased international normalized ratio (INR). Interactions between these drugs are due to the pharmacokinetics and the common metabolising pathway by hepatic cytochrome P450 isoenzyme-CYP2C9. Our patient was detected to be homozygous for CYP2C9*3 by PCR-RFLP analysis resulting in markedly decreased metabolism of both the drugs. Given that these two drugs are often given concomitantly in the medical out patient department, and that CYP2C9 polymorphisms are not uncommon, clinicians should be aware of this interaction and suspect this in patients with toxicity to these drugs.

INTRODUCTION
Polymorphisms in genes that encode determinants of the pharmacokinetics of a drug, in particular, the metabolizing enzymes, can effect the drug concentration, and thus determine the therapeutic and adverse drug responses. The study of these genetic variations that determine a patient’s response and reaction to drugs is called pharmacogenetics. Hepatic cytochrome P450 isoenzymes (CYPs) are responsible for metabolizing the vast majority of therapeutic drugs, with the most active CYPs being CYP2C, CYP2D and CYP3A subfamilies. Many clinically relevant drug interactions are due to inhibition or induction of these enzymes eg. rifampicin reducing phenytoin levels. Variant alleles of their encoding genes can also cause marked variation in the therapeutic effect and safety of drugs.

Acenocoumarol and diphenylhydantoin (phenytoin) are commonly prescribed drugs. Each drug has a narrow therapeutic range, making the resulting drug interactions clinically significant. When these drugs are prescribed concurrently, the potential for interaction and toxicity is high due to their pharmacokinetic properties. It can also be due to genetic polymorphisms in the metabolizing enzyme (CYP2C9) as illustrated by this case report.

CASE REPORT
A 27-year-old pregnant lady, with a history of rheumatic heart disease and mitral valve replacement 10 years ago on long-term anticoagulation (acenocoumarol 0.5-mg daily), presented with status epilepticus at 20 weeks of gestational age (GA). Clinical examination at presentation was unremarkable. In view of a past history of untreated generalised tonic clonic seizures two years prior to this presentation and at 5 weeks gestational age, a diagnosis of a primary seizure disorder was made and treatment initiated with phenytoin at a dose of 100 mg thrice daily after an initial loading dose of 18 mg/kg (Weight:50kg). Imaging of the brain was deferred as she was pregnant. At discharge her International Normalised Ratio (INR) was 2.35 on acenocoumarol 0.5 mg once daily.

She presented again 3 weeks later with vomiting and giddiness. Clinical examination revealed neurological signs compatible with acute phenytoin toxicity. A computed tomography (CT) of the brain did not show any evidence of haemorrhage in the cerebellum. Serum phenytoin concentrations were in the toxic range > 40 mcg/ml (Reference range 10-20 mcg/ml) and the INR was 6.57 on 0.5mg of acenocoumarol (Reference range 1.5 to 2.5). A drug interaction between phenytoin and acenocoumarol was considered in view of the clinical presentation and laboratory evidence of elevated INR and phenytoin concentrations. Phenytoin was discontinued with gradual resolution of symptoms and signs over the next three days. Serum phenytoin concentrations and INR three days later were 26.3 mcg/ml and 3.84 respectively.

The patient’s previous records showed that she had very high INR values with small doses of acenocoumarol. In the absence of any acquired predisposing factor for phenytoin and acenocoumarol toxicity, a genetic
polymorphism was suspected. Among the hepatic microsomal enzymes, enzyme CYP2C9 plays a major role in the metabolism of both acenocoumarol and phenytoin. PCR-RFLP (Polymerase Chain reaction-Restriction Fragment Length Polymorphism) analysis of her serum for genetic polymorphisms revealed that this patient was homozygous for CYP2C9*3 and heterozygous for the CYP2C19 alleles. Phenytoin was substituted with sodium valproate which is metabolized mainly by hepatic conjugation and the patient remained seizure free subsequently.

**DISCUSSION**

The observed clinical effects in this patient can be explained based on the pharmacokinetic interaction between phenytoin and acenocoumarol and the genetic polymorphism in the CYP 450 enzyme system.

**Pharmacokinetic interactions**

When acenocoumarol and phenytoin are administered concomitantly there is a high risk of drug interactions due to the pharmacokinetic properties of these agents.

1. Phenytoin displaces coumarins from its albumin-binding sites, increasing the free, active form resulting in a prolonged INR. However, the increased free fraction can undergo rapid clearance, thereby lowering the total drug concentration.

2. As phenytoin and S-coumarins are substrates of CYP2C9, phenytoin initially may compete with S-coumarins, thus increasing their serum concentrations and anticoagulant effect. On chronic concomitant therapy, however, phenytoin induces hepatic microsomal enzymes CYP450, mainly CYP2C9 and CYP2C19, increasing the metabolism of coumarins and decreasing the INR.

3. Phenytoin can increase the metabolism of vitamin K-dependant clotting factors and thereby prolong the prothrombin time.

**Genetic polymorphism**

There are large differences in levels of expression of each CYP between individuals due to the presence of genetic polymorphisms and differences in gene regulation. Several human CYP genes exhibit polymorphisms, including CYP2A6, CYP2C9, CYP2C19, and CYP2D6.

