12 - G. Elimination kinetics

G. Elimination kinetics:

© SPMM Course fall in the plasma drug concentration, which is caused by redistribution of the drug from the blood circulation into other tissues. The time taken for this redistribution to halve the initial peak concentration is the distribution half-life. Following this, the process of drug elimination occurs. The time taken by this elimination process to halve the plasma drug concentration is the elimination half-life. Most often, clinicians are interested in the elimination half-life. G. Elimination kinetics: Drugs can undergo two different types of clearance (similar to absorption) when administered. When a constant fraction of drug is cleared per unit time, it is called as first order kinetics. This means that when the amount of drug in plasma or dose of administered drug increases, the clearance proportionately increases as a stable fraction of plasma concentration. In other words, the higher the amounts of a drug present, the faster the elimination. When represented graphically, first-order elimination follows an exponential decay versus time. Using this exponential curve, the time to eliminate 50% of a given amount (or time to achieve a decrease in plasma level to 50% of original) is the elimination half-life (t1/2). For example, if t1/2 is 2 hours for a drug A then the plasma concentration changes as follows 100mg/ml (2hours) □ 50mg/ml (2hours) □ 25mg/ml (2hours) □ 12.5mg/ml Most psychotropic drugs follow first order kinetics. In first order kinetics, the rate depends only on the drug concentration. It is not dependent on any other rate-limiting step. When the system facilitating such clearance of drugs gets saturated, drugs follow zero-order kinetics. Here a constant amount, not a fraction, of the drug is cleared per unit time. This means that irrespective of the amount of drug in plasma or dose of drug administered, the body clears only a fixed unit of the drug. As such, increasing dose might result in serious toxicity in this case. Certain drugs have propensity to undergo zero order kinetics even at therapeutic dose levels. Here the concept of half-life does not hold true as ‘half life’ depends on the dose administered. 100mg (2hours) □ 80mg (2hours) □ 60mg (2hours) □ 40mg In the above example, 20mg of the drug is metabolized in every 2 hours. The apparent ‘half-life’ of 100mg dose is about 5 hours, but the apparent ‘half-life’ of 80mg dose is only 4 hours. Slow release preparations (e.g. lithium MR, depot preparations) follow zero-order absorption kinetics; drugs that rapidly saturate enzymes such as alcohol and phenytoin follow zero-order elimination kinetics. In very high supratherapeutic doses, saturation of enzymes can happen for drugs such as fluoxetine, wherein first order elimination switches to become zero order. Note that in zero order kinetics, the rate does NOT depend on the drug concentration; it depends on some other rate limiting step e.g. availability of enzymes, slow release formula, etc.

© SPMM Course Steady state: When a drug is administered episodically, the plasma values acutely rise immediately after administration and then fall when the continuous input of drug does not take place. But before the fall in levels reaches a flat trough, the next dose gets administered

(depending on t ½ of the specific drug, dosing interval varies). Hence, the actual plasma level starts building up gradually with every subsequent dose. It is estimated that it takes 4-5 t½ for a drug to reach the steady plasma level. When steady state is reached, fluctuations in plasma level do not get eliminated. But the average plasma concentration between 2 successive doses remains the same. Steady state is reached when for a given drug, rate in = rate out. The time to reach steady state is dependent on the elimination t½ of a drug; the actual level of the steady state is independent of the frequency of administration; instead it depends on the actual dose administered. Loading doses can help achieving steady state more rapidly.

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