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ORAL ABSORPTION AND SECRETION OF DRUGS

To achieve a systemic pharmacological effect drugs may be injected subcutaneously, intramuscularly or intravenously and can be put into a few orifices, but the commonest route of administration is by mouth. This is convenient for the patient and allows a wide margin of therapeutic safety. At present, oral medications are most commonly administered in tablets or capsules and the active constituents are released in the stomach or small intestine prior to absorption.

The term 'oral administration' implies that medicines are swallowed but Fantus (1926) suggested that the words should be changed to 'peroral administration' because 'perlingual administration' is more truly the oral route. Such pedantic terminology was not accepted although the author cited supporting literature. He considered perlingual (or sublingual) administration to be effective because a drug is absorbed directly into the blood stream and escapes 'the digestive ferments and destructive influence of the liver cells'. Clinical impressions had suggested that morphine, atropine, nitroglycerine, strychnine, strophanthin and possibly insulin might be absorbed efficiently from the mouth. Walton & Lacey (1935) compared in dogs the pharmacological effects of drugs administered subcutaneously and sublingually. Those studied were apomorphine, codeine, dilaudid, atropine, insulin and adrenaline. The last two produced no significant effects even when administered in high doses sublingually. The others were absorbed to a variable degree which could be defined by the ratio of the effective sublingual to subcutaneous doses. Limited work in normal volunteers suggested that human oral mucosa is less permeable than the dog's. Walton (1935) also demonstrated that the oil-water distribution coefficient was an important factor in the selective sublingual absorption of a large number of alkaloids.

More recently, literature describing the reliability of drug absorption through the oral mucosa was reviewed by Gibaldi & Kanig (1965). Although absorption is more rapid from solutions, tablets are more convenient. The authors used anatomical drawings to demonstrate that a good blood supply ensures drug absorption whether a tablet is placed under the tongue or against the buccal mucosa. They discussed cardiovascular drugs, steroids, barbiturates, insulin, heparin and enzymes. Results could be considered impressive only with glyceryl trinitrate, methacholine chloride, isoprenaline and some of the early steroid preparations such as desoxycortisone acetate.

There are obvious disadvantages with sublingual administration of drugs. The patient experiences interference with eating, drinking and talking and there is the danger of inhaling a tablet on falling asleep. At present the only drug to be administered regularly in this way is glyceryl trinitrate. Isoprenaline and oxytocin sublingual tablets are available but alternative routes of administration are preferred.

Human oral mucosa was found to be a useful *in vivo* model for the passive transfer of drugs through lipid membranes (Beckett & Triggs, 1967). The basis of this 'buccal absorption test' was that buffered solutions of a compound should be swilled around the mouth for a fixed time before being spat out and that the expelled fluid should be analysed to determine what percentage of the drug had been lost in the mouth. No pharmacological tests were performed nor were blood levels of the drugs measured. It was, however, assumed that drugs had been absorbed to a variable degree. The model was used to determine the relative order of partitioning into biological lipids of a wide variety of drugs and to predict their urinary excretion (Beckett, Boyes & Triggs, 1968; Beckett & Moffat, 1970; Beckett & Moffat, 1971). Others used some of these data to demonstrate that the octanol-water partition coefficient was an important parameter in determining buccal absorption (Lien, Koda & Tong, 1971).

The action of drugs usually ends with their metabolism and/or elimination in urine or to a lesser extent in bile, expired air or directly through the intestinal wall. A minor role is played by sweat, tears, breast milk and saliva (George, 1976). Saliva is not truly an excretory route however as it is usually swallowed, thus allowing some drugs to be reabsorbed from the gastrointestinal tract. Drugs do not appear in saliva merely by a reversal of the proposed buccal absorption mechanism. Saliva (mixed saliva or spit) consists of parotid, submandibular, sublingual and minor gland secretions along with gingival fluid. Mason & Chisholm (1975) gave a detailed description of important features such as pH, flow rate, protein and carbohydrate content, urea, electrolytes and enzymes for mixed saliva and its components. Gingival fluid is different from glandular saliva particularly regarding albumin, globulin and

fibrinogen concentrations which are similar to those in plasma.

