REMEDIAL OF NON-SPECIFIC REACTIVITY INDICATORS IN MINI-PIGS WITH EXPERIMENTAL OBSTRUCTIVE JAUNDICE

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Introduction: The minipig, a porcine model, has garnered increasing interest in pharmaceutical research and development as a non-rodent in vivo model for toxicological evaluation (Bode et al. Citation2010; Ganderup et al. Citation2012), formulation advancement (Henze et al. Citation2019), and pharmacokinetic (PK) modelling that aids in predicting human PK (Yoshimatsu et al. Citation2016; Ding et al. Citation2021). This is partly attributable to the parallels in biochemistry, physiology, and anatomy between them and humans (Achour et al. Citation2011; Swindle et al. Citation2012). Moreover, their comparatively diminutive size, ease of accessibility, and manageable nature provide them a compelling option to canines and non-human primates (NHP), especially when evaluated in the context of the 3Rs and social limitations (Forster et al. Citation2010; Singh et al. Citation2016). Additionally, multiple facets of drug disposition have been examined both in vitro and in vivo across different pig breeds, notably the Göttingen minipig, demonstrating their applicability for clinical translation (Dalgaard Citation2015; Lignet et al. Citation2016; Wilkinson et al. Citation2017; Poulin et al. Citation2019). Human pharmacokinetic prediction is a crucial late-stage research endeavour due to its influence on dosage estimations, exposure characteristics, and therapeutic index, and is extensively used to evaluate the technical quality of innovative drug candidates (McGinnity et al. Citation2007). When validated across many pre-clinical pharmacokinetic species, physiologically based pharmacokinetic (PBPK) models, in conjunction with in vitro to in vivo extrapolation (IVIVE), may provide dependable

predictions of human small molecule pharmacokinetics (Jones et al. Citation2006; Jones et al. Citation2011). The accuracy and robustness of future forecasts rely on the prudent extrapolation of human in vitro data and corresponding animal data (Jones et al. Citation2015; Miller et al. Citation2019). Hepatic metabolic clearance (CLhep,met) is a crucial metric affecting the bioavailability and systemic half-life of oral medications. As a result, drug discovery programs focus on developing drug candidates with low projected hepatic clearance (CLhep,met), leading to significant efforts in producing quantitative clearance (CL) predictions using different in vitro-in vivo extrapolation (IVIVE) approaches. Several of these utilise empirical scaling factors to address the systematic underestimation of clearance (CL) frequently observed from scaled in vitro intrinsic clearance (CLint) data. It is well established that demonstrating acceptable in vitro-in vivo extrapolation (IVIVE) of clearance (CL) for candidate drugs in animal pharmacokinetic (PK) models enhances prediction accuracy and diminishes uncertainty in human CL predictions when employing the same scaling methodology on human in vitro data (Jones et al. Citation2006; Sohlenius-Sternbeck et al. Citation2012). Typically, rats, dogs, and, when warranted, non-human primates (NHP) are utilised for this purpose; however, minipigs present a compelling non-rodent alternative due to the aforementioned reasons and the reported metabolic similarities between minipigs and humans concerning various cytochrome P450 (CYP450) and non-CYP450 enzymes, including CYP2C, CYP3A, N-acetyl transferases (NAT), and aldehyde oxidase (AO) (Thorn et al. Citation2011; Dalgaard Citation2015; Wilkinson et al. Citation2017). Thus far, few studies have examined the intravenous pharmacokinetics of small molecule medicines in minipigs, and even fewer have investigated the predictability of clearance in this species based on in vitro data (Lignet et al. Citation2016; Yoshimatsu et al. Citation2016; Ding et al. Citation2021). This study seeks to enhance the systemic pharmacokinetics characterised in female Göttingen minipigs (Siefert et al. Citation1999; Suenderhauf et al. Citation2014; Lignet et al. Citation2016; Patel et al. Citation2017; Ding et al. Citation2021) by utilising a

comprehensive reference set that encompasses both central nervous system (CNS) and non-CNS acting drugs, featuring a wide array of physicochemical properties and addressing numerous critical human drug-metabolizing enzymes. To the author's knowledge, this is the first comparison of several IVIVE techniques for predicting CL in Göttingen minipigs using a substantial dataset. A reference set is provided to enable other researchers to determine their own 'regression offset' for the practical and transparent adjustment of CLhep,met predictions in minipigs, similar to previous work conducted with rats and humans (Sohlenius-Sternbeck et al. Citation2010, Citation2012). This should enable the implementation of a standardised in vitro scaling method across pre-clinical animals and humans, while also addressing the systematic under-prediction often seen in in vitro data.

Background: Hepatocellular insufficiency in obstructive jaundice significantly worsens the prognosis and increases the risk of adverse outcomes. Since the severity of hepatic dysfunction correlates with the degree of immunological impairment, optimizing post-operative immunocorrection remains a critical issue.

Aim: To investigate the state of non-specific reactivity following biliary decompression in an experimental model of obstructive jaundice in mini-pigs and to evaluate the effect of an immunomodulatory drug during the post-decompression period.

Materials and Methods: TThe investigation was performed at the RyazSMU WetLab from November 2022 to February 2024, including 25 laboratory mini-pigs. The animals were randomly assigned to two groups: a Control Group (n=12) and a Comparison Group (n=13), both of which received the immunocorrective agent Aminodihydrophthalazindione sodium. The research included three phases: Phase I: Induction of experimental obstructive jaundice by laparoscopic occlusion of the common bile duct. Stage II: Ligature removal on day 7; the post-decompression healing period extended for 7 days. Phase III: Euthanasia. Blood samples were obtained at each stage for clinical, biochemical, and immunological examination, in conjunction with excisional liver biopsies.

Results of the research: Four conventional criteria were evaluated to characterise liver morphology: septal sclerosis, lymphocyte infiltration, bile duct proliferation, and hepatic lobule integrity. The Control Group exhibited progressive morphological deterioration from the onset of decompression to the concluding phase. A distinct association was seen between fibrosis and the development of false lobules, pronounced sclerosis of the portal tracts, and significant bile duct proliferation. Biliary cirrhosis was identified in 10 of the 12 control animals. Conversely, the Comparison Group (administered Aminodihydrophthalazindione sodium) had a more advantageous morpho-functional condition, with early-stage biliary cirrhosis detected in just 5 out of 13 animals. Moreover, the Comparison Group demonstrated markedly expedited normalisation of laboratory values. **Conclusions**: Morphological alterations in the liver, occurring within one week following bile duct closure, are strongly associated with variations in non-specific reactivity markers. The use of Aminodihydrophthalazindione sodium in the comprehensive treatment during the post-decompression phase expedites the normalisation of these parameters and enhances hepatic recovery.

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