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Pharmacogenetics in Clinical Practice: can we still do without…?!?

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Interindividual variation in drug metabolism is a complicating factor which affects drug therapy: it causes that the standard dose of drug may result in adverse drug reactions in some patients, or that drugs fails to work properly. In fact, adverse drug reactions are responsible for 7% of hospitalizations and are the 5th cause of death. On the other hand, only 25-60% of drugs are effective.

Part of this interindividual variation in drug response can be predicted by a simple DNA analysis: pharmacogenetics. A prominent role in this are cytochrome P450 enzymes, which are involved in the metabolism of 80% of all drugs. Knowledge about the genetic make-up of a patient enables dose adjustment prior to starting therapy. Thereby decreasing adverse drug reactions and increasing effectivity of therapy, benefitting patient, health care provider and society. Currently, the FDA has included pharmacogenetic information in the drug label of over 100 drugs. However, translation of this knowledge into routine patient care is going much slower than anticipated, although there is currently an exponential increase in test requests.

In this presentation, the current status of clinical pharmacogenetics in the Netherlands will be highlighted. Experiences of the last 8 years from the Dept. Clinical Chemistry of implementing pharmacogenetics into routine care will be discussed, covering both successes as well as (unexpected) dissapoinments.

Curriculum Vitae

Name: Ron H.N. van Schaik
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Position: Full Professor Pharmacogenetics /European Specialist Laboratory Medicine

Work experience:

2013-present	Full Professor Pharmacogenetics
2008 - 2013	Associate Professor Pharmacogenetics, Erasmus MC Rotterdam
2003 - present	European Specialist Lab Medicine, Dept. Clinical Chemistry, Erasmus MC
1999-2003	Resident Clinical Chemistry, Dept. Clinical Chemistry, Erasmus MC
1997-1999	Post-Doctoral fellow, Dept. Clinical Chemistry, Erasmus MC Rotterdam: "Pharmacogenetics for optimizing drug therapy".
1996-1997	Post-Doctoral fellow, Dept. Molecular Biology, Dr. Daniel den Hoed Cancer Center, University Hospital Rotterdam: "Screening for Colorectal cancer using molecular biological techniques"
1992-1996	Post-doctoral fellow, Dept. Endocrinology & Reproduction, Erasmus University Rotterdam on a grant of the Dutch Cancer Society (NKB): "Expression of activin and inhibin in endocrine tumours."

Education:

1992	PhD-degree biochemistry: Immunological and Molecular characterization of rat liver Phospholipase A2
1987-1991	PhD. student, Dept. Biochemistry, Center for Biomembranes and Lipid Enzymology, Utrecht University (NWO)
1981-1987	Chemistry, Utrecht University Biochemistry, Clinical Chemistry, Molecular Biology

Selected publications:

1. de Graan AJ, Teunissen SF, de Vos FY, Loos WJ, **van Schaik RH**, de Jongh FE, de Vos AI, van Alphen RJ, van der Holt B, Verweij J, Seynaeve C, Beijnen JH, Mathijssen RH. Dextromethorphan As a Phenotyping Test to Predict Endoxifen Exposure in Patients on Tamoxifen Treatment. J Clin Oncol. 2011 Jul 18; (IF 18.4)
2. Schenk PW, van Fessem MA, Verploegh-Van Rij S, Mathot RA, van Gelder T, Vulto AG, van Vliet M, Lindemans J, Bruijn JA, **van Schaik RH**. Association of graded allele-specific changes in CYP2D6 function with imipramine dose requirement in a large group of depressed patients. Mol Psychiatry. 2008 Jun;13(6):597-605. (IF 13.7)
3. **van Schaik RHN**. CYP450 pharmacogenetics for personalized cancer therapy. Drug Rest Updates 2008 Jun;11(3):77-98 (IF 9.6)
4. **van Schaik RHN**, van der Heiden IP, van den Anker JN, Lindemans J. CYP3A5 variant allele frequencies in Dutch Caucasians. Clin Chem. 2002 Oct; 48:1668-71 (IF 7.9) (159 citations; 13.25 ciattions/year)
5. de Graan AJ, Elens L, Sprowl JA, Sparreboom A, Friberg LE, van der Holt B, de Raaf PJ, de Bruijn P, Engels FK, Eskens FA, Wiemer EA, Verweij J, Mathijssen RH, **van Schaik RH**. CYP3A4*22 genotype and systemic exposure affect paclitaxel-induced neurotoxicity. Clin Cancer Res. 2013 May 2. (IF: 7.7)
6. de Graan AJ, Elens L, Smid M, Martens JW, Sparreboom A, Nieuweboer AJ, Friberg LE, Elbouazzaoui S, Wiemer EA, van der Holt B, Verweij J, **van Schaik RH**, Mathijssen RH. A pharmacogenetic predictive model for paclitaxel clearance based on the DMET platform. Clin Cancer Res. 2013 Aug 5. (IF: 7.7)
7. Hesselink DA, Bouamar R, Elens L, **van Schaik RH**, van Gelder T. The Role of

Pharmacogenetics in the Disposition of and Response to Tacrolimus in Solid Organ Transplantation. Clin Pharmacokinet. 2013 Nov 19. (IF 6.1)
8. **van Schaik RH**, van Agteren M, de Fijter JW, Hartmann A, Schmidt J, Budde K, Kuypers D, Le Meur Y, van der Werf M, Mamelok R, van Gelder T. UGT1A9 -275T>A/-2152C>T polymorphisms correlate with low MPA exposure and acute rejection in MMF/tacrolimus-treated kidney transplant patients. Clin Pharmacol Ther. 2009 Sep;86(3):319-27 (IF: 6.0)
9. Swen JJ, Nijenhuis M, de Boer A, Grandia L, Maitland-van der Zee AH, Mulder H, Rongen GA, **van Schaik RH**, Schalekamp T, Touw DJ, van der Weide J, Wilffert B, Deneer VH, Guchelaar HJ. Pharmacogenetics: From Bench to Byte- An Update of Guidelines. Clin Pharmacol Ther. 2011 Mar 16; (IF 6.0)
10. Hesselink DA, **van Schaik RHN**, van der Heiden IP, van der Werf M, Smak Gregoor PJH, Lindemans J, Weimar W, van Gelder T. Genetic polymorphisms of the CYP3A4, CYP3A5 and MDR-1 genes and pharmacokinetics of the calcineurin inhibitors cyclosporine and tacrolimus. Clin Pharmacol Ther, 2003: 74:245-54. (IF 6.0; 345 citations (average 31 citations/year))