"Microsomal activity variations, from one anatomic compartment to another, within the same subject"

A perspective

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Introduction

Every human subject displays genetic discrepancy when it comes to hepatic microsomes and LADME (liberation, absorption, distribution, metabolism and excretion) of medicines.

In terms of microsomal cyp450 activity the majority of drugs are known to interact well with the cyp3a4 liver enzymes during first pass metabolism which is not an universal rule, but very frequent across patients worldwide, similarly to what happens with protein binding in the systemic circulation.

Recent studies

Among those drugs that are filtered during first pass metabolism there exists genetic variability for which an individual's organism favours one microsomal compartment over another, this seemed to at least be the "case" or better yet, our knowledge, more than 20 to 50 years ago.

Naturally drug metabolism classification is based upon cyp450 prevalent substrate affinity for the drug in question. An example is the predominant metabolism demonstrated by alcohol on the cyp2c9 and cyp2c19 microsomes or again the one of anti-dyslipidemic drug atorvastatin which is metabolised at cyp3a4 level.

In reference to that, it has been recently discovered that this microsomal preference, or variation, has an impact on whether the drug will display side effects.

Discussion

Previously, it was thought that being either a fast or slow metaboliser, taking interacting medications, possessing diverse multi-drug resistant (MDR) genes, or simply lacking microsomal cyp 'subtypes' anatomically, genetically and pathologically, were reasons why a ligand would be toxic.

Nevertheless, drugs that ligate with a CYP substrate also can have an impact on other cyp compartments, as well as on different organs.

It is my opinion that most drugs that go through first pass metabolism interact with all CYP microsomes and not just selectively or singularly on some or a few of them. This has lately been proven in the case of tamoxifen which was initially thought being metabolised by just one or two (cyp3a4 and cyp2c9) cytochromes. In fact it turned out the anti-tumoral agent is metabolised by multiple, cyp2d6, cyp3a5, and so on [1]; in particular, when tamoxifen is bound to one of its substrates, cyp2d6, preferentially, it leads to toxicity across the population where the aforesaid metabolic variance is present. The binding affinity between

one P450 enzyme family over the other is what determines metabolic activity rather than an exclusive single interaction with one family subtype, thus absence of activity on others. As an example, mutations or lesions at the level of P450 2D6 do cause binding susceptibility towards 2C9 and 3A4 which are structurally similar as opposed to 2D6, however, that should not entirely preclude the binding to both 2D6 and 2C9/3A4 within the same individual.

Conclusion

It is unquestionable that in the absence of either system of microsomes, the one that the patient expresses genetically is favoured, nonetheless, the physiological and non-mutational (non-pathological) co-presence of all CYPs should not be automatically excluded in healthy patients. Metabolism can also be affected by the anatomical location of the cytochrome with respect to the organ's position, shape and size, which differs from person to person; by the number of microsomes, and above all, the drug liberation and absorption phases which also influence the metabolic pathway and can vary between individuals. Therefore these scenarios should be considered when evaluating the likely metabolism of a novel compound, and especially the fact that in a healthy patient any drug which goes through first-pass metabolism will bind all its microsomes, even if not all drug-CYPenzyme interactions have been identified at the time of the clinical trial study.

References

1. APA Cronin-Fenton, D. P., Damkier, P., & Lash, T. L. (2014). Metabolism and transport of tamoxifen in relation to its effectiveness: new perspectives on an ongoing controversy. *Future oncology* (London, England), 10(1), 107–122. <https://doi.org/10.2217/fon.13.168>