



## Commentary

## NAT2 Genotype and Isoniazid Medication in Children



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## ARTICLE INFO

## Article history:

Received 24 August 2016

Accepted 25 August 2016

Available online 26 August 2016

## Keywords:

N-acetyltransferase 2

Tuberculosis

Isoniazid

Children

Tuberculosis is an infectious disease which can be treated better when the applied dose of the anti-tuberculosis drug is optimal. The basic antituberculosis drug isoniazid (INH) was one of the first medical drugs for which individual differences in the metabolism were reported more than 50 years ago (Jenne, 1960). Later it was shown that the polymorphic xenobiotic metabolizing enzyme *N*-acetyltransferase 2 (NAT2) was responsible for the observed metabolic differences which were associated with different serum or urine levels of the parent compound and its main metabolites. In a meta-analysis of 13 randomized studies in adults, fast acetylators had higher rates of therapy failure and acquired drug resistance than slow acetylators (Pasipanodya et al., 2012). The observed metabolic differences are also associated with different adverse drug effects. Slow acetylators were reported to present more hepatotoxicity and more peripheral neurotoxicity (Preziosi, 2007). A large meta-analysis of 26 studies, mostly from East Asia, showed that adult slow acetylators have a significantly higher risk (OR 3.10, 95% CI 2.47–3.88) for antituberculosis drug-induced hepatotoxicity (Du et al., 2013).

The most common adverse effect of INH therapy is liver toxicity. In adults, up to 20% of the treated patients show increased alanine aminotransaminase levels and overt liver toxicity may occur in up to 2% of the patients (Hassan et al., 2015). More important is the fact that serious liver damage may also occur. In some cases the liver damage can only be treated by a very sophisticated therapy like temporary use of an artificial liver or, as ultima ratio, by liver transplantation (Li et al., 2015).

Compared to the situation of physicians in adult medicine, pediatricians have clearly less information for an optimal dose of the antituber-

culosis drug INH. From the pharmacological point of view, the first step to improve the therapeutic possibilities is to investigate the kinetics of the parent compound isoniazid, responsible for the therapeutic effect and for the adverse effect as well, and its main acetylated metabolite acetylisoniazid (ac-INH).

It is well known that the liver of newborns is immature and that maturation of the liver takes years. Therefore, investigating the acetylation capacity of NAT2 with regards to the known specific liver toxicity of INH is warranted.

The paper of Rogers et al. (2016) is a first step to enhance this knowledge concerning the reaction kinetics of INH and ac-INH in children. The authors describe an age of about 5.3 years when the non-linear modification of the contribution of the NAT2 genotype to the INH metabolism ends.

The applied non-parametric regression approach *multivariate adaptive regression splines* (MARS) is a sophisticated extension of the linear regression model using functions (so-called *basic functions*) of the influence factors (or *independent variables*) instead of the variables themselves. It is particularly designed to model non-linear effects as well as their interaction which are both of special interest in this study. MARS includes variable selection to obtain a good fit of the model with a minimum set of most relevant influence factors. Cross validation is used to assure model validity. One advantage of MARS is the good interpretability of the results allowing for the above described conclusion of Rogers et al. (2016): an age of 5.3 years is a change point for NAT2 modulation of INH metabolism.

During this decade, ultra-slow NAT2 have entered the stage (Ruiz et al., 2012, Selinski et al., 2013, 2015). Slow acetylators in general have a lower metabolic capacity, compared to rapid acetylators. It is remarkable that ultra-slow acetylators have about 30–40% decreased metabolic capacity, compared to all other slow NAT2 genotypes (Ruiz et al., 2012, Selinski et al., 2013). It will be very interesting to find out whether the ultra-slow acetylation status has a detectable impact on INH metabolism in children and in adults as well – and whether the age of the matured liver will change.

For the clinician, it is important to note that the child's height and age, and not the body weight which is often used to adapt the dose in young children, are the most important predictors for liver maturation. The authors conclude that at 5.3 years maturation of the liver in the South African children of African descent is complete. It demands further research whether this age is also applicable to children of Asian or Caucasian descent where the distribution of the NAT2 haplotypes is different and, even more importantly, whether this age is relevant also for the application of other medical drugs or not. Particularly the latter

DOI of original article: <http://dx.doi.org/10.1016/j.ebiom.2016.07.031>.

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is an unexplained pediatric space (Kearns et al., 2003) which is of utmost clinical and theoretical relevance.

### Disclosure

The authors declared no conflicts of interest.

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