Rectal administration of drugs has been used since Ancient times to produce local effects. In addition, the rectal route may be used for systemic administration of drugs for the following reasons (De Boer et al., 1982):
(a) the presence of nausea and vomiting, or when the patient is unconscious;
(b) the presence of disease of the upper gastrointestinal tract which affects absorption of drugs given orally;
(c) an objectionable taste (a factor which may be particularly important in children);
(d) the achievement of a rapid systemic effect by giving a drug in a suitable solution (as an alternative to parenteral administration);
(e) drug absorption may be easily discontinued in the event of an accidental overdose;
(f) the rate of drug absorption is not influenced by ingestion of food or the rate of gastric emptying;
(g) first-pass elimination of high clearance drugs may be partly avoided;
(h) contact with digestive fluids of the upper gastrointestinal tract is avoided, thereby preventing breakdown of some drugs.

The disadvantages associated with administration of drugs rectally include:
(a) interruption of absorption by defaecation, which may occur particularly with irritant drugs;
(b) the surface area of the rectum is far smaller for absorption than that of the duodenum;
(c) the fluid contents of the rectum are much smaller than those of the duodenum and this may produce problems with dissociation of some drugs;
(d) degradation of some drugs by micro-organisms may occur in the rectum;
(e) patient acceptability may be a problem, at least in some countries.
Rectal drug formulations

Several drug formulations may be used rectally. These comprise suppositories (suspensions and emulsions), gelatine capsules (solutions and suspensions) and enemas (macro—100 ml or more—and micro—1–20 ml—solutions and suspensions). The technical and pharmaceutical aspects of these formulations have been reviewed extensively by Thoma (1980).

The suspension suppository is the formulation used most widely clinically and this type has been the subject of extensive research in vitro (Crommelin, 1979; Schoonen, 1980) and in vivo (Rutten-Kingma, 1977; Moolenaar, 1979). Its release characteristics are influenced by many pharmaceutical and physiological factors related to the active drug, the suppository base and factors related to rectal environment (De Blaey and Polderman, 1980). Although drugs may be absorbed rectally from an aqueous solution faster than via the oral route, in general, absorption is slower with non-aqueous formulations. A critical factor in rectal absorption is the limited amount of water available in the rectum for drug dissolution.

Physiological factors influencing rectal drug absorption

Two factors are of major importance with respect to the venous drainage of the rectum and consequently the transport of absorbed drug into the systemic circulation: site of absorption and direction of blood flow. If the drug is absorbed in the upper part of the rectum, it is transported to the portal system and passes through the liver while, following absorption in the lower rectum, the drug is transported directly to the systemic circulation. In general, this implies that hepatic first-pass elimination is avoided when a drug is administered in the lower part of the rectum. However, a complicating factor is that there is no precise anatomical division between the area draining to the portal and that draining to the systemic circulation, because of the presence of anastomoses.

De Boer and colleagues (1979) have shown that, with lignocaine, it is possible partly to avoid hepatic first-pass elimination following rectal administration of the drug (fig. 2). On average, systemic availability was increased by almost 100% following rectal administration compared with the oral route for the same dose. These results were reproducible.
when repeated in the same subjects and it was calculated that the mean fraction of the rectally administered dose escaping hepatic first-pass elimination was 57%. Other high-clearance drugs, for example salicylamide and propranolol, did not exhibit an increase in mean bioavailability with the rectal route compared with oral administration (De Boer, 1979; De Boer et al., 1983). However, it is possible that incomplete rectal absorption may have masked the “bypass” effect.

In rats, these three drugs (lignocaine, salicylamide and propranolol), when given rectally, exhibit a far greater systemic availability compared with oral administration (De Boer, 1979; De Boer et al., 1980; De Boer, Gubbens-Stibbe and Breimer 1981; De Boer et al., 1981).

Rectal gut-wall metabolism and metabolism by micro-organisms in the rectal lumen may decrease bioavailability, but there is very little information on this, although gut-wall metabolism is known to be very important in the upper part of the gastrointestinal tract for some drugs (Curry, D'Mello and Mould, 1970; Rivera-Calimlin et al., 1971; Barr, 1972; Dollery and Davies, 1972; Conway et al., 1973). Although this latter process is not likely to be important in the rectal wall, metabolism by microorganisms may be significant for some drugs, especially when hydrolytic and reductive reactions occur (Scheline, 1973). Unfortunately there is little information on this topic in the human.

