European and Swiss Congress of Internal Medicine 2014

14-16 May 2014
Geneva, Switzerland

Abstracts

A joint venture of

the 13th European Congress of Internal Medicine of the European Federation of Internal Medicine (EFIM)
and
the 82nd Annual Meeting of the Swiss Society of General Internal Medicine (SGIM)

www.escim2014.org

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Is HLA-A*3101 screening cost-effective for preventing carbamazepine-induced severe hypersensitivity reactions ?

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Introduction: Carbamazepine is associated with a significant risk of hypersensitivity reactions, including severe toxidermia such as Stevens-Johnson syndrome (SJ), toxic epidermal necrolysis (TEN) or drug rash with eosinophilia and systemic symptoms (DRESS). Predisposition to such reactions has recently been linked to the HLA-A*3101 allele in caucasian populations and the Swiss Agency for Therapeutic Products (Swissmedic) now recommends genotyping for this allele before starting carbamazepine. The aim of this review was to critically analyze the data that support this recommendation for preventing severe toxidermia.
Method: Data from literature were reviewed to assess HLA-A*3101 prevalence in European populations, frequency of severe toxidermia associated with carbamazepine, sensitivity and specificity of HLA-A*3101 testing for predicting these toxidermia. The number needed to screen for preventing one severe reaction was calculated on the basis of these data and screening costs were estimated accordingly.
Results: The prevalence of HLA-A*3101 is 2 to 5% in Northern Europe. The estimated incidence of carbamazepine-induced SJ/TEN and DRESS is at most 6 cases in 10´000. The sensitivity and specificity of the HLA-A*3101 allele for these severe toxidermia is 38% and 96%, respectively. Thus the number needed to screen for preventing one serious reaction is 4333 subjects. The screening costs for preventing one reaction are estimated at about 585'000 Swiss francs (considering the current test price of 135 Swiss francs).
Conclusion: According to currently available data, routine HLA-A*3101 screening before starting carbamazepine is of disputable cost-effectiveness for preventing severe hypersensitivity reactions such as SJ, TEN or DRESS.

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A physiologically-based pharmacokinetic model for oxycodone and assessment of drug-drug interactions

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Objectives: Oxycodone is an agonist of μ-opioid receptors. Cytochromes P450 (CYP) 3A and 2D6 are reported to be the main isoenzymes involved in its metabolism. Development of a physiologically-based pharmacokinetic (PBPK) model is an approach to predict *in vivo* pharmacokinetic (PK) profile of oxycodone and its metabolites in different drug-drug interaction (DDI) scenarios.
Method: A PBPK model was developed for oxycodone and its two primary metabolites, oxymorphone and noroxycodone, based on published *in vitro* and *in vivo* data using the Simcyp Population-based Simulator. Models were refined by top-down approach using a published clinical trial by Samer *et al.* (2010) where PK profiles of oxycodone and its 3 metabolites were monitored in 4 DDI scenarios: oxycodone administered alone or co-administered with CYP3A inhibitor ketoconazole and/or CYP2D6 inhibitor quinidine. The fraction of the dose metabolized by every isoenzyme was modified in order to match the DDI prediction reported in the reference study. Ultimately, the reliability of the model was tested against seven published DDI scenarios. The impact of CYP3A and CYP2D6 inhibition by