Toxicology assignment problem 16

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April 24, 2018

Answer a)

Aristolochic acid (AA) is a medium sized molecule with a molecular weight of approximately 990 g/mol. It has an aromatic backbone consisting of three benzene rings which are highly lipophilic. Attached to this backbone we find a carboxyl group, a nitro group and a methoxy group and a five-membered ring with two oxygens. These features add to the hydrophobic nature of the molecule, especially the carboxyl and nitro groups. In total the molecule should be considered weakly hydrophobic. The 7 oxygen atoms can be acceptor sites for hydrogen bonding but only one of them (on the carboxyl group) is bound to hydrogen, meaning that only this one can initiate hydrogen bonds. The relatively large size combined with the possibility of forming hydrogen bonds likely results in a relatively high boiling point/low volatility.

The carboxyl group bears some extra attention. Depending on the surrounding pH this group will either be protonated or de-protonated, resulting in the being more hydrophilic at higher pH's.

Uptake, transport and excretion

Exposure is assumed to be oral, given the history of the compound as a component in herbal medicine. The weakly hydrophobic quality of the molecule means that it will likely mix well with the intestinal content while it's quite lipophilic nature will allow it to migrate easily though the cell wall of the gut and into the blood. It is likely hydrophobic enough to be blood-soluable and is transported via the blood to the liver and then the kidneys. AA itself is likely not directly toxic based on it's structure, however, as will be seen in answer to question b), some of it's metabolites are highly toxic.

Answer b)

The metabolic transformations of Aristolochic acid (AA) of significant concern are Phase 1 transformations in the mitochondria by Cytochrome P450. As stated above, AA can be distributed through cell membranes, this is due to it's AA formal charge of zero and it's non-polarity. Through the Phase 1 transformations it's structure changes in ways that make hydrogen-bonds possible and thus water-soluble.

In it's original form, AA can be metabolised in two ways. First, the metoxi group can be oxidised by P450, putting in it's stead a hydroxyl group, increasing the molecule water-solubility and thus non-toxic as it can be excreted by the urine. Second, the nitro group can be reduced by P450 creating an equilibrium between the nitro, nitroso, hydroxyl amine and amin forms. In the case of AA the form that is of concern is the hydroxyl amine whereafter the de-protonated carboxylic carbon does a nucleophilic attack on the hydroxyl amine, creating N-hydroxyaristolactam. From this point, the molecule can again either be toxically activated or detoxified. The toxic activation occurs when the hydroxyl amine gets protonated, causing water to act

as a leaving group. This leaves a positively charged molecule called Aristolactam nitrenium ion, which is electrophilic and can form DNA-adducts with Adenine and Guanine, making it carcinogenic. The main species of toxicological interest in the bioactivation of AA can be seen in Fig. 1.

Aristolactam nitrenium ion is transported with the blood to the liver for excretion. The concentration of this carcionogenic compound in the kidneys and urine bladder leads to them being the main target organs for the toxic (carciongenic) effects of AA.

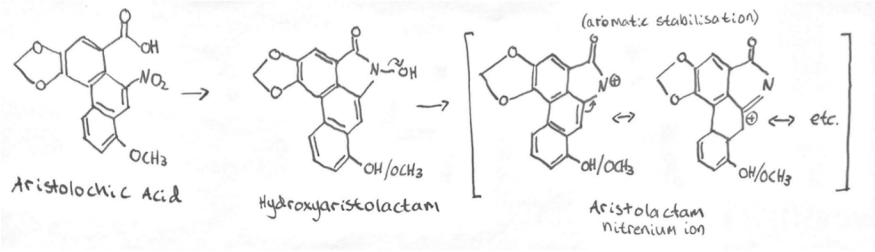

Figure 1: Figure showing the main metabolates of AA of concern from a toxicological perspective.to