

# RESISTANCE TO ORAL ANTICOAGULANT THERAPY — CASE REPORT AND REVIEW OF LITERATURE

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## SYNOPSIS

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 exceptional resistance to Warfarin in the hope that an awareness of this phenomenon may turn up similar cases for study.

## INTRODUCTION

Resistance to oral anticoagulants is an uncommon phenomenon which may be hereditary or acquired. Hereditary resistance to coumarin anticoagulant drugs has, to date, been reported in only two families (1, 2, 3, 4). Acquired causes for oral anticoagulant tolerance may arise as a result of patient noncompliance, malabsorption of the drug, the inadvertent ingestion of natural foods (5) or health food preparations (6) high in vitamin K content or the concomitant intake of hepatic enzyme-inducing drugs (7). Recently we encountered a case of exceptional resistance to Warfarin therapy in a Singapore-born Indian man referred for oral anticoagulant management following the installation of a mitral valve prosthesis.

## Case Report

The patient is a 49 year old laboratory assistant who underwent mitral valve commissurotomy in 1959 and mitral valve replacement in 1979. Attempts to anticoagulate him as an outpatient were unsuccessful. In April 1981 he was warded.

Examination revealed a well-nourished Indian man with an anterior chest scar and the characteristic valvular click over the mitral area. Physical findings were otherwise unremarkable.

Investigations included a normal full blood count, normal liver function tests, normal coagulation profile with normal levels of coagulation factors II, VII, IX, X (vitamin K dependent factors). D-xylose and vitamin absorption tests were normal.

From the initial 5 mg Warfarin daily, the dose was steadily increased, monitored by daily Thrombotest. After 19 days of close monitoring the therapeutic Thrombotest range (10–15% of the normal control) was achieved with 150 mg of Warfarin daily. The patient was retained in hospital for a further 7 days to ensure the Thrombotest remained in the desired range.

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During the hospitalization the possibility of non-ingestion of the drug was excluded as the daily Warfarin dose was ingested by the patient in the presence of a nurse. He ate a regular Indian diet and no drugs were given apart from Warfarin. Malabsorption was not considered clinically and basic absorption tests were normal. Family study to confirm hereditary resistance to Warfarin was thwarted by the following factors: both parents were deceased, patient himself never fathered any children, his only living kin, an older sister, had been lost to contact since her emigration to England 20 years ago.

## DISCUSSION

Tolerance to oral anticoagulant therapy is rare. The literature provided only 2 families with this disorder and they represent the first well documented cases of hereditary resistance to the therapeutic action of any drug in man (1, 2, 3). The true incidence of this defect is unlikely to be known as its inheritance does not predispose the victim to any clinical disadvantage and it is not revealed unless the need for oral anticoagulation arises. Family study constitutes the ultimate proof for this hereditary disorder. Where this is impossible as was the situation in our patient, the diagnosis is entertained only after the exclusion of acquired causes which include surreptitious non-ingestion of the anticoagulant, simultaneous ingestion of liver enzymatic inducers (barbiturates), or the ingestion of foods or health food preparations rich in vitamin K and malabsorption.

Based on the two families reported (1, 3) the inheritance of this defect is through an autosomal dominant gene. The resistance is not absolute and can be overcome by large doses of the anticoagulant drugs. O'Reilly (3) postulated the disorder to be caused by hepatic receptor site impaired sensitivity to coumarin drugs with normal or increased sensitivity to vitamin K. In support of this postulate was the discovery that the propositi of both reported families showed

extreme responsiveness to minute doses of exogenous vitamin K during chronic, well-controlled Warfarin therapy (3, 4).

Although we were unable to diagnose hereditary resistance to Warfarin conclusively, due to the lack of family members for study, our patient's daily Warfarin requirement (150 mg) was of the same magnitude as that reported in O'Reilly's cases (90-145 mg). We also excluded acquired causes as far as we could. It remains for us to recommend that future cases of oral anticoagulant resistance (the average daily Warfarin dosage for the local adult patient is 2-5 mg) be referred to a single investigational unit in order that proper documentation of prevalence and etiology may be carried out.

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