

CYTOCHROME 2C9 (CYP2C9 *1, *2 AND *3, METABOLISM OF SINTROM AND WARFARINE)

PATOGENESI

The genetic polymorphisms of the enzymes involved in the metabolism of drugs contribute, together with other factors such as diet, age, sex, to its inter-individual differential response. CYP2C9 is important for the elimination of many drugs with a narrow therapeutic range such as phenytoin (antiepileptic) or the anticoagulants Warfarin and Sintrom. There are several allele variants of CYP2C9, the most common being CYP2C9 * 2 (R144C) and CYP2C9 * 3 (I359L), with an allele frequency in the Caucasian population of 8-18% and 4-10%, respectively. Several studies conducted on patients receiving warfarin have shown that the alleles * 2 and * 3 metabolize the drug more slowly (low-metabolizers) and therefore require a lower dosage of the drug. These alleles have been strongly associated with an increased sensitivity to warfarin and the risk of bleeding during anticoagulant treatment. Acenocoumarol (Sintrom) is the coumarin derivative most used in Europe as an oral anticoagulant. Recently, the CYP2C9 allele * 3 has been found with a higher prevalence in patients requiring a low dose of Sintrom, a higher frequency of over-anticoagulation at the start of therapy and an unstable response to treatment. The utility of performing a CYP2C9 genotyping before starting a therapy with Sintrom is supported by two recent "case reports" where the administration of 4 mg / day led to an over-anticoagulation with an INR greater than 9 at the first control. Genotyping revealed the presence, for both patients, of a homozygosity for the CYP2C9 * 3 allele. Blood / EDTA, 5 ml (even a smaller quantity in case of difficult withdrawal). Daily

TREATMENT

Optimal dose of acenocoumarol according to the CYP2C9 genotype:

Genotipo	Dose mediana (mg/sett.)
CYP2C9*1/*1(wild-type)	15.8
CYP2C9*1/*2	13.5
CYP2C9*1/*3	10.5
CYP2C9*2/*2	13.0
CYP2C9*2/*3	11.6

TEST

Evidence of CYP2C9 * 2 (R144C) and * 3 (I359L) polymorphisms by PCR and restriction analysis. The results are provided by specifying the allelic form (eg. CYP2C9 * 1 / * 3) with the related comment on the enzymatic activity (normal or slow).

SAMPLE TAKING

Blood/EDTA, 5 ml.

EXECUTION

Daily.

Laboratorio
di diagnosi
molecolare
clinica

Further information or bibliographic references can be asked to the laboratory.