**Examples of Rectally Administered Drugs**

**Anaesthetics, premedication and hypnosedative agents**

Relatively little is known regarding rectal drug administration for anaesthetic purposes. In principle, most drugs which are used for anaesthetic purposes can be used rectally in premedication. In this respect, attention should be directed to the elimination kinetics of the drug (short vs. long elimination half-life), the absorption characteristics and the formulation used in the rectum.

**Thiopentone.** Thiopentone is a very lipophilic drug and distributes very rapidly into the brain and other well-perfused tissues (Gillis, De Angelis and Wynn, 1976). Rapid onset of sedative action has been shown to occur following rectal administration of the drug in aqueous suspension (Boyd and Singh, 1967; Burckart et al., 1980) and in a suppository containing the sodium salt (Lindsay and Shepherd, 1969).

Burckart and colleagues (1980) found, in children, that, following rectal administration of a suspension of 25 mg kg$^{-1}$ the mean duration of sedation was 2.75 h. They considered that rectal thiopentone was an effective alternative to i.m. administration of a sedative “cocktail” (pethidine, chlorpromazine and promethazine) for sedating patients before performing CT-scans. Similar results were found following rectal administration of a suppository containing the sodium salt of thiopentone to children (Burckart et al., 1980). A dose of 42.3 mg/kg body weight produced hypnosis or adequate sedation. However, recovery took more than 24 h, which may be explained by the half-life of the parent drug (8 h), while that of the primary metabolite (pentobarbitone) is 26 h.

**Methohexitone.** Methohexitone is also a very lipophilic drug. Rectal administration of its sodium salt (10% aqueous solution) to children, undergoing elective surgical procedures, resulted in satisfactory premedication (Liu, Goudsouzian and Liu, 1980). The recovery time following rectal administration of 25 mg kg$^{-1}$ was not significantly different than that after i.v. administration of 5 mg kg$^{-1}$ (Liu, Goudsouzian and Liu, 1980). A major advantage of this agent is that the elimination half-life is very short (1.2 - 2.1 h) while that of thiopentone is much longer (Breimer, 1977). This suggests that, theoretically, the recovery time following administration of methohexitone should be shorter than that following thiopentone.

**Benzodiazepines.** Diazepam is very well absorbed rectally from water-ethanol and propylene glycol-water-ethanol solutions and has been shown to be effective in the treatment of acute convulsions (Agurell et al., 1975; Knudsen, 1977; Dulac et al., 1978; Langslet et al., 1978; Meberg et al., 1978; Magnussen et al., 1979; Moolenaar et al., 1980; Breimer, 1983).

Rectal administration of an aqueous solution of flunitrazepam 0.07 mg kg$^{-1}$ resulted in a satisfactory premedication in more than 400 children aged between 1 month and 12 yr (Govaerts, 1980). However, Cano and colleagues (1977) found an absolute bioavailability of only 50% following rectal administration of flunitrazepam in a suppository. The mean absorption rates following oral administration of a solution and a tablet and rectal administration of a suppository were 1.8 (range 0.7–3.3), 1.9 (range 1.2–2.5) and 1.6 (range 0.7–2.5) min$^{-1}$ respectively.
Clonazepam is absorbed very slowly following rectal administration from a propylene glycol-water-ethanol solution (Dijkhuis, unpublished observations), whereas nitrazepam in the same type of solution resulted in a rapid absorption and an average absolute bioavailability of 79% in healthy subjects (Jochemsen et al., 1981). In contrast, Caillé and colleagues (1983) studied the absorption of lorazepam from a tablet following sublingual and oral administration to 12 healthy volunteers. The mean absorption half-lives for the sublingual and the oral routes were 15 and 55 min respectively. During maintenance treatment the time to steady-state was approximately 3 days, which correlated well with the value predicted from single-dose studies. The mean maximum and mean steady-state concentrations were independent of the formulation used.

**Etomidate.** Although attempts have been made to administer etomidate rectally, inadequate sedation has followed, despite the use of several different formulations (water; water-ethanol-propylene glycol; PEG-water) (De Boer et al., 1983; unpublished results). It should be a suitable agent for rectal administration for premedication or sedation, since the drug has a relatively short elimination half-life of 4 h (De Ruiter et al., 1981).

