

## **Digging deep to uncover rare CYP genotype**

### **Solanidine analysis during TDM revealed rare CYP2D6 poor metabolizer genotype: a case report**

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#### Background:

CYP2D6 catalyses the metabolism of around 25% of all clinically used drugs. In Caucasians, 5-10% are homozygous carriers of variant alleles encoding no CYP2D6 enzyme activity and classified as poor metabolisers (PMs). These patients are at increased risk of adverse effects when using CYP2D6 substrates. Challenges related to genotyping comprise selection of appropriate clinical CYP2D6 variant alleles, and costs required to identify CYP2D6 PMs in general. Recently, we showed that measurements of solanidine and its CYP2D6-dependent metabolite 4-hydroxysolanidine predicted CYP2D6 PMs with excellent accuracy. Here we report a case where solanidine and 4-hydroxysolanidine measurements in a therapeutic drug monitoring sample facilitated identification of a CYP2D6 PM with a rare genotype, previously genotyped as *CYP2D6* \*1/\*1 and interpreted as a normal metaboliser.

#### Methods:

We have included measurements of solanidine and 4-hydroxysolanidine in our ultra-high performance liquid chromatography high-resolution mass spectrometry method, thus allowing routinely phenotyping of CYP2D6 as part of our therapeutic drug monitoring practice. A low 4-hydroxysolanidine-to-solanidine metabolic ratio below the threshold value of  $-4.28$  (ln transformed) provides a recommendation for genotyping.

#### Results:

In October 2024, a metabolic ratio of  $-7.86$  was calculated in a therapeutic monitoring sample from a patient who had been genotyped as *CYP2D6* \*1/\*1 and interpreted as a normal metaboliser in 2020. The patient had a history of side effects during use of the CYP2D6 substrates perphenazine and aripiprazole at standard doses. Upon reanalysis with an extended genotyping panel, a rare CYP2D6 genotype (*CYP2D6*\*7/\*7) encoding PM status was revealed.

#### Conclusion:

The report shows the clinical value and feasibility of routine analysis of solanidine and 4-hydroxysolanidine to identify patients predicted to be CYP2D6 PMs, including patients with rare variants. Solanidine and 4-hydroxysolanidine measurements can be used as a complementary tool to genotyping and substantially reduce the number-needed-to-genotype for identification of CYP2D6 PMs in clinical practice.

Reference:

Størset et al. Solanidine analysis during therapeutic drug monitoring revealed rare CYP2D6 poor metabolizer genotype: A case report. *Br J Clin Pharmacol* 2025;91:2745