Arq Neuropsiquiatr 2011;69(2-A):151-152

Pharmacogenetics

Reality or fiction? Or are we there yet?

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The paper by Twardowschy et al.[1] is certainly opportune since phenytoin is considered extremely effective as a drug treatment for focal seizures and focal epilepsy syndromes[2] and it is still one of the most used antiepileptic drugs worldwide, including in the USA[3]. Experts in the field of epilepsy have a tendency to reduce the use of phenytoin mainly due to its adverse effects and because it is a potent inducer of the hepatic microsomal system which may lead to serious potential drug interactions.

The word pharmacogenetics was first introduced in the late 1950s[4] and today is used to indicate the existence of DNA sequence variations that may impact the way the body responds to drugs. Overall these DNA variations can occur in genes coding for [i] drug transporters, [ii] enzymes involved in drug metabolism or [iii] in proteins related to drug targets[5]. Over the past decade there has been a greater understanding on how changes in DNA sequence may lead to changes in protein function. This was achieved mainly by the advances in our understanding of the human genome, starting with the completion of the Human Genome Project[6] and the subsequent studies[7]. However, it remains a major challenge to effectively apply this knowledge into the daily clinical practice. Recently, regulatory agencies approved the clinical use of some pharmacogenetic tests[8]; however, the promise of 'personalized medicine' is still a futuristic vision and for the most skeptical an unattainable reality[9]. In the specific case of antiepileptic drugs a serious allergic cutaneous reactions caused by CBZ therapy was found to be significantly more common in patients with a particular human leukocyte antigen (HLA) allele: HLA-B* 1502. This allele occurs almost exclusively in patients with Asian ancestry. A recent FDA alert recommends that patients withancestry of an at-risk population be screened for the HLA-B* 1502 allele prior to starting CBZ and that positive patients not be exposed to it[10]. Controversy aside, the fact of the matter is that experience has taught us that one should never underestimate the complexity of human biology, and this is certainly true for the genetic influences on proteins regulating pharmacokinetic and pharmacodynamic processes which are far from being fully understood. Until then we will have an incomplete view, and therefore subject to error. At this point a more broadly application of pharmacogenetics to clinical practice is still a promise; however, the field offers already opportunity for a very interesting area of scientific investigation as well illustrated by the paper by Twardowschy et al.[1].

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FARMACOGENÉTICA: REALIDADE OU FICÇÃO? JÁ CHEGAMOS LÁ?

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