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Predictivity of toxicological findings for first-in-man safety

Typical issues encountered in preclinical studies include clinical and target organ toxicity in the toxicological species often associated with low safety ratios (SRs). SRs are derived from a comparison of systemic drug exposures in patients at therapeutic doses and animals at the no-observed-adverse-effect level (NOAEL). For New Chemical Entities (NCEs), SRs would be expected to be ≥ 20, but for some classes including CNS drugs, SRs often are <1 ("negative"). In the latter class, dose-limiting clinical intolerance in animals and healthy volunteers at doses well below those tolerated in patients is frequent. Typical features may include the lack of a histopathological correlate, reversibility upon cessation of dosing and not uncommonly, an amelioration with continued dosing. CNS toxicity generally presents as signs consistent with exaggerated pharmacology such as tremors, decreased activity/sedation, recumbency, loss of balance/ataxia, hypothermia (rats), seizures/convulsions and death. Examples include clozapine, haloperidol, risperidone, bupropion, tricyclic antidepressants, AChE inhibitors (rivastigmine) and benzodiazapines.

Examples of target organ toxicity for a variety of drugs include the liver, CNS/PNS, endocrine system, lung or retina or may feature as phospholipidosis across a number of organs. *Hepatotoxicity* can be present in one or more preclinical species and generally is predictive for humans. Characteristics may include elevated serum enzymes, increased liver weight and morphological alterations (hepatocyte hypertrophy, vacuolation, lipid deposition, degeneration or hepatobiliary changes). Hepatocyte hypertrophy often is adaptive due to stimulation of drug metabolism and non-adverse; this change could however proceed to potentially severe toxicity at higher doses or upon prolonged treatment. In contrast, idiosyncratic liver toxicity in man is not predicted from animal studies and often due to metabolic differences in (individual) humans or immunologically mediated. In general, animal species are poor predictors of adverse human immunological issues. Morphological changes of the *nervous system* are variable and can include findings such as vacuoles in the neurones, in their axons, in glial cells and/or in the myelin sheath, as neuronal pigmentation and as necrosis, reflecting neuronal damage. They may be the result of a direct neurotoxic action of a drug and/or result from vascular injury. Such alterations may or may not be reversible and/or be associated with a functional deficit. Examples from animal studies include a number of drugs e.g. interacting with the NMDA receptor, such as phencyclidine, MK-801 or memantine. Morphological findings in the CNS are non-monitorable in the clinic, unless they were reliably identifiable by a biomarker indicating a fully reversible functional stage well preceding any changes at the histopathological level. For obvious reasons, such monitoring is severely hampered by medical and technical limitations, and mostly, compounds with such findings are not developed further. *Endocrine disorders* can for instance be caused by dopamine D_2 antagonists through elevated circulating prolactin levels, possibly associated with pituitary and mammary proliferative changes or disruption of male and female reproductive function, or dopamine agonist which may reduce prolactin levels. Examples include risperidone and aripiprazole. *Retinal atrophy* particularly in the albino rat may feature as a loss of nuclei of the outer nuclear layer with thinning of the photoreceptor layer and proceed to the loss of all layers with disruption of the pigment epithelial layer. This alteration has been described for a number of drugs, e.g. pregabalin, pramipexole, aripiprazole and citalopram, none of which has been associated with retinal changes in humans, suggesting a general lack of predictability for this type of toxicological finding in albino rats. *Phospholipidosis* caused by cationic amphiphilic drugs for many different indications is characterised by excessive accumulation of polar phospholipids in cells, is lysosomal in origin and presents with a lamellar structure often in lungs but possibly also in lymphoid and other tissues (e.g. liver, kidney). Rats are usually considered more sensitive than mice, dogs or monkeys. The severity (extent of accumulation) varies between drugs. Phospholipidosis does not usually disrupt organ function; however, the accumulation in rat lungs (foamy macrophages) in chronic studies may be severe and cause early mortality. The toxicological significance is uncertain, but macrophage function tests are used to assess the immune system status. There are no validated biomarkers available for clinical use as yet. Examples include aripiprazole, amiodarone, memantine and fluoxetine.

If issues are identified during non-clinical development, the following steps are recommended:
1) Do not stop development but 2) review the finding in detail first to answer the following questions: Is it a real finding? What is its nature? Exacerbation of a spontaneous finding? Known class finding? Statistically significant? Species specific? Reversible? Monitorable in the clinic? Considered predictive or

relevant for man? 3) These results will determine an appropriate action plan which should be worked out and discussed with governmental regulators at an early stage.

In *conclusion*, preclinical issues and low SRs are not necessarily impediments to successful drug development. Many issues would be "stoppers" for NCEs with "soft" indications however not necessarily for "hard" indications. Some preclinical issues do not appear to be predictive for patients. Others are predictive but are monitorable clinically and safety can be ensured, whereas non-monitorable and severe toxicities may indeed require discontinuation of further development of the drug concerned. Clinical tolerance of CNS drugs is often greater in patients than in animals and healthy volunteers and is an important factor regarding the safety of this class. Many successfully marketed CNS drugs but also other drugs have "negative" SRs (i.e. <1) based on preclinical toxicological data.

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