ADELEYE ADERONKE.T.

HUMAN BIOLOGY

17/SCI04/001

BCH 306

ASSIGNMENT

1. Effect of Food Additives and Preservatives

The effects of food additives may be immediate or may be harmful in the long run if one have constant exposure or accumulations. Immediate effects may include headaches, change in energy level, and alterations in mental concentration, behavior, or immune response. Long-term effects may increase one's risk of cancer, cardiovascular disease and other degenerative conditions. Some modern synthetic preservatives have become controversial because they have been shown to cause respiratory or other health problems. Allergic preservatives in food or medicine can cause an anaphylactic shock in susceptible individuals, a condition which is often fatal within minutes without emergency treatment.. The reaction from these additives can be very mild to life-threatening. They can be immediate or build up in the body over time.

2. CATEGORIES OF TOXICITY TESTS

(a) Acute Toxicity

Historically, acute toxicity tests were the first tests conducted. They provide data on the relative toxicity likely to arise from a single or brief exposure, or sometimes multiple doses over a brief period of time. Standardized tests are available for oral, dermal, and inhalation exposures, and many regulatory agencies still require the use of all or some of these tests.

(b) Subchronic Toxicity

Subchronic toxicity tests are employed to determine toxicity likely to arise from repeated exposures of several weeks to several months. Standardized tests are available for oral, dermal, and inhalation exposures. Detailed information is obtained during and after the study, ranging from body weight, food and water consumption measurements, effects on eyes and behavior, composition of blood, and microscopic examination of selected tissues and organs.

(c) Chronic Toxicity

Chronic toxicity tests determine toxicity from exposure for a substantial portion of a subject's life. They are similar to the subchronic tests except that they extend over a longer period of time and involve larger groups of animals.

(d) Carcinogenicity

Carcinogenicity tests are similar to chronic toxicity tests. However, they extend over a longer period of time and require larger groups of animals in order to assess the potential for cancer.

2b. Toxicity test for liver:

Obtain liver function tests (LFTs). Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) concentrations begin to rise within 24 hours after an acute ingestion and peak at about 72 hours. In severe overdose, transaminase elevation can be detected as early as 12-16 hours post-ingestion. Toxicity is defined as serum AST or ALT concentrations greater than 1000 IU/L. A rapid progression of transaminase values to 3000 IU/L or greater reflects severe hepatotoxicity. Include bilirubin and alkaline phosphatase concentrations.

A proposed strategy for predicting hepatotoxicity involves multiplying the acetaminophen concentration times the ALT concentration. Products and risk levels are as follows:

* < 1500 - Low risk

* 1500-10,000 - Low to moderate risk

* > 10,000 - High risk.

(b) toxicity test for kidney:

Routine tests monitor kidney function before and after treatment.

High levels of protein or a waste product called creatinine, indicate that the kidneys might not be working well.

Results from blood and urine tests calculate how well your kidneys are processing creatinine.

Dipstick urine tests

Urine tests can show abnormal levels of protein, blood, white blood cells, glucose and markers for diabetes.

Blood tests

Blood tests can measure protein and creatinine and are used to estimate glomerular filtration rate (eGFR).

eGFR

Estimated GFR is a common way to grade kidney function. It is measured in mL/min per 1.73 m2.

3. ROUTES OF DRUG ADMINISTRATION

A. Enteral Routes

1. Sublingual (buccal)

Certain drugs are best given beneath the tongue or retained in the cheek pouch and are absorbed from these regions into the local circulation. These vascular areas are ideal for lipid-soluble drugs that would be metabolized in the gut or liver, since the blood vessels in the mouth bypass the liver (do not undergo first pass liver metabolism), and drain directly into the systemic circulation. This route is usually reserved for nitrates and certain hormones.

2. Oral

By far the most common route. The passage of drug from the gut into the blood is influenced by biologic and physicochemical factors (discussed in detail below), and by the dosage form. For most drugs, two- to five-fold differences in the rate or extent of gastrointestinal absorption can occur, depending on the dosage form. These two characteristics, rate and completeness of absorption, comprise bioavailability. Generally, the bioavailability of oral drugs follows the order: solution > suspension > capsule > tablet > coated tablet.

