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QUESTION 1

FACTORS AFFECTING DRUG METABOLISM

Drug metabolism is the metabolic breakdown of drugs by living organism, usually through specialized enzymatic systems. A number of factors may influence the metabolic rate of a drug. Some of them are;

**CHEMICAL FACTORS:**

1. **ENZYME INDUCTION:** The phenomenon of increased drug metabolizing ability of enzymes by several drugs and chemicals is called an enzyme induction and the agents responsible for this are called enzyme inducers. Mechanisms of enzyme induction include;

* Increase in both liver size and liver blood flow.
* Increase in both total and microsomal protein content.
* Increased stability of enzymes.
* Increased stability of cytochrome P-450.
* Decreased degradation of cytochrome P-450.
* Proliferation of smooth endoplasmic reticulum.

Consequences of enzyme induction include;

* Decrease in pharmacological activity of drugs.
* Increased activity where the metabolites are active.
* Altered physiological status due to enhanced metabolism of endogenous compounds such as sex hormones.

Some examples of drug induction include;

**Oral contraceptive steroids** **CYP3A4** **Inactive, excreted**

**induction**

**Rhifampin**

1. **ENZYME INHIBITION:** A decrease in the drug metabolizing ability of an enzyme is called enzyme inhibition. The process of inhibition may be direct or indirect.

* **Direct inhibition:** It may result from interaction at the enzymic site, the net outcome being a change in enzyme activity. It can occur by;

**Competitive inhibition:** It occurs when structurally similar compounds compete for the same site on an enzyme.

**Non-competitive inhibition:** It occurs when a structurally unrelated agent interacts with the enzyme and prevents the metabolism of drugs.

**Product inhibition:** It occurs when the metabolic product competes with the substrate for the same enzyme.

* **Indirect inhibition:** It can be caused by;

**Repression:** It may be due to fall in the rate of enzyme synthesis or rise in the rate of enzyme degradation.

**Altered physiology:** It may be due to nutritional deficiency or hormonal imbalance.

Examples of enzyme inhibition include;

**Terfenadine Active anti-histamine**

**inhibition**

**Erythromycin ketoconazole**

1. **ENVIRONMENTAL CHEMICALS:** Several environmental agents influence the drug metabolizing ability of enzymes. They include;

* Halogenated pesticides such as DDT and polycyclic aromatic hydrocarbons contained in cigarette smoke have enzyme induction effect.
* Organophosphate insecticides and heavy metals such as mercury, nickel, cobalt and arsenic inhibit drub metabolizing ability of enzymes.
* Other environmental factors include; temperature, altitude, pressure, atmosphere e.t.c.

**BIOLOGICAL FACTORS:**

1. **Age:** The drug metabolic rate in different age groups differs mainly due to variations in the enzyme content, enzyme activity and hemodynamics.

* In neonates and in infants, the microsomal enzyme system is not fully developed. Hence, many drugs are metabolized slowly. E.g. caffeine has a half-life of 4 days in neonates compared to 4 hours in adults.
* Children metabolize several drugs much more rapidly than adults as the rate of metabolism reaches a maximum somewhere between 6 months and 12 years.
* In elderly persons, the liver size is reduced, the microsomal enzyme activity is decreased and hepatic blood flow also declines. All these contribute to decreased metabolism of drugs.

1. **Diet:**

* Low protein diet decreases and high protein diet increases the drug metabolizing activity of an enzyme.
* Fat-free diet depresses cytochrome P-450 levels.
* Grapefruit inhibits the metabolism of many drugs.
* Dietary deficiency of vitamins like Vitamin A, B2, B3, C and E and minerals such as Iron, Calcium, Magnesium and Zinc retard the metabolic activity of enzymes.
* Starvation results in decreased amount of glucuronides formed than under normal conditions.

1. **Sex difference:** Sex-related differences in the rate of metabolism may be due to sex hormones. In rats, male rats have greater drug metabolizing capacity. In humans, women metabolize benzodiazepines slowly than men. Women on contraceptive pills metabolize a number of drugs at a slow rate.
2. **Altered physiological factors:**

* **Pregnancy:** It affects hepatic drug metabolism. Physiological changes during pregnancy are probably responsible for the reported alteration in drug metabolism. These include elevated concentrations of hormones such as estrogen, prolactin, progesterone, and so on.
* **Disease states:** Disease states that affect the metabolism of drugs include; cirrhosis of liver, cholestatic jaundice, diabetes mellitus, acromegaly, malaria, various bacterial and viral infections, e.t.c.
* **Hormonal imbalance:** Higher level of one hormone may inhibit the activity of few enzymes while inducing the others. Examples include; alloxan-induced diabetes, adrenolectomy and thyroidectomy.

**PHYSICOCHEMICAL PROPERTIES OF THE DRUG:** Molecular size and shape, acidity/basicity, pKa, lipophilicity and stearic and electronic characteristics of a drug influence interactions with the active sites of enzymes and the metabolism to which it is subjected.

In conclusion, the efficiency,toxicity and biological half-life of a drug depends on the metabolism of the drug and a number of factors affect the metabolism of a drug. Hence, these factors must be considered during administration and also in proper dosing of any drug to patients.