

Influence of genetic variation on PON1 activity and susceptibility to organophosphate toxicity

Jintana S (1), Sming K (1), Krongtong Y (2), Thanyachai S (1). *1.Department of Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand;*
2.Department of Pharmacology, Faculty of Science, Mahidol University, Bangkok, Thailand

Objective: The hydrolysis of toxic oxon metabolites of organophosphates (OPs) by paraoxonase (PON1) is one of the important factors determining their toxicity to human. Thus, this study was to determine genetic variation of PON1, PON1 activity and effect on cholinesterase activity.

Methods: Cholinesterase and PON1 activities were measured once for the control group (n=30) and twice for exposed (n=90) groups, over high and low exposure period. Three polymorphisms of PON1 (T-108C, Q192R and L55M) were identified, by PCR-RFLP method, only in the exposed group. **Results:** The results demonstrated that AChE activity in both high (20.73 U/gHb) and low exposure periods (29.8 U/gHb) of the exposed group were significant different from control group (38.98 U/gHb, $p < 0.01$). For BuChE activity, the exposed group also showed the statistically lower level in both periods (high exposure period; 3.73 U/mL and low exposure period; 4.91 U/mL) than those in the control group (5.96 U/mL). The PON1 genotype and allele frequencies of PON1 were similar to those found in the Asian population and did not deviate from Hardy-Weinberg equilibrium expectation. The PON1 Q192R was in linkage disequilibrium with the PON1 L55M and T-108C. PON1 activities toward three substrates (paraoxon, phenylacetate and diazoxon) were partly determined by genetic variation, as seen in each genotype and haplotype individual. There was a significant relationship between observed high paraoxonase activity haplotype (211) with high BuChE activity. **Conclusion:** A functional defect of PON1 or reduction in PON1 level is expected to affect cholinesterase particularly susceptible to anti-cholinesterase exposure. Individuals with low PON1 activity in that genotype are more susceptible to OP toxicity than those with high activity PON1.