There are methods for collecting the components of mixed saliva (Stephen & Speirs, 1976) but most published studies of salivary drug concentrations relate only to mixed saliva. Low concentrations of sulphapyridine (M & B 693) were detected in the saliva of patients who had received oral or intramuscular therapy (Fickling, Pincus & Boyd-Cooper, 1939). Following a combined i.m. injection of benzylpenicillin and streptomycin and after single i.v. injections of chloramphenicol or chlortetracycline, only low levels of each could be detected in saliva (Bender, Pressman & Tashman, 1953a, b, c). There were no correlations between serum and saliva levels of these antibiotics. Phenoxymethylpenicillin, ampicillin, cloxacillin, cephalexin, erythromycin stearate, sodium fusidate, tetracycline hydrochloride, pristinamycin and lincomycin hydrochloride could not be detected in mixed or parotid saliva of normal volunteers after a single oral dose. Antibacterial activity was occasionally detected in these secretions with spiramycin and erythromycin estolate. Sulphadimidine, clindamycin and rifampicin were regularly present in mixed and parotid saliva (Speirs, Stenhouse, Stephen & Wallace, 1971; Stephen & Speirs, 1972). Antibiotics were detected to a variable degree in gingival fluid even when none was found in mixed saliva and its other components (Stephen & Speirs, 1972; Macfarlane, McCrosson, Stephen & Speirs, 1974). Sulphonamides and antibiotics which are active against *N. meningitidis* are likely to be of value as chemoprophylactic agents against meningococcal disease if they can be detected in mixed saliva (Devine, Knowles, Pierce, Peckinpaugh, Hagerman & Lytle, 1969; Hoeprich, 1971).

Failure to detect many antibiotics in saliva does not mean that they were not present. The sensitivity of bioassay procedures is usually limited to concentrations of antibiotics which are likely to be of clinical significance. Physicochemical and radioimmunological methods can detect nanogram quantities of drugs which may be of pharmacological or at least pharmacokinetic importance. Such techniques have been used to measure saliva concentrations of salicylic acid (Graham & Rowland, 1972), paracetamol (Glynn & Bastain, 1973), theophylline (Koysooko, Ellis & Levy, 1974), tolbutamide (Matin, Wan & Karam, 1974), amylobarbitone (Inaba & Kalow, 1975), digoxin (Huffman, 1975; Joubert, Müller & Aucamp, 1976), antipyrine (Chang, Wood, Dixon, Conney, Anderson, Eiseman & Alvares, 1976; Brooks, Bell & Burns, 1976) and phenytoin (Reynolds, Ziroyanis, Jones & Smith, 1976). Phenytoin has been measured in saliva of patients receiving also phenobarbitone and primidone concomitantly (Schmidt & Kupferberg, 1975).

These publications showed good correlations between serum (or plasma) and saliva concentrations of the drugs. Some indicated that saliva concentrations were similar to the non-protein-bound fraction in blood. Inaba & Kalow (1975) suggested that if the total concentration of a drug in plasma were known, salivary secretion data might provide an estimate of its plasma protein-binding. Schmidt (1976) considered that saliva and plasma concentrations should be identical for primidone and ethosuximide which are not protein-bound. Reynolds *et al.* (1976) however, noted that mixed salivary concentrations of phenytoin were higher than those of free drug in plasma and suggested that the discrepancy might be due to drug binding by salivary proteins. Paxton and his colleagues (1976, 1977) found that phenytoin concentrations were similar in parotid and submandibular saliva but mixed saliva levels were 16% lower. They suggested that adsorption of phenytoin to oral cell debris might be responsible for this difference (Paxton, Whiting, Rowell, Ratcliffe & Stephen, 1976; Paxton, Whiting & Stephen, 1977). Following a rapid i.v. infusion of procainamide, saliva concentrations were higher than those in plasma and the saliva : serum ratio changed continuously. Saliva measurements could not be used to predict plasma levels of procainamide but they were more closely related to its pharmacological effect (Galeazzi, Benet & Sheiner, 1976).

Mixed saliva samples are easy to obtain and might be useful alternatives to blood samples in bioavailability studies or drug monitoring for individual patients. Antipyrine metabolism was assessed in West African villagers, despite adverse study conditions, by obtaining saliva instead of blood samples (Fraser, Bulpitt, Kahn, Mould, Mucklow & Dollery, 1976). Measurement of drug concentrations, in mixed saliva can be inaccurate however as it is a fluid of variable content. The state of oral hygiene, presence of phenytoin–induced gum hypertrophy and absence of teeth (thus absence of gingival fluid) are factors which might influence salivary drug concentrations and deserve further investigation.

Parotid saliva is more difficult to obtain but gives a more accurate assessment of drug secretion than mixed saliva. In an investigation of industrial personnel for absorption of mercury, mixed saliva samples were unsatisfactory but there was a good correlation between blood and parotid saliva concentrations of mercury (Joselow, Ruiz & Goldwater, 1969).

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