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Stress and Drug Pharmacokinetics

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Various factors are involved in drug pharmacokinetic such as age, food, body weight, presence of disease, stress condition as well as coadministration of other drugs (1). Many drugs are reversibly bound to plasma proteins as albumin, a1 acid glycoprotein, lipoproteins a and b and γ globulins. Two distinct binding sites I and II on human serum albumin have been characterized. The degree of drug binding to albumin and other proteins is generally unchangeable, although either endogenous substances or drugs may display a competition to their protein binding sites. The drug unbound fraction is the active form, able to interact with the receptors, to be metabolised, excreted and express its pharmacodynamic effect. The levels of albumin may be altered under the influence of certain factors such as age, liver, renal, immune system diseases, stress and starvation. These factors may lead to increased free fraction of drugs. Consequently, the administration of drugs such as phenytoin, warfarin, NSAIDs requires dosage adaptation to prevent side effects (2-9).

Stress is defined from Hans Seyle as the nonspecific response syndrome, the alarm reaction of the body to any demand, in term to be adapted to its environment for the maintenance of the *milieu interieur* (homoemostasis). The body response is direct, general and spontaneous (10,11).

Pain is a stress phenomenon but stress in not always painful.

Stress or pain is not only a described feeling that can be assessed quantitavely. The sense of tension, alertness and restleness is followed by the release of adrenaline, cortisol and other stress hormones. The body response is manifested with the increase of heart rate, blood pressure, breath rate, central nervous system alertness, liver, muscle, cerebral perfusion, glucose, cholesterol, platelet, coagulation factors and the decrease of, skin blood flow, bowel perfusion, renal flow (12-17).

These changes of body functions may alter the pharmacodynamic effect even by dose individualization and this perspective induces speculation concerning therapeutic actions.

Many stress models are used in order to approach the influence of stress on the serum drug levels.

1. Swimming stress induces enhancement of serum and tissue (liver, mandible, femur) ampicillin levels in rats. In parallel a remarkable increase of free fatty acids in serum as well as of the adrenal weight is observed (18).
2. Experimental trauma-surgical operation in rats leads to increase of serum and tissue (liver, mandible, femur) quinolones and lidocaine pka was related to drug levels (19).
3. Constant darkness and 12h light/12h darkness exposure of rats showed an increase of serum and tissues (skin, femur) quinolones (20).
4. Experimental (Freud's adjuvant) arthritis results an increase of serum and tissue (liver, mandible, femur) quinolones and lidocaine (21).

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