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Strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products

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Traditionally, first in human clinical trials were mostly associated with a single ascending dose (SAD) design, which were subsequently followed by a multiple ascending dose (MAD) CT. Since then, integration of the non-clinical data available before FIH administration and the pharmacokinetic (PK), pharmacodynamic (PD) and human safety data emerging during a trial has evolved. Consequently, the increasing practice is to perform FIH trials and early phase CTs with integrated protocols that combine a number of different study parts, e.g. SAD, MAD, food effects, etc. The non-clinical testing and experimental approaches for FIH/early CTs are used to identify factors influencing the risks associated with an IMP. Special attention should be given to the estimation of the initial dose to be used in humans and to the subsequent dose escalations to a predefined maximum dose. In defining an appropriate development program for a new medicinal product, information on safety needs to be integrated from many sources and reviewed in an iterative process. This workshop is intended to discuss the transition from non-clinical to early clinical development by outlining factors influencing risk and how these should be mitigated in protocol design.

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Drug-induced hyperammonemia: Are there specific therapies?

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Objective: The objective of this study was to give an overview about drugs capable to induce hyperammonemia (HA), to discuss their pathophysiology and to provide treatment options for HA.

Methods: Literature review on PubMed and common textbooks.

Results: Valproate (VPA) frequently induces HA, even if not overdosed. VPA and its metabolites inhibit enzymes of mitochondrial ß-oxidation, which may cause depletion of carnitine and lower acetyl-CoA, essential for the synthesis of N-acetylglutamate (NAG). The latter is an allosteric co-factor of carbamoyl-phosphate-I-synthase, ultimately impairing detoxification of ammonia. Topiramate, Carbamazepine, Barbiturates, Salicylates may each contribute to HA, whereby underlying pathomechanisms are largely speculative or unknown. Finally, acetaminophen as the parent drug has been demonstrated to induce decreased activity of both, carbamoyl-phosphate-synthase-I and glutamine synthase. This was accompanied by HA indicating that CPS-I and/or glutamine synthase were inhibited *in vivo* to an extent sufficient to compromise ammonia clearance. Chemotherapeutics (CTX) frequently induce HA either by reduction in the expression of glutamine synthase, carbamoyl-phosphate synthase, and ornithine-transcarbamylase. CTX also may lead to functional arginine deficiency secondary to increased catabolism.

Treatment Options: Immediate withdrawl of the offending drug suspicious for HA should be followed. Oral rifaximine can reduce bacterial ammonia synthesis in the gut, lactulose enema can entrap ammonia and hemodialysis may serve as a rescue therapy. Sodium-benzoate or phenylbutyrate can reduce ammonia synthesis and eliminate glycine and glutamine. Adequate amounts of dextrose (e.g. a 10% dextrose solution) and fatty acids should be provided, while protein intake should be paused. More specific treatment options include L-carnitine in deficient patients or infusion of L-arginine in patients with VPA-overdose. Administration of carglumic acid may overcome proximal inhibition of enzymes of the urea cycle.

Conclusion: Although infrequent, HA may be a severe medical condition occurring during therapeutic pharmacological treatment or drug overdose. Understanding the pathophysiology, general or more specific treatment options may become life-saving.

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