3. Rectal

The administration of suppositories is usually reserved for situations in which oral administration is difficult. This route is more frequently used in small children. The rectum is devoid of villi, thus absorption is often slow.

B. Parenteral Routes

1. Intravenous injection

Used when a rapid clinical response is necessary, e.g., an acute asthmatic episode. This route allows one to achieve relatively precise drug concentrations in the plasma, since bioavailability is not a concern.

Most drugs should be injected over 1-2 minutes in order to prevent the occurrence of very high drug concentrations in the injected vein, possibly causing adverse effects. Some drugs, particularly those with narrow therapeutic indices or short half-lives, are best administered as a slow IV infusion or drip.

2. Intra-arterial injection

Used in certain special situations, notably with anticancer drugs, in an effort to deliver a high concentration of drug to a particular tissue. Typically, the injected artery leads directly to the target organ.

3. Intrathecal injection

The blood-brain barrier limits the entry of many drugs into cerebrospinal fluid. Under some circumstances, usually life-threatening, antibiotics, antifungals and anticancer drugs are given via lumbar puncture and injection into the subarachnoid space.

4. Intramuscular injection

Drugs may be injected into the arm (deltoid), thigh (vastus lateralis) or buttocks (gluteus maximus). Because of differences in vascularity, the rates of absorption differ, with arm > thigh > buttocks. Drug absorption may be slow and erratic. The volume of injection, osmolality of the solution, lipid solubility and degree of ionization influence absorption. It should not be assumed that the IM route is as reliable as the IV route.

5. Subcutaneous injection

Some drugs, notably insulin, are routinely administered SC. Drug absorption is generally slower SC than IM, due to poorer vascularity. Absorption can be facilitated by heat, massage or vasodilators. It can be slowed by coadministration of vasoconstrictors, a practice commonly used to prolong the local action of local anesthetics. As above, arm > thigh.

6. Inhalation

Volatile anesthetics, as well as many drugs which affect pulmonary function, are administered as aerosols. Other obvious examples include nicotine and tetrahydrocannabinol (THC), which are absorbed following inhalation of tobacco or marijuana smoke. The large alveolar area and blood supply lead to rapid absorption into the blood. Drugs administered via this route are not subject to first-pass liver metabolism.

7. Topical application

a. Eye

For desired local effects.

b. Intravaginal

For infections or contraceptives.

c. Intranasal

For alleviation of local symptoms.

d. Skin

Topical drug administration for skin disorders minimizes systemic exposure. However, systemic absorption does occur and varies with the area, site, drug, and state of the skin. Dimethyl sulfoxide (DMSO) enhances the percutaneous absorption of many drugs, but its use is controversial because of concerns about its toxicity.

e. Drug patches (drug enters systemic circulation by zero order kinetics – a constant amount of drug enters the circulation per unit time).

4. **Drug absorption** depends on the **lipid solubility** of the **drug**, its formulation and the route of administration. A **drug** needs to be **lipid soluble** to penetrate membranes unless there is an active transport system or it is so small that it can pass through the aqueous channels in the membrane. Because the cell membrane is lipoid, **lipid**-soluble **drugs** diffuse **most rapidly**. Small molecules **tend** to penetrate membranes **more rapidly** than larger ones. **Most drugs-are** weak organic acids or bases, existing in un-ionized and ionized forms in an aqueous environment.

5. MOLECULAR TARGET CONCEPT

The toxic action of a chemical is a consequence of the physical/chemical interaction of the active form of that chemical with a molecular target within the living organisms e.g. proteins (Arhylhydrocarbon (Ah) receptor- Dioxin), Lipids (Carbon tetrachloride), DNA(Aflatoxin)

