Session 1: Drug Disposition

Prediction of Drug Absorption and Disposition Based on the BCS

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The Biopharmaceutics Classification System (BCS) was developed to allow prediction of *in vivo* pharmacokinetic performance of drug products from measurements of permeability and solubility Although the BCS is useful for characterizing drugs in Class 1 (high permeability; high solubility) for which drug dosage form dissolution alone may be amenable for waiver of *in vivo* bioequivalence studies, there is little predictability concerning drugs in Classes 2 (high permeability; low solubility), 3 (low permeability; high solubility) and 4 (low permeability; low solubility). Last year (Pharm Res 22:13-22, 2005), we suggested that a modification of such a classification system, designated the Biopharmaceutics Drug Disposition Classification System (BDDCS), may be useful in predicting overall drug disposition including: routes of drug elimination; the effects of efflux and absorptive transporters on oral drug absorption; when transporter-enzyme interplay will yield clinically significant effects (e.g., low bioavailability and drug-drug interactions); the direction, mechanism and importance of food effects; and transporter effects on post-absorptive systemic drug concentrations following oral and i.v. dosing. In BDDCS, Classes 1 and 2 drugs are predominantly eliminated by metabolism, while Classes 3 and 4 drugs are predominantly eliminated unchanged via urinary or biliary excretion. Transporter effects will be negligible for Class 1 compounds. Efflux transporter effects will predominate in predicting the oral exposure of Class 2 compounds, while absorptive transporters will have a major influence on the oral exposure of Class 3 compounds. We suggest that the BDDCS, using elimination and solubility criteria, may provide predictability of disposition profiles for all classes of drugs.

Non-P450 Drug Metabolism

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The vast array of metabolic reactions of xenobiotics can be conveniently classified as either oxidations, reductions, conjugations, or nucleophilic trapping processes. Most conjugations involve S_N2 reactions of electrophilic adenosine-containing cofactors with nucleophilic sites in xenobiotics, while formation of amino acid conjugates requires prior activation of the carboxylic acid substrate. Nucleophilic trapping processes involve reactions of water, glutathione, or other cellular nucleophiles (including protein and nucleic acid) with electrophilic xenobiotics. Categorization of each general route of drug metabolism as resulting in either increase or decrease in toxicity and pharmacological activity is problematic. For example, although glucuronidation is traditionally regarded as a route of detoxification, acyl glucuronides and narcotic analgesic ether glucuronides have been associated with toxicity and pharmacological activity, respectively. The gene families of many non-P450 enzymes are well categorized (e.g., UGTs and GSTs), and in some cases genetic variations are a potential major factor in affecting interindividual variations (FMO3, NAT2, TPMT, UGT1A1). Virtually any type of metabolic reaction may play a role in drug activation; widely quoted examples include O-acetylation of aromatic amines, glutathione S-conjugation of haloalkanes, and O-sulphation of various N-hydroxy functional groups. Although drug toxicity cannot be accurately predicted, approaches can be used in drug discovery and development to minimize potential problems. These approaches include use of structure-metabolism relationships in drug design, small molecule trapping agents, and radiolabelled substrate. Selected routes of non-P450 drug metabolism will be discussed, including involvement in contributing to interindividual variation and bioactivation.

Cellular localization and function of ABC membrane-associated drug efflux transporters in the brain

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Not available at time of publication.

Medicinal Cannabis and a New Oro-mucosal aerosol

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THC inhibits cAMP through G-protein receptor coupling. It is a partial agonist on CB_1 receptors, especially in pain pathways. THC actions include analgesia, muscle relaxant and anti-inflammatory effects. Cannabidiol (CBD) has anti-anxiety, anti-psychotic, anti-oxidant, anti-inflammatory, immunomodulatory effects, and prevents glutamate excitotoxicity.

Sativex® is a well-characterised botanical drug product derived from two clonal cannabis chemovars, one THC-predominant (Tetranabinex®) and another CBD-predominant (Nabidiolex®), yielding a botanical drug substance (BDS) of defined composition with controlled reproducibility. THC and CBD comprise some 70% (w/w) of the BDS, with minor cannabinoids (5 – 6%), terpenoids (6 – 7%, most GRAS), sterols (6%), triglycerides, alkanes, squalene, tocopherol, carotenoids and other minor components (also GRAS). Sativex is administered oromucosally with each 100 µL pump-action spray providing 2.7 mg of THC and 2.5 mg of CBD, in an ethanol: propylene glycol vehicle with 0.05% peppermint flavouring. To date, RCTs show Sativex to have statistically significant benefits in several medically intractable conditions: pain associated with peripheral neuropathy, rheumatoid arthritis, cancer pain unresponsive to opiates and neuropathic pain in multiple sclerosis (indication for the NOC/C of Sativex in Canada in 2005), as well as spasticity, and lower urinary tract symptoms associated with MS, and sleep quality in these various disorders. In all studies, Sativex has been used as add-on therapy in patients who have not responded adequately to their existing medication. These trials and their safety-extension studies (up to four years) have demonstrated no abuse or diversion of Sativex, no tolerance to symptomatic benefits, or significant withdrawal effects upon sudden discontinuation.