
Case Report

Warfarin Resistance, a Case Report

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Abstract

In tolerance to oral anticoagulant drugs may arise as an inborn genetic defect resulting in insensitive hepatic receptor sites to oral anticoagulants or it may be due to one of several acquired causes such as noningestion or malabsorption of the drugs, simultaneous ingestion of barbiturates or the inadvertent consumption of foods with a high vitamin K content. It is an uncommon phenomenon and the genetic defect is usually not recognized until the need for oral anticoagulation arises. We report here a case of resistance to Warfarin in the hope that an awareness of this phenomenon may turn up similar case of study.

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Introduction

Resistance to oral anticoagulants is an uncommon phenomenon which may be hereditary or acquired. Hereditary resistance is very rare, Acquired causes for oral anticoagulant tolerance may arise as a result of patient noncompliance, malabsorption of the drug, the inadvertent ingestion of natural foods or health food preparations high in vitamin K content or the concomitant intake of hepatic enzyme-inducing drugs. Patients vary markedly in their requirement of Warfarin, but 95% of subjects need more than 1 and less than 9mg/day. Subjects requiring more are therefore classed as Warfarin-resistant, Warfarin resistance may be due to several factors(either pharmacokinetic, pharmacodynamic) or due to poor concordance(compliance). The important causes of warfarin resistance are listed in Table 1.

Table 1- Important Causes of Warfarin Resistance

Pharmacokinetic
Decreased absorption (Cholestyramine,colestipol)
Enhanced elimination (e.g. enzyme inducers)
Pharmacodynamic
Excess vitamin K intake
Hyperlipidemia
Certain drugs
Hereditary resistance (extremely rare)
Acquired resistance (very rare)

Case report

The patient was a 35 yrs old housewife who was candidated for MVR (Mitral valve replacement). In 2007 she underwent MVR with a mechanical Mitral valve. Attempts to anticoagulate her as an outpatient began with a 5mg/day dose of Warfarin and increased to 40mg/day, although there were no significant changes in the patients PT and INR. In the January 2008 she was hospitalized. Examinations revealed a young woman with an anterior chest scar and the characteristic valvular click over the Mitral area. Physical findings were otherwise unremarkable and at the time of examination, no other drugs were consumed by patient. During hospitalization of the patient and close control which was done at the hospital and

according tests which was done, we could not find the type of her resistance to warfarin. At the late January 2008 she underwent Mitral valve replacement with a biologic valve.

Discussion

Tolerance to oral anticoagulant therapy is very rare, although with considering this, several causes can be studied in any patient with the resistance to oral anticoagulants (e.g.warfarin). The most common cause of resistance to oral anticoagulants is malabsorption, Interference with other drugs and interference with vitamin K,^{1,2} in most cases of resistance to warfarin studies can reveal the cause, but in some others (like our case mentioned above) none of these, is not the cause. Pharmacokinetic causes include enhanced Warfarin metabolism. This may be due to enzyme induction, particularly by certain drugs (e.g. barbiturates, carbamazepine and rifampine). Impairment of absorption of warfarin (it is normally completely absorbed from the gut) can occur due to binding by cholestyramine,colestipol or charcoal. Poor concordance may simulate a pharmacokinetic cause, since the ingested dose is lower than that intended to be taken.³ Pharmacodynamic cause of resistance include ingestion of excess vitamin K in certain health foods or weight-reducing diets or in enteral feeds. Oestrogens, Griseofulvin, 6-Mercaptopurine and Haloperidol may cause diminish of anticoagulant effect in some individuals,although the mechanisms are poorly understood. Patients with hyperlipidemia (particularly hypercholesterolemia) may be relatively resistant to Warfarin and although the effect appears to have a pharmacodynamic basis, the cause is unknown. Finally an extremely rare form of hereditary warfarin resistance has been described in two human kindreds.^{4,5} The trait is inherited in an autosomal dominant fashion and a mutation of the receptor site shared by Warfarin and vitamin k is postulated ,although the locus of the mutation is unknown. Another important cause of resistance to Warfarin can be hypothyroidism.



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