Discussion Topics

Thursday September 19

Toxicokinetics and Uncertainty

Topic 1: Regional absorption mechanisms

Lead discussant: Dr. Max Costa

Hexavalent chromium is rapidly absorbed by all cells via a nonspecific anionic transport system due to structural similarity to phosphate and sulfate oxyanions (Wetterhahn and Hamilton, 1989). Conversely, trivalent chromium is taken up by cells at a much reduced rate and is thought to be mediated by passive diffusion or endocytosis (Eastmond et al., 2008; Cohen et al., 1993). Are there any aspects of the gastrointestinal tract (anatomical, physiological, or biochemical/enzymatic) that may cause higher anionic uptake or transport of either of these oxidation states in particular regions? These may include complexes that hexavalent chromium compounds may form with organic ligands or differences in the permeability of the mucosa along the alimentary canal. Regions to consider include the oral cavity/tongue, esophagus, stomach, and sections of the small intestine. Are there any known species differences in anionic GI transport to consider?

Topic 2: Reduction mechanisms

Lead discussant: Dr. Sean Hays

A number of reducing agents are present in the gastrointestinal tract lumen, including glutathione, ascorbic acid, gut bacteria, and food contents (Kirman et al., 2013). Is it possible to significantly deplete or overwhelm any of these reducing agents in small rodents by administering repeated doses of a xenobiotic that undergoes a reduction reaction? Is it possible to deplete or saturate reduction capacity in humans? Are there examples in the literature or based on your experience (aside from hexavalent chromium) where the saturation or depletion of enzymatic or other non-enzymatic molecules (not necessarily limited to reducing agents) in the gastrointestinal tract lumen occurred following ingestion of pharmaceuticals, essential elements, or toxic chemicals?

Which reducing agents in the gastrointestinal tract lumen are most at risk of being inhibited, saturated, or depleted by xenobiotics?

Topic 3: Gastrointestinal pharmacokinetics

Lead discussant: Dr. John Crison

There exist generalized commercially available pharmacokinetic models of the gastrointestinal tract for use in estimating the dissolution, transit, metabolism, and absorption of xenobiotics along different regions of the intestinal tract (Simcyp, Gastroplus, etc.). How much uncertainty is typically encountered or assumed regarding their predictions (both in terms of reliability and variability)? This can include uncertainties in extrapolating gastrointestinal models from rodents to humans.

Are there any chemicals (metals, non-metals, pharmaceuticals) that have pharmacokinetic properties similar to hexavalent chromium in the gastrointestinal tract (i.e., rapid oxidation/reduction reactions in the lumen)?

Topic 4: Gastrointestinal toxicity markers

General discussion (time permitting)

A variety of mechanisms are possible for therapeutic or toxic agents to induce effects on the epithelium of the gastrointestinal tract. Effects may be induced by direct contact with, and uptake to, the intestinal wall. Effects may also be induced systemically, either by delivery of chemical to the intestine via blood perfusion, or by acting on other systems affecting the intestine. Are there any well-established biomarkers for gastrointestinal tract toxicity or damage that could indicate systemic versus point-of-contact toxicity?

Wednesday September 25

Susceptibility

[Extra time will be available on Day 2 if topics from Day 1 were not covered.]

Topic 5: Disease states and medical factors

Lead discussant: Dr. Kim Barrett

Several conditions and medical treatments are known to impact the human digestive system. These may include infection, chronic disease, genetic polymorphisms, medications, surgical procedures, dietary factors, gut microbiota, fed status, or circadian rhythms. Some of these could potentially impact susceptibility to Cr(VI)-induced toxicity (e.g., a drug that raises gastric pH would slow the reduction of Cr(VI)). Please discuss these conditions, their postulated mechanisms, and their relative incidences and potential contributions to susceptibility in the general population.

Topic 6: Dietary and nutritional factors

General discussion

Essential element status has been known to impact the absorption, distribution, and toxicity of metals such as lead and cadmium. For example, low iron status may cause increased gastrointestinal absorption of lead. Are any essential element deficiencies likely to impact hexavalent chromium absorption?

Topic 7: Lifestages

General discussion

What differences exist among human lifestages, including infants and the elderly, in the GI tract that could impact anionic GI uptake or transport?

References

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