**Chloral hydrate.** Simpson and Parrott (1980) administered chloral hydrate and chloral betaine orally and rectally to healthy male volunteers. Rectal administration in suppositories (base: beeswax and cocoa butter) resulted in recovery of smaller amounts of trichloroacetic acid (the major metabolite) from urine than when both were administered orally. Breimer, Cox and Van Rossum (1973) administered chloral hydrate in various suppository bases (estarine D and PEG 1540: PEG 6000 4:1; particle size < 150 μm) and in rectioles (PEG 300 and sesame oil; particle size < 150 μm). The absorption rate, measured as the rate of appearance of the active metabolite (trichloroethanol) in blood was comparable for all formulations (peak times after 0.5—2 h). The extent of absorption was greater with the PEG formulations. In comparison with the PEG suppository, the mean relative availabilities were 61%, 84% and 60% for the estarine D suppository, the PEG rectiole and sesame oil rectiole respectively.

**Analgesic drugs**

**Acetylsalicylic acid (ASA) and sodium salicylate (SA).** Rectal absorption of ASA and SA is influenced strongly by the type of formulation (Cacchilo and Hassler, 1954; Samelius and Aström; 1958; Coldwell et al., 1969; Parrott, 1971; Gibaldi and Grundhofer, 1975; Superstine, Superstine and Penchas, 1978). Moolenaar, Oldenhof and colleagues (1979) showed that the absorption of ASA may be as fast rectally as with oral absorption, but the pH is a critical factor in this respect. An aqueous micro-enema (20 ml; pH 4.0) gives the best results. For SA, comparable plasma concentration—time curves are obtained when SA is given either rectally in a suppository (cocoa butter, particle size 125—250 μm) or orally in a tablet (fig. 3).

**Paracetamol.** In contrast with ASA, the pH of a micro-enema is not a critical factor in the absorption of paracetamol. However, the amount of enema used is very important and the volume should be 20 ml (Moolenaar, Olthof and Huizinga, 1979). When suppositories are used, relatively small particle sizes promote more rapid absorption, although absorption rate is still slower than from an enema (Moolenaar, Schoonen et al., 1979).

**Indomethacin.** Absorption of indomethacin rectally seems to be comparable to that following oral administration. Baker and colleagues (1979) found no differences in clinical effects, plasma concentrations and AUC following oral and rectal administration. Kwan and colleagues (1976) found an absolute bioavailability of 80% following rectal administration in a suppository.

**Propionic acid derivatives and other analgesics.** The analgesics derived from propionic acid, for example naproxen (Desager, Vanderbist and Harveyt, 1976), benoxaprofen (Jones et al., 1980) and ketoprofen (Ishizaki et al., 1980) are all well absorbed rectally in healthy volunteers when administered in a suppository. The same is true for alclofenac (Roncucci et al., 1971; Van Ginneken, 1976) and diclofenac (Riess et al., 1978).

**Narcotic analgesics**

Narcotic analgesics are usually administered by the i.v., i.m. or oral routes. However, severe pain is often associated with nausea and vomiting, which
prohibit oral administration of drugs. The rectal route is therefore a suitable alternative, but unfortunately few studies have been conducted in this area.

**Pentazocine, ketobemidone, oxymorphone and morphine.** Beckett and colleagues (1970) found that higher doses of pentazocine were needed with suppositories to produce plasma concentrations comparable to those following oral administration. Simonis, Eichner and Ecker (1975) found that pain relief in patients with moderate and severe pain was obtained following rectal administration of pentazocine 50 or 100 mg given in suppositories. Although the authors provided no experimental evidence they suggested that 75\% of the rectal administered dose entered the general circulation without passage through the liver. However, the use of pentazocine in suppositories was found to be less effective than i.m. injections, particularly in the treatment of severe pain, and was slower in onset of action (Schenk, 1974; Copsidas and Ward-McQuaid, 1979).

Most narcotic analgesics have not been studied extensively with regard to rectal administration. However, for ketobemidone, Anderson and colleagues (1981) found a mean rectal availability of 44\% following rectal administration in suppositories. For oxymorphone Beaver and Feise (1977) showed that rectal administration was as effective in treatment of postoperative pain as was i.m. administration. Plasma concentrations of morphine following rectal administration in a suppository were too low to be effective (Lindahl, Olsson and Thomson, 1981).

**Drug acting on the respiratory system**

Theophylline. Theophylline is frequently administered rectally in a suppository and with most of the formulations, bioavailability is lower than after oral administration (Bolme et al., 1979). Bolme and colleagues (1979) compared theophylline enemas with suppositories in young children (2 months to 4 yr) with asthma. The administration of suppositories resulted in a variable bioavailability (8–100\%, mean 80\%) and a mean absorption half-life of 43 min. In contrast, the enema was absorbed rapidly with a mean absorption half-life of 5.5 min, while bioavailability averaged 100\%. Three-times daily enema administration (6–8 mg/kg body weight) produced continuously therapeutic
(8–20 μg ml⁻¹) theophylline concentrations. The administration of single solutions rectally produced a therapeutic effect and reproducible plasma concentrations (Yunginger et al., 1966).

