Role of Transporters in Toxicity

ASCPT Webinar Presented by the ASCPT Journal Family & Membrane Transporter (MT) Community

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Moderator: Jason Sprowl, PhD

Presentation Questions:

1.) Are there older age-related changes in transporter function?
   a. Studies have suggested the ontogeny of transporters is most pronounced at a younger age. For example, causal links on the ontogeny of mRNA and protein expression of selected transporters, such as hepatic transporters OCT1, OATP1B3, P-gp were previously reported.

2.) Is transporter-mediated toxicity a concern for non-small molecule compounds? If so, what are major mechanisms for which modality?
   a. Only recently has this been considered for protein-based drugs. Some examples included ASG-5ME, which is a SLC44A4 targeting ADC (used in Phase I for prostate cancer in 2019), but high toxicity was noted, likely due to expression in other tissues. Additionally, SLC46A3 is a lysosomal transporter that mediates efficacy of ADCs with DM1. It’s currently unknown whether it relates to toxicity. Common molecules often used with ADCs (DM1, DM4 and MMAF) have poor membrane permeability potential and various toxicities, so it is expected that transporters play a role in disposition within sensitive tissues.

3.) Could you speak a bit more on neonate/infant transporter activity in regard to production of breastmilk and transmission?
   a. ABCG2 is also expressed in mammary gland - in this orientation though, it places substrates into the milk. This is considered a double edge sword for the offspring (ABCG 2 protects offspring in placenta but delivers chemicals to offspring via milk). Of course, there are other PK differences (i.e., lipid content) etc. that will influence overall chemical disposition between the two tissues.

4.) Could you comment on the change in plasma level of bile acid may not be necessarily a true reflection of liver toxicity as the bile acids could have been blocked at uptake levels too.
   a. Great comments. Inhibition of NTCP can also increase the plasma BA level, and it does not cause DILI (in contrast, it is a protective mechanism). In vitro transporter interactions need to be characterized before pinpointing the mechanisms of BSEP/MDR3.