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Pharmacokinetic and Pharmacodynamic considerations for drugs binding to alpha-1-acid glycoprotein

Sherri A Smith
Relay Therapeutics, USA

According to the free drug hypothesis only the unbound drug is available to act at physiological sites of action. Albumin, the most abundant plasma protein (~50 mg/mL), and alpha-1-acid glycoprotein (AAG, ~1 mg/mL) are both involved with drug binding and distribution. While albumin levels are similar across species, marked species, age, and disease state differences in AAG expression, homology and drug binding affinity have been reported. Drug binding to plasma proteins can help aid and improve the translation of pharmacokinetic/pharmacodynamic (PK/PD), safety margin predictions, and relationships from preclinical species to human as well as adults to neonates (Smith and Waters, 2019). The impact of AAG binding on PK has been reported for multiple drug/candidate molecules including pinometostat (Smith et al., 2016), vismodegib (Gianetti et al., 2011), imatinib (Widmer et al., 2006), and UCN-01(Fuse et al., 1998). Obtaining accurate fraction unbound (fu) values, especially for highly bound drugs, is critical to PK and safety predictions (Di et al., 2017). The role of plasticizers used in blood collection bags has recently been reported to contribute to inaccurate overestimation of fu for drugs that preferentially bind to AAG (Butler et al., 2015, Ingram et al., 2019). Experimental considerations as well as recommendations for understanding the potential impact of AAG on PK through drug discovery and early development will be reviewed.

Recent Publications:

1. Smith S and Waters N (2019) Pharmacokinetic and pharmacodynamic considerations for drugs binding to alpha-1-acid glycoprotein. Pharm Res 36(2):30, doi.org/10.1007/s11095-018-2551-x.
2. Smith S, Gagnon S, Waters N. (2016) Mechanistic investigations into the species differences in pinometostat clearance: impact of binding to alpha-1-acid glycoprotein and permeability-limited hepatic uptake. Xenobiotica, 47(3)185-93, doi: 10.3109/00498254.2016.1173265.
3. Gianetti A, Wong H, Dijkgraaf G, Dueber E, Ortwine D, Bravo B et al. (2011) Identification, characterization, and implications of species-dependent plasma protein binding of the oral hedgehog pathway inhibitor vismodegib (GDC-0449). J Med Chem, 54(8):2592-601, doi: 10.1021/jm1008924.
4. Widmer N, Descosterd L, Csajka C, Leyvraz S, Duchosal M, Rosselet A, et al. (2006) Population pharmacokinetics of imatinib and the role of alpha-acid glycoprotein. Br J Clin Pharmacol, 62(1):97-112, doi: 10.1111/j.1365-2125.2006.02719.x.
5. Fuse F, Tanni H, Kurata N, Kobayashi H, Shimada Y, Tamura T, et al. (1998) Unpredicted clinical pharmacology of UCN-01 caused by specific binding to human alpha 1-acid glycoprotein. Cancer Res, 58(15):3248-53.
6. Di L, Breen C, Chambers R, Eckley S, Frick R, Ghosh A. et al. (2017) Industry perspective on contemporary protein-binding methodologies: considerations for regulatory drug-drug interaction and related guidelines on highly bound drugs. J Pharm Sci, 106(12):3442-52, doi: 10.1016/j.xphs.2017.09.005.
7. Butler P, Frost K, Barnes K, Smith S, Rioux N, Waters N (2015) Impact of blood collection method on human plasma protein binding for compounds binding preferentially to α-1-acid glycoprotein. Drug Metab Rev, doi: 10.1080/03602532.2016.1191843.
8. Ingram N, Dishinger C, Wood J, Hutzler JM, Smith S, Huskin N (2019) Effect of the Plasticizer DEHP in Blood Collection Bags on Human Plasma Fraction Unbound Determination for Alpha-1-Acid Glycoprotein (AAG) Binding Drugs. AAPS J 16;21(1):5, doi: 10.1208/s12248-018-0276-8.

Biography

Sherri Smith is experienced in drug metabolism and Pharmacokinetics (DMPK) of small molecules from discovery through clinical development in the pharmaceutical industry. Recent publication efforts have focused on explaining discrepancies in plasma protein binding values due to interference of plasticizers commonly used in blood collection bags, to highlight species, ontogeny, and disease state differences in expression of α-1-acid glycoprotein (AAG) and to provide examples where human PK of drugs have been impacted by preferential binding to AAG. The overall aim is to bring attention to the relevance of accurate measurement of fraction unbound for the prediction human PK and pharmacodynamics.

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