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Advances on Clinical Pharmacokinetics towards Drug Selection in Pregnant Women

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DESCRIPTION

Over the last decade, analytical technology and methodologies for Drug Metabolism and Pharmacokinetics (DMPK) research in the pharmaceutical industry and academic research organisations have progressed fast. On the one hand, small molecule drug candidates require an earlier and better knowledge of their Absorption, Distribution, Metabolism, and Excretion (ADME) in humans, as well as their interactions with metabolising enzymes, transporters, and therapeutic targets such as receptors and DNA. On the other hand, various novel drug modalities and delivery systems have been brought into the drug pipeline, including peptide and protein therapies, Antibody-Drug Conjugates (ADC), and nano drug delivery systems. Their bioanalysis and ADME examination *in vitro* and *in vivo* provide significant obstacles, necessitating the employment of analytical methods and methodologies that may differ significantly from those often utilised in DMPK investigations of small compounds. This special issue of the Journal of Pharmaceutical Analysis focuses on recently developed analytical technologies and methods for improving the efficiency and quality of ADME studies in support of traditional drug discovery programmes or for investigating the metabolism and disposition of new drug modalities and delivery systems. Cancer and pregnancy co-occurring is an uncommon clinical scenario (1/1000 pregnancies), with breast cancer being the most common solid tumour in pregnant individuals. Recent clinical data suggest that systemic treatment in breast cancer patients during the second and third trimesters of pregnancy should be as close to that used in non-pregnant patients as possible (level of evidence 2b), with the exception of trastuzumab, which has renal toxicity for the foetus due to significant trans placental transfer.

Although clinical evidence suggests that anthracyclines and taxanes are well tolerated throughout the second and third trimesters of pregnancy, the known physiological differences in drug pharmacokinetics during pregnancy pose major considerations about the appropriate medication dose in pregnant patients. Indeed, the favourable toxicity profile of these medicines throughout the late trimesters of pregnancy raises the possibility that pregnant patients may acquire suboptimal plasma concentrations compared to non-pregnant patients, resulting in lower anti-tumor efficacy. In the beginning, most anti-cancer drugs are administered based on Body Surface Area (BSA), resulting in

Significant inter-patient variability even outside of pregnancy. Too far, no data are available to support the use of different dosage strategies in the context of pregnancy, and dosing based on BSA, using the actual patient's weight, remains the norm. Target-Area Under the Curve (AUC)-based carboplatin dose, on the other hand, is not indicated in pregnant patients (in platinum-sensitive illnesses such as triple-negative breast cancer, lung cancer, and gynecological malignancies). Second, during the late trimesters of pregnancy, the activity of key enzymes involved in the metabolism of taxanes and anthracyclines (such as cytochrome p450 isoform CYP3A4) increases, potentially leading in lower drug exposure. Whereas anthracycline exposure does not appear to be significantly altered by pregnancy, taxanes exposure was dramatically reduced in pregnant patients. These findings are corroborated in part by recent studies on doxorubicin pharmacokinetics in pregnant individuals, which show that pregnancy has no negative impact on doxorubicin AUC over 48 hours. As a result, current anthracycline dosage strategies should generally be maintained, but physicians should be mindful of the possibility of suboptimal exposure while using taxanes.

Third, while maternal medication exposure is a problem in terms of treatment efficacy, anti-cancer agent Tran's placental transfer is crucial for foetal safety. Data on Trans placental transfer rates show similar and comforting results for doxorubicin, epirubicin, and taxanes, although with significant inter-patient variability, notably with docetaxel. As a result, in terms of foetal safety, paclitaxel should probably be favored to docetaxel in the setting of pregnancy. More research on placental transporters and their impact on drug disposition is being conducted, which will most likely aid in the administration of taxanes to pregnant patients. To now, it is unclear if increasing the dose of paclitaxel would result in I enhanced anti-tumor activity and (ii) different foetal toxicity. As a result, further clinic-pharmacological research is required before we change our approach about chemotherapy dose during pregnancy. Although taxanes appear to be safe in the second and third trimesters of pregnancy, anthracycline-based chemotherapy should be used as the first line of treatment in breast cancer patients until concerns about paclitaxel exposure and effectiveness in pregnant patients are addressed.