Constant plasma theophylline concentrations have been obtained in healthy volunteers by the continuous rectal infusion of a solution using an osmotic delivery system (De Leede et al., 1981, 1982). The steady-state theophylline plasma concentrations could be predicted on the basis of the in vitro release rate of the system (which was identical to that in vivo) and the clearance of the subject. The plasma concentration profile was not influenced by renewing the delivery system or by defaecation (fig. 4).

Thiasinamium. Quaternary ammonium drugs exhibit poor absorption characteristics because these compounds are ionized at all pH values.

Jonkman (Jonkman, 1977, 1979; Jonkman et al., 1979) administered thiasinamium orally and rectally to healthy volunteers. Rectal administration in a lipophilic (Whitepsol HI5) and hydrophilic (PEG) base was associated with a bioavailability of 6%—of the same order of magnitude as with oral administration.

Promethazine. Moolenaar and colleagues (1981) found that rectal absorption of promethazine from a micro-enema in healthy volunteers was fast, but that bioavailability was comparable to that with oral administration (25%).

Cardioactive drugs

Propranolol. Absorption of propranolol rectally was faster than following oral administration, while mean systemic availability following oral and rectal administration was 33 and 40% respectively in the same subjects (De Boer and Breimer, 1980).

De Leede and colleagues (1983) administered propranolol rectally to healthy volunteers at a constant rate with an osmotic system for 24 h and obtained constant plasma concentrations and a good correlation between concentration and beta-blockade measured by the isoprenaline challenge test (fig. 5). The mean rectal bioavailability (33%) was comparable to that found by De Boer and Breimer (1980). A disadvantage of this route is that the drug is irritating to the mucosa and therefore not suitable for long term administration rectally.

BUCCAL AND SUBLINGUAL ADMINISTRATION OF DRUGS

Physiology of the Sublingual and Buccal Area

Although the total buccal and sublingual area is small (200 cm²) and has a pH of 6.2–7.4 (Danhof and Breimer, 1978) the potential exists for rapid absorption of drugs since these areas are rich in blood and lymphatic vessels (Spence, 1942; Goldberg, 1961; Hollinshed, 1968); thus rapid systemic action may be achieved by administering drugs sublingually or buccally. An important advantage of these routes is that the drug passes directly into the systemic circulation. Thus, hepatic high-clearance drugs, or drugs which are subject to presystemic gut-wall metabolism or decomposition in the gastrointestinal tract, or both, will exhibit higher systemic availability following sublingual, compared with oral, administration.

An important disadvantage of these routes is the maintenance of the drug in the buccal and sublingual area. This varies between subjects and is dependent upon the drug formulation, disintegration, flow of saliva and rate of drug absorption.

Sublingual and buccal formulations

Tablets are used almost exclusively for buccal and sublingual drug administration. Large tablets are inconvenient because of their physical size and therefore only potent drugs are suitable for administration by these routes.

Solutions are used only for studies of buccal
absorption (Beckett and Triggs, 1967), while a paste has also been used (Erdle et al., 1979). These two formulations spread throughout the whole mouth, which increases the chance of early swallowing of the drug.

There has been little work on the development of optimum drug delivery systems designed for long-term sublingual or buccal use.

Physiological factors influencing sublingual and buccal absorption

Absorption is highly dependent on the residence time of the drug in the sublingual and buccal area and this may vary considerably. In addition, bad taste or irritation caused by the drug may lead to voluntary expulsion or swallowing. The residence time of the drug used is dependent upon the formulation: a solution has a shorter residence time than a tablet. Saliva flow is important since it affects the rate of dissolution of the drug and, if the saliva flow is considerable, there is an increased likelihood that part of the drug will be swallowed before absorption. Therefore the patient must learn to adapt to these routes of administration in order to avoid sucking on the tablet, swallowing the drug before absorption and excessive salivation by the presence of drug in the mouth (Gibaldi and Kanig, 1965).

During sublingual administration, the patient is not allowed to eat, drink, talk, smoke or chew—all of which influence tablet disintegration and residence time of drug in the mouth. In buccal administration, the patient may talk but should avoid drinking, eating and so on (Gibaldi and Kanig, 1965). An advantage of both routes is that drug absorption can be easily terminated.

Various models have been proposed to describe the mechanism of absorption of drugs from these areas (Beckett and Triggs, 1967; Dearden and Tomlinson, 1971; Ho and Higuchi, 1971; Vora, Higuchi and