Phenytoin is metabolized predominantly by CYP2C9 with a minor contribution of CYP2C19. The wild type CYP2C9*1 allele has normal (100%) enzymatic activity (assessed for phenytoin metabolism), while the CYP2C9*2 (Arg144*Cys) and CYP2C9*3 (Ile359*Leu) alleles have only 12% and 5% of this activity, respectively. As reported by Achuthan et al polymorphisms are not infrequent with frequencies of CYP2C9*1, *2 and *3 of 88%, 4% and 8% respectively reported in their series from South India. There has been a recent report from India of phenytoin toxicity in a patient homozygous to CYP2C9*3. Such patients have been noted to have markedly prolonged elimination half-life, as much as 103 hours (the standard elimination half-life of phenytoin being 22 hours). There is data supporting a 25% to 30% reduction in dose requirements among these patients.

Coumarins, including acenocoumarol, are also metabolized by CYPs mainly by CYP2C9 with minor contributions from CYP1A2 and CYP2C19. Therefore clinically relevant interactions have to be expected for drugs that are inhibitors or substrates of CYP2C9. Moreover, the variant alleles CYP2C9*2 and CYP2C9*3 inactivate coumarins much less efficiently in comparison to wild type CYP2C9*1 allele resulting in lower acenocoumarol dose requirements, a higher frequency of over-anticoagulation at the initiation of therapy and an unstable anticoagulant response. Patients requiring a dose of acenocoumarol of less than 1 mg to maintain a therapeutic INR have been shown to have a high prevalence of CYP2C9 polymorphism.

Considering the high frequency of the mutant CYP2C9 alleles in South India (12%), one has to be extremely vigilant when using substrates of CYP2C9. Genetic polymorphism should be suspected in patients who require extremely small doses of coumarins and when patients develop features of acute phenytoin toxicity with therapeutic doses.

Pharmacogenetic tests can locate genetic polymorphisms thus identifying a subset of patients who are at high risk for toxicity or poor response to medications. This helps in dosage individualization to improve outcomes and decrease short- and long-term adverse effects, especially in drugs with high toxicity and a narrow therapeutic window like anticancer drugs.

**Acknowledgements**

Mr. Salamun Desire -Clinical Hematology, Christian Medical College and Hospital, Vellore.
REFERENCES

API Announcement
Elections for Posts of API
(Full details circular No. 2/2008)

Election process is on for the following Post of API and ICP for the year 2008-2009
1. President-Elect - 1, 2. One Vice President - 1, 3. Hon. Treasurer - 1, 4. Elected Members - 4

Nominations shall be made on prescribed forms stating the office for which nominations are filled. The nomination shall be proposed by one valid member and seconded by another valid member and duly signed by them and shall also be signed by the candidate signifying his/her willingness to stand for election and serve on the Governing Body if elected. Separate nominations must be submitted for each post.

Every member is supplied with a nomination form. The nomination form completed in all respects should reach the API Office not later than 31st May, 2008. For every post on the Governing Body, the nomination must be accompanied by a sum of Rs. 2,500/- (Rupees Two Thousand Five Hundred only) in the form of Demand Draft payable at Mumbai. The nomination paper NOT accompanied by the Bank Draft of Rs. 2,500/- will be deemed invalid.

Rules Relating to Qualification for Election to Governing Body
1. President Elect: To contest for the post of President Elect the candidate should be a life member of API for at least 10 years and have completed at least two full terms of 3 years each in any elected position in the Governing Body.
2. Vice President and Hon. General Secretary: To contest for the post of Vice President and Hon. General Secretary the candidate should be a life member of API for at least 5 years and have completed at least one continuous full term of 3 years in any elected position in the Governing Body.
3. To contest for the all the other elected positions of the Governing Body, continuous membership of the Association for at least 3 years is mandatory.
4. A member shall not contest simultaneously for more than one post (i.e. President-Elect, Vice-President, Honorary Secretary, Honorary Treasurer or Elected Member of the Governing Body - General and Zonal). Also a member will not contest any post in the API or ICP simultaneously. Post means not only an office-bearer but also member of Governing Body or Faculty Council of ICP.

Important
Canvassing in any form should not be done by the candidate for the election. Instead, they are requested to send a short bio-data NOT MORE THAN 200 words along with the nomination paper which will be printed and circulated along with the ballot paper. Excess of bio-data beyond the first two hundred words shall be deleted. Canvassing in any form or in favour of the candidate shall not be permitted.

THE CANDIDATE WILL HAVE TO CERTIFY AND SIGN THAT THE INFORMATION PROVIDED IN HIS/HER BIO-DATA IS CORRECT.

The results will be declared at the end of counting of votes and announced in the subsequent issue of JAPI. The report will be placed before the Governing Body for intimation.

DEAD LINES OF ELECTION PROCEDURE
Last date to receive the nomination at API Office 31st May 2008
Last date for withdrawal 20th June 2008
Last date to receive ballot papers at API Office 31st August 2008

The full circular No. 2/2008 is available both on API and JAPI website

Dr. Sandhya A Kamath, Hon. Gen. Secretary