SECTION I

ABSORPTION, DISTRIBUTION AND EXCRETION OF FOREIGN CHEMICALS

by
M. Jakubowski

Absorption of Foreign Chemicals

Absorption is usually defined as the passage of a given substance from its site of administration (experimental toxicology or medicine) or site of contact (industrial or environmental toxicology) into the systemic circulation. Depending on the area of toxicology, the roles of the particular routes of absorption will differ. In industry, toxic substances are absorbed mainly by inhalation or through the skin; in acute intoxications, the main route of absorption is through the alimentary tract. In environmental toxicology, foreign chemicals are absorbed mainly by inhalation or from the alimentary tract.

Regardless of the site of absorption, a toxic substance must cross one or more barriers: the surface epithelia, the capillary endothelia, the plasma membranes of the cell and the intracellular membranes. Both the surface epithelia and the capillary endothelia are ultimately derived from the plasma membrane that surrounds every individual cell. According to the simple Danielli-Davison model, the biological membrane is composed of a bimolecular lipid leaflet consisting of lipid molecules arranged with their lipophilic tails oriented towards the centre of the leaflet. Protein molecules are adsorbed as a monolayer on to the polar heads of the lipids to give stability to the structure. The membrane is not continuous but has aqueous pores which allow the passage of small hydrophobic molecules. Present in the membrane are selective carriers which have specific affinity for particular substances and cause their active transport through the membrane. Foreign chemicals may be transported through the biological membranes by passive diffusion, active transport, pinocytosis and filtration.

Passive diffusion

Passive diffusion is the most important mechanism for the transmembrane movement of foreign chemicals. According to Fich's law:

$$V = \frac{K \cdot A\ (C_1 - C_2)}{d}$$

The rate of diffusion depends on the:

- magnitude of the concentration gradient $(C_1 - C_2)$;
- area of the membrane (A);
- thickness of the membrane (d); and
- diffusion constant (K) of the substance, which depends on the molecular weight of the substance, molecular structure, lipid solubility and the degree of ionization.

In practice, the lipoid nature of the biological membranes permits only lipid-soluble, nonionized molecules to diffuse through the membranes. The relative concentrations of ionized and nonionized forms of weak acids and bases can be calculated according to the Hendeson-Hasselbach law:

$$pK_a - pH = \log \frac{M}{I} \quad \text{for acids}$$

$$pK_a - pH = \log \frac{I}{M} \quad \text{for bases}$$

where: M = nonionized form and I = ionized form.

In general, the velocity of the passive transmembrane transport increases with the increase of lipid solubility of nonionized forms of the weak acids and bases as well as compounds which do not ionize. Other mechanisms of the transmembrane transport are less important for foreign chemicals.

Absorption from gastrointestinal tract

The gastrointestinal tract (buccal cavity, stomach, intestines and rectum) is lined with the mucous membrane, which behaves as a lipoidal barrier to the passage of foreign chemicals. Therefore, only nonionized lipid-soluble molecules can be absorbed. As a general

rule, at least 0.3% of a substance must be in nonionized form before rapid absorption can occur. This absorption will depend on the pK_a value of the given substance and the pH in the given part of the gastrointestinal tract. At about pH 1 in the stomach, weak acids are practically nonionized and are absorbed, more or less rapidly, according to their lipid solubility. Conversely, many basic drugs are highly ionized, and some, such as quinine or morphine, pass from the plasma into the gastric juices. The same rules are also valid in the other parts of the gastrointestinal tract. Absorption from the small intestine is much more efficient than from the stomach.

Absorption from the gastrointestinal tract can be affected by factors such as gastrointestinal secretion altering the pH of the gastric juices, gastric emptying, residence time in small intestine, blood flow and intestinal mobility. After oral application, drugs pass through the liver and may be partially metabolized before reaching the general circulation. This process can be avoided by means of buccal, sublingual or rectal application.

Inhalation of gas and vapours

The mechanism of absorption of gases and vapours is based on diffusion. Efficiency of absorption depends on several factors: solubility in blood and body tissues, cardiac output, alveolar-venous differences, ventilation and metabolism.

