

# Rate Controlled Drug Delivery

Pages with reference to book, From 273 To 274

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Pharmaceutical research aims to find out drugs with least side effects and desirable therapeutic properties. Dose responsive curve denotes the amount of drug taken and consequent beneficial or adverse effects. Optimal therapy is a dose high enough to produce beneficial results without adverse effects. When the dose for optimal benefit borders on that producing adverse effects, then careful adjustment is required to penetrate a narrow therapeutic-window. The serum levels rather than the dose are the best index of the amount of drug present in the body (Koch-Weser, 1972). Any drug given orally or parenterally is not released in the systemic circulation at a constant rate and multiple peaks and valleys are registered in its concentration in the serum. Transient cardiac arrhythmias were detected in patients within a few hours following their daily dose of digoxin evidenced by a sudden rise in the serum levels of the drug (Manninen et al., 1976). The effects of a drug also vary with the serum concentration e.g., antihistaminic activity of diphenhydramine occurs at lower serum levels than its sedative effect (Carruthers et al., 1978). Undesirable effects could be separated from the desirable by eliminating peaks. Intravenous infusion of morphine works better in controlling post-operative pain than the usual high dose given intramuscularly (Rutter et al., 1980). Moreover respiratory function is better controlled in the former group. Changes in the dosage and schedule of furosemide (Wilson et al., 1975) and chlor-thiazide (Murphy et al., 1961) are associated with altered water and electrolyte excretion. Deferoxamine is more effective in removing iron in siderosis, when given continuously (Propper et al., 1977).

Intravenous infusion, monitored by infusion pump or drop counter, is the familiar form of controlled release drug delivery. Pumps and reservoirs can be worn externally (Tamborlane et al., 1979) or subcutaneously (Blackshear et al., 1972). The programmed infusion of insulin might offer good means of correcting metabolic abnormalities in diabetics (Tamborlane et al., 1979; Blackshear et al., 1972; Rupp et al., 1982). Similarly, constant infusion of heparin may be more effective in preventing thrombosis (Buchwald et al., 1980). Pumps have been used experimentally to perfuse liver and central nervous system with chemotherapeutic agents (Buchwald et al., 1980; Buchwald et al., 1980; Dakhil et al., 1981).

Devices to provide rate controlled administration of drugs by the transdermal route are also in use. Scopolamine for motion sickness when given by transdermal route at a constant rate of 0.5 mg over 3 days, significantly reduced motion sickness as compared to placebo or other drugs. Dry mouth was the only more frequent side effect that occurred in control subjects (Price et al., 1981). The appropriate skin site for transdermal drug delivery is behind the ear. Varying doses of Nitroglycerine alter the tone of the blood vessels (Abrams, 1980; Imhof et al., 1980). By sublingual route it is rapidly absorbed and metabolized by the liver and other tissues. With a half life of only few minutes (Armstrong et al., 1979; McNiff et al., 1981) such doses produce vascular changes although it is not suitable for anginal prophylaxis. Transdermal nitroglycerine infusion at a constant rate provides a constant serum concentration thereby avoiding all these side effects.

Devices exist which deliver the drug to a specific organ at a controlled rate. pilocarpine, for example, used in the treatment of glaucom, not only lowers the intraocular pressure but also decreases the visual acutely due to miosis and myopia (urguhart, 1979). these side effects are noted within one hour of administration, denoting excessive concentration of the drug. the drug is moreover, rapidly expelled by the tear, flow, requiring frequent administration. ocusert, a device placed under the lower eyelid by the patient, delivers pilocarpine at a rate of 20-40 ug/hr for one week after which it can be replaced. a constant reduction in the intra-ocular pressure is thus seen with low incidence of side effects.

Betaadrenergic blocker timolol, when used as eye drops in glaucoma may produce its side effects (asthma) in susceptible patients (FDA Drug Bull., 1981). Progestasert, an intra-uterine device, is beneficial in controlled delivery of progesterone in birth control, by its constant action on the uterus. One device lasts for one year and then should be replaced (Martinez-Manauton, 1975). When Cancer chemotherapy in mice with Lewis lung carcinoma was done with bleomycin by constant infusion, the response was better and pulmonary toxicity was low as compared with a twice daily injection (Sikie et al., 1978).

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