6. TOXICOLOGICAL EFFECT OF A NAMED FOOD PRESERVATIVE (SUCRALOSE)

Sucralose: The presence of chlorine in sucralose is thought to be the most dangerous component of sucralose. Chlorine is considered a carcinogen and has been used in poisonous gas, disinfectants, pesticides, and plastics. The digestion and absorption of sucralose is not clear due to a lack of long-term studies on humans. The majority of studies were done on animals for short lengths of time. The alleged symptoms associated with sucralose are gastrointestinal problems (bloating, gas, diarrhea, nausea), skin

irritations (rash, hives, redness, itching, swelling), wheezing, cough, runny nose, chest pains, palpitations, anxiety, anger, moods swings, depression, and itchy eyes. The only way to be sure of the safety of sucralose is to have long- term studies on humans done. Splenda is a product that contains the artificial sweetener sucralose, but that is not all that it contains. Sucralose does have calories, but because it is 600 times sweeter than sugar, very small amounts are needed to achieve the desired sweetness so you most likely won't consume enough to get any calories.

7. CARCINOGENESIS:

Cancer is a disease where damaged cells do not undergo apoptosis. This means that the damaged cells will continue to grow but as mutants, very different from the original normal cell. The growth of the damaged cells will no longer be under normal control and the metabolic processes may be altered. Cancerous cells are not controlled but are free to proliferate independent of the cells around them. Cancer is a highly complex, multifactorial disease caused partly by metabolic issues or other imbalances associated with age or genetic makeup and partly by a wide variety of external factors including diet, lifestyle, ionizing radiation and xenobiotics.

8. VARIOUS EXCRETORY PATHWAY OF TOXICANTS

(a) Urinary Excretion

Elimination of substances by the kidneys into the urine is the primary route of excretion of toxicants. The primary function of the kidney is the excretion of body wastes and harmful chemicals. The functional unit of the kidney responsible for excretion is the nephron. Each kidney contains about one million nephrons. The nephron has three primary regions that function in the renal excretion process, the glomerulus, proximal tubule, and the distal tubule. These are identified in the illustrations.

Three processes are involved in urinary excretion: filtration, secretion, and reabsorption.

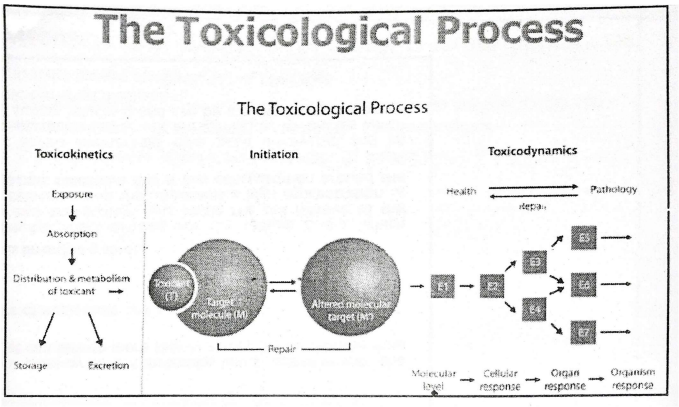
(b) Fecal Excretion

Elimination of toxicants in the feces occurs from two processes: excretion in bile, which then enters the intestine, and direct excretion into the lumen of the gastrointestinal tract. The biliary route is an important mechanism for fecal excretion of xenobiotics and is even more important for the excretion of their metabolites. This route generally involves active secretion rather than passive diffusion. Specific transport systems appear to exist for certain types of substances, e.g., organic bases, organic acids, and neutral substances. Some heavy metals are excreted in the bile, e.g., arsenic, lead, and mercury. However, the most likely substances to be excreted via the bile are comparatively large, ionized molecules, such as large molecular weight (greater than 300) conjugates.

(c) Exhaled Air

The lungs represent an important route of excretion for xenobiotics (and metabolites) that exist in a gaseous phase in the blood. Blood gases are excreted by passive diffusion from the blood into the alveolus, following a concentration gradient. This occurs when the concentration of the xenobiotic dissolved in capillary blood is greater than the concentration of the substance in the alveolar air. Gases with a low solubility in blood are more rapidly eliminated than those gases with a high solubility. Volatile liquids dissolved in the blood are also readily excreted via the expired air. The amount of a liquid excreted by the lungs is proportional to its vapor pressure. Exhalation is an exception to most other routes of excretion in that it can be a very efficient route of excretion for lipid-soluble substances. This is due to the very close proximity of capillary and alveolar membranes, which are thin and allow for the normal gaseous exchange that occurs in breathing.

9.



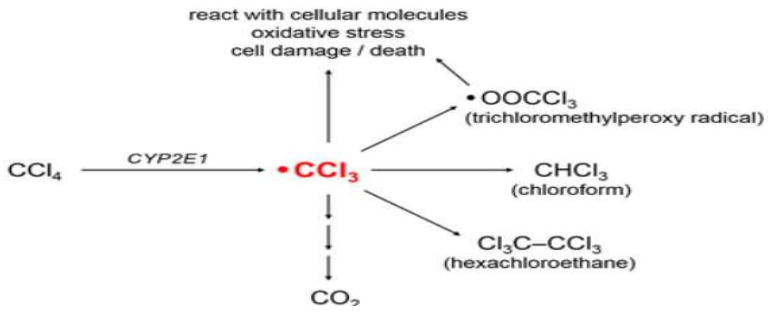
10. CARBON TETRACHLORIDE:

Carbon tetrachloride is metabolized primarily in the liver.

The first step in metabolism is a phase I dehalogenation reaction, which converts CCl_4 to the trichloromethyl radical (CCl_3). This reaction is governed primarily by the cytochrome P450 isoform CYP2E1, though additional isoforms such as CYP3A4 can also metabolize CCl_4 when it is present in high concentrations. The centrilobular localization of CYP2E1 in the liver explains the histopathological findings of CCl_4-induced liver damage.

The CCl_3 radical can have several different fates. It might

- React with intracellular molecules to cause lipid peroxidation and other forms of oxidative damage,
- Be converted to the trichloromethyl peroxy radical, OOCCl3
- Acquire a hydrogen atom to form chloroform (CHCl3),
- Combine with other CCl3 radicals to form hexachloroethane (Cl3CCCl3), or
- Be further metabolized to carbon dioxide (CO2) by successive oxidation reactions.



Common metabolic fates of CCl3.

One animal model estimates that 60% of an inhaled dose of CCl4 is metabolized, and the remaining 40% is excreted unchanged. Approximately 96% of this metabolized CCl4 generates free radicals, as described above; the remaining 4% is ultimately converted to CO2.

10(b). Ethanol Metabolism:

Ethanol is metabolized by oxidation to acetaldehyde by the enzyme ADH, by the CYP2E1-dependent MEOS, or by catalase and further to acetate by ALDH

Ethanol Metabolism via ADH

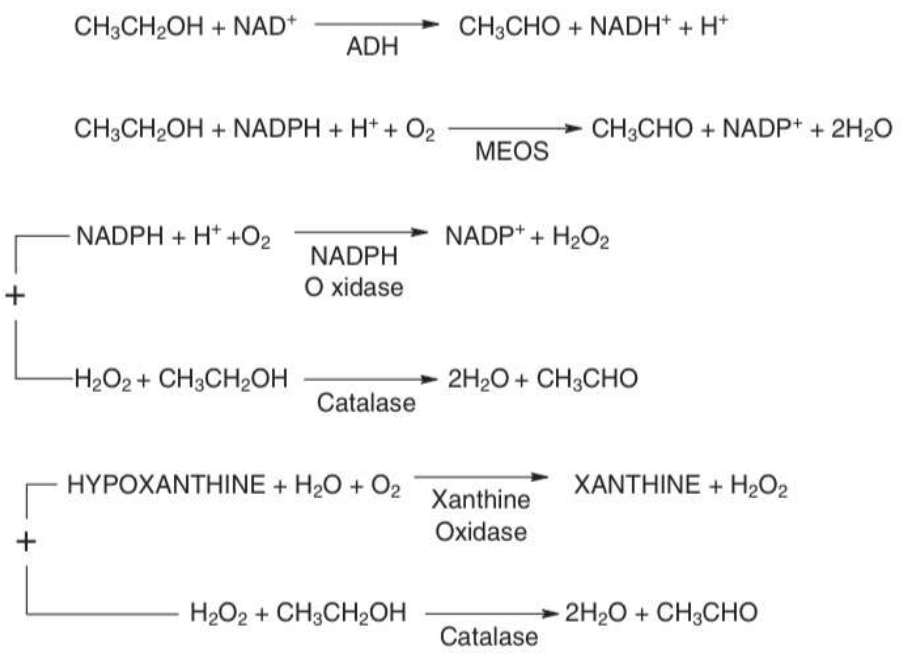
ADH is localized in the cytoplasm of all cells, but predominantly in hepatocytes.

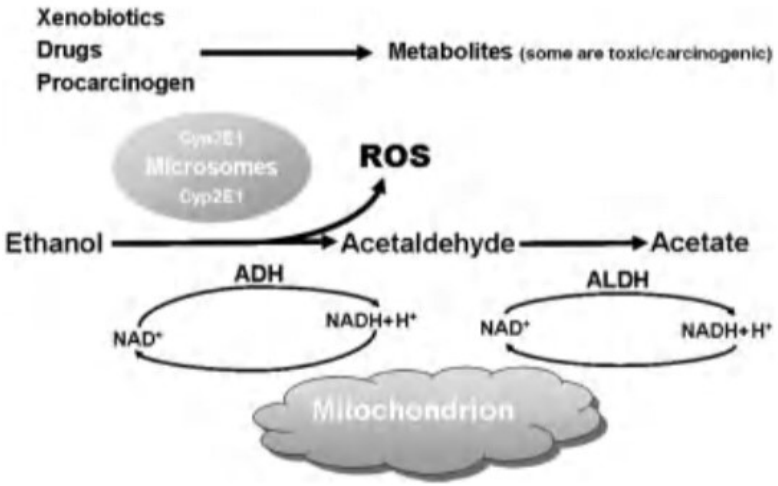
ADH requires as cofactor NAD , which is reduced to NADH + H during the

metabolism of ethanol to acetaldehyde. ADH is a zinc-containing enzyme with a molecular weight of 80 000 and a predominant location around the central vein within the hepatic lobule. It is a dimer

consisting of three polypeptide chains (α, β, and γ). ADH oxidizes ethanol first to acetaldehyde, which is then further oxidized to acetate. The reactions involve an intermediate carrier of electrons,

NAD , which is reduced to NADH. The electrons that originated in ethanol to produce NADH are ultimately transferred to oxygen via a number of other inter- mediate carriers in the mitochondrial electron transport chain and oxygen is reduced to water at the terminal enzyme (cytochrome oxidase). The final oxidation creates energy as ATP (1 g of ethanol equivalents 7.1 kcal). This intramitochondrial electron transport may generate ROS if not controlled adequately. A small portion of oxygen that is reduced in the mitochondria is released as the one-electron- reduced form–superoxide. Increased mitochondrial activity and NADH use generate more superoxide. As a protection against intramitochondrially generated ROS, the mitochondria possess manganese superoxide dismutase, which destroys superoxide.





11. Toxicokinetics is essentially the study of "how a substance gets into the body and what happens to it in the body". Four processes are involved in toxicokinetics.

(a) absorption: the transfer of a drug from its of administration to the blood stream.

(b) distribution: the process by which a drug reversibly leaves the blood stream and enters extra cellular fluid (interstitium) and the cells of the tissues.

(c) metabolism: the body changes(transforms) the substance into new chemicals (metabolites).

(d) excretion: the substance or it's metabolites leave the body.

11(b). Toxicodynamics describes the mechanism or mode of action of toxicants, how they can cause tissue damage, and under what conditions in terms of tissue concentrations and time of tissue exposure/dose do adverse effects on tissue structure and function occur.

The mechanism of action (toxicodynamics) of OPs is based on irreversible AChE inhibition at the cholinergic synapses. Under normal conditions, acetylcholine forms from acetate and coenzyme A. This reaction is catalyzed by enzyme choline acetyltransferase When a signal is transmitted, a quantum of acetylcholine stored in synaptic vesicles is released to the synaptic cleft where it binds to the acetylcholine receptor; there exist minimally muscarinic and nicotinic receptors (and their subtypes). The muscarinic receptor belongs to the metabotrophic G-protein–coupled receptors family. Five

subtypes (M1–M5) have been recognized. The nicotinic receptors are ligand-gated ion channels comprising usually five units.