The greater the solubility in blood and tissues, the greater the uptake of gases and vapours. Solubility is generally expressed as a blood/gas partition coefficient. Coefficient values can greatly differ, e.g. from 0.42 for nitrous oxide, through 9.2 for trichloroethylene or 10.3 for chloroform, to such values as 2000 for ethanol.

The greater the gas partial pressure difference between the alveoli and the pulmonary venous blood, the greater the uptake. This difference diminishes when all body tissues achieve equilibrium with the alveolar partial pressure (concentration in venous blood equal to the concentration in arterial blood). Without metabolic processes and excretion through routes other than the lung and at constant exposure, saturation of the internal organs and brain (vessel-rich group with 75% of cardiac output) would be complete after 10-15 minutes and

saturation of skin and muscle (18% of cardiac output) after 90 minutes. Saturation of adipose tissue (5% of cardiac output) depends on the solubility of particular substances in the fat. Metabolism may influence the partial pressure of the gas in the venous blood leaving the organ or tissue where given substances are metabolized.

The influence of pulmonary ventilation and cardiac output on the absorption of gases and vapours depends on the blood/gas partition coefficient of the substance being inhaled. If the gas has a low solubility in the blood, the difference between the concentration in inspired air and and that of alveolar air is low, and uptake becomes mainly a function of cardiac output, metabolism and accumulation. If the gas is very soluble in the blood, alveolar concentration is low compared with the concentration in inhaled air, and an increase of ventilation will increase alveolar concentration and, in effect, absorption. An increase of cardiac output during intensive work may increase the rate of gas uptake.

Absorption of foreign chemicals present in the air as aerosols depends on particle size and solubility. Particle size of aerosols can differ greatly, from 10^{-2} µm to 10^{2} µm, depending on the kind of substance and the manufacturing processes. Large particles (diameter above 1-2 µm) are efficiently deposited in the nasopharynx region, from which they are removed or swallowed.

Small particles (respirable fraction) can enter the tracheobronchital system and alveolar compartment and are absorbed according to their solubility. Insoluble or low soluble particles may be removed from the tracheobronchital system to the nasopharynx region by the mucociliary escalator mechanism or may be absorbed from alveoli to the circulation by pinocytosis.

Dermal absorption

Foreign chemicals may be absorbed through the skin via the hair follicles or sweat ducts or by diffusion through the lipid barrier located within the epidermal layer. In the case of electrolytes and some salts of heavy metals, transfollicular absorption takes place, whereas the absorption of other substances occurs through the lipid membrane by the general mechanism of diffusion. The

relative thickness of skin makes penetration of foreign chemicals slower than in the case of other body membranes. In addition, factors such as skin hydration, blood flow, temperature, skin age and disease state can affect absorption through the skin.

Distribution of Foreign Chemicals

After absorption, foreign chemicals enter the blood, which constitutes the central compartment and functions as the transport system for distribution of absorbed substances throughout the body and their removal by excretion. The rate of removal of foreign compounds from the blood may be affected by such factors as binding to red blood cells or protein binding. The concept of apparent volume of distribution is helpful for evaluating the distribution kinetics and distribution of the drug in the body.

Excretion of Foreign Chemicals

Foreign chemicals can be excreted from the organism in unchanged form or, after metabolic processes, mainly by renal, pulmonary or biliary excretion. Other routes such as milk, perspiration or lacrimal fluid are of limited value.

Pulmonary excretion

Pulmonary excretion is an important route for volatile substances. Excretion of such substances depends upon their air/blood or air/water partition coefficients. According to existing data, substances may be measurably excreted through the lungs when their air/water partition coefficient is higher than 10^{-3} - 10^{-4}. High efficiency of elimination is attained by such substances as benzene, trichloroethylene and carbon disulfide (partition coefficients of 0.1 - 1.0).

Renal excretion

Renal excretion of foreign compounds or their metabolites constitutes a complex phenomenon which may involve several processes: glomerular filtration, active tubular secretion, passive reabsorption and active reabsorption.

Depending on which process dominates, the renal excretion of drugs can be either an important or insignificant route of elimination.

The process of urine formation starts with the filtration of fluid from plasma at the glomeruli. In humans, the normal rate of filtration is about 125 ml/min (180 l/day). Of this volume, only about 1.5 l/day are excreted as urine. Thus, a given compound filtered through the glomeruli and not reabsorbed will be concentrated about one hundred times. Glomerular filtration is a nonselective process; compounds of molecular weight below 5000 pass freely while molecules of molecular weight above 60 000 barely appear in the filtrate. Most toxic agents are filtered through the glomeruli, but their rate of filtration can be limited after binding to the serum proteins.

The final chemical composition of the urine depends on the processes taking place in the renal tubules. In the proximal tubule, 60%-80% of water and saline will be reabsorbed into the blood. Other compounds present in the filtrate will be concentrated and, depending on the lipid solubility, can be passively reabsorbed. Besides passive reabsorption, substances important to the organism, such as glucose or amino acids, will be reabsorbed in the proximal tubule through the active absorption mechanism. In addition to passive and active reabsorption in the proximal tubule, at least two other mechanisms of active transport of foreign chemicals and their metabolites from plasma to the lumen are possible. One mechanism transports organic anions such as hippurates, glucuronides, sulfonamides and the other cations, including choline, morphine, quinione and piperidine. The distal parts of the nephron, the loop of Henle and distal tubule, are responsible for the final reduction in urinary volume through passive diffusion.

All these described mechanisms have a net effect on the renal excretion of chemicals. This effect may be quantitatively evaluated as the clearance of a certain volume of plasma per minute or:

$$C = \frac{U \cdot V}{P}$$

where: $U \cdot V$ = urinary excretion of compound/min;
P = plasma concentration; and
C = clearance (ml/min).

For compounds such as insulin, which are completely filtered at the glomerules but neither secreted nor reabsorbed by the tubules, the clearance is a measure of the glomerular filtration ratio (GFR) and amounts to about 125 ml/min. Compounds which undergo reabsorption in the tubules will have clearance values lower than GFR. In the case of some lipid-soluble drugs, such as glutethimide or short- or medium-acting barbiturates, clearance values are very low (about 1-2 ml/min). Such compounds can be eliminated from the organism only after metabolic processes produce more polar and water-soluble compounds. For compounds secreted into the tubule by means of active mechanism clearance, the value will exceed GFR (e.g. p-aminohippuric acid at 650 ml/min). Elimination of foreign compounds through the kidney can be increased in two ways: an increase of urine flow (intensive diuresis) or a change of the pH of the glomerular filtrate to obtain higher ionization of a given compound, resulting in a lower degree of reabsorption (e.g. phenobarbital). Both methods are used for the treatment of acute intoxication with drugs; however, the real value of such treatment is limited to selected compounds.

Biliary excretion

Foreign chemicals reach the bile mainly through active secretion. Mechanisms of active secretion have been distinguished for organic acids, organic bases and neutral compounds. Excretion of foreign chemicals in the bile depends on such parameters as physicochemical properties, protein binding and species and sex differences. Only compounds of relatively high molecular weight are excreted in the bile. Compounds with molecular weights lower than 300 undergo renal or pulmonary excretion. In addition, the presence of strongly polar groups is necessary for the biliary excretion of foreign chemicals. Therefore, lipid-soluble substances of relatively high molecular weight must first be metabolized to the more polar compounds.

Some conjugates of foreign chemicals excreted in the bile can be hydrolyzed by the gut microflora and subsequently reabsorbed to the systemic circulation. This activity, known as enterohepatic circulation, can prolong the effect of toxic compounds and lower their rate of elimination from the body.

BIBLIOGRAPHY

Brodie, B.B. & Gilette, J.R. Concepts in biochemical pharmacology, Part I. Berlin, Springer-Verlag, 1971.

Gorrod, J.W. & Beckett, A.H. Drug metabolism in man. London, Taylor & Francis, 1978.

Hanke, J. & Piotrowski, J.K. Biochemiczne podstawy toksykologii [Biochemical foundations of toxicology]. Warsaw, PZWL, 1980.

La Du, B.N. et al. Fundamentals of drug metabolism and drug disposition. Baltimore, Williams & Wilkins, 1971.

Saunders, L. The absorption and distribution of drugs. London, Bailliére Tindall, 1974.