Title: THE DEXTROMETHORPHAN PHENOTYPING TEST ACCURATELY PREDICTS DEBRISOQUIN HYDROXYLASE PHENOTYPE

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Introduction. Wide intersubject variability in oxidative drug metabolism and its ability to affect response to drug therapy are well recognized. A defect in the hydroxylation of debrisoquin (DBQ) is thought to be inherited as an autosomal recessive trait in 5 to 10% of Caucasians. Poor metabolizers of DBQ have also been shown to be poor oxidizers of some other drugs and there has been recent interest in examining the effect of this genetic polymorphism on the clearance of drugs used in anesthesia (e.g., alfentanil or midazolam). To do this it is necessary to determine accurately the DBQ oxidative phenotype in volunteers and patients.[1] However, DBQ is not an ideal genetic probe drug because: (1) a single oral dose (for phenotyping) may cause orthostatic hypotension, (2) it is not licensed for use in the U.S.A., and (3) the assay is time-consuming and is not robust, making other pharmacologic studies difficult (e.g., plasma kinetics and in vitro microsomal work). Therefore, the recent finding that the O-demethylation of dextromethorphan (DMP), a common antitussive, is effected by the DBQ hydroxylase isozyme is of great interest if the suggested phenotyping test[2] can correctly specify the DBQ oxidative phenotype in a large group of individuals of unknown phenotype. We hypothesize that in a large randomly chosen sample (of a population) a high degree of correlation will be observed between the oxidative metabolic phenotypes determined by the DBQ and DMP techniques and that the separation between the rapid and slow phenotypes will be equally unambiguous. In addition, by application of the statistical method known as Gaussian mixture distributions[3] to this polymorphism, the ability to correctly identify the value of the metabolic ratio cutpoint (or antimode) for each genetic probe drug between extensive metabolizer (EM) and poor metabolizer (PM) phenotypes should be enhanced.

Methods. One hundred forty-nine healthy, unrelated residents of Spain (77 females and 72 males) were tested. On one occasion 146 of them were given 30 mg DMP before bedtime. An 8-hr overnight urine collection was obtained and the concentrations of DMP and dextrorphan (DP), its major metabolite, were measured by gas chromatography (GC). On another occasion 10 mg of DBQ was given to 127 of the subjects following an overnight fast. A 6-hr urine collection was obtained and the concentration of DBQ and its 4-hydroxy metabolite were measured by GC. For each test performed on this sample a mixture of Gaussian distributions was sought on the natural logarithm (ln) of the metabolic ratios. The chi-square test was used to test whether there was an improvement of fit with a mixture of two ln normal distributions over a single ln normal distribution. Data were also considered jointly to determine if they represented a mixture of two bivariate normal distributions. Pooled within component correlation between phenotyping tests was sought by linear regression analysis.

Results. Ninety percent of the sample phenotyped by the DMP test are EMs (-4.268 ± 0.830, mean ± SD) and 10% are PMs (0.792 ± 0.830). The chi-square test of improvement in fit considering the data as a mixture of two rather than a single ln normal distribution was significant X^2_2 = 125.2, p<0.0001). The optimal ln-cutpoint is -1.43 or 0.24 in the original metric. For those tested with DBQ, 89% are EMs (-0.724 ± 0.772) and 11% are PMs (3.075 ± 0.772). The chi-square value was 72.5 ($p < 0.0001$). The optimal ln-cutpoint for DBQ is 1.50 or 4.48 on the original metric. When considered jointly, the ln transformed data exhibit a mixture of two bivariate normal distributions (X^2_2 = 101.1, $p < 0.0001$). The estimated proportions belonging to EM and PM phenotypes was 0.897 and 0.103, respectively. The pooled within component correlation between DMP and DBQ is r = 0.6026.

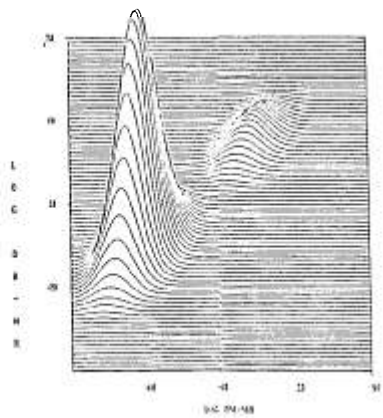

Figure 1. Mixture of 2 bivariate normally distributed ln-transformed metabolic phenotype data

Discussion. In order to examine the relationship between the variable oxidative metabolism of drugs used in anesthesia and known metabolic polymorphisms, a readily available phenotyping test is needed. Our study is the first to compare oxidative phenotyping tests in a systematic manner. The DMP phenotyping test clearly discriminates between EMs and PMs and Fig. 1 demonstrates that both phenotyping tests separate the sample population in the same way (i.e., results of the mixture analysis are significant for mixture of two bivariate normal distributions). In addition, the within phenotype correlation between DMP and DBQ is significant. Therefore, we may use the preferable DMP test to establish DBQ oxidative phenotypes as part of a study of the effect of this genetic polymorphism on alfentanil clearance.

References.
1. Eichelbaum M. Clin Pharmacokinet 7:1, 1982.
2. Schmid B, et al. Clin Pharmacol Ther 38:618, 1985.
3. Gibbons RD, et al. Biol Psych 19:935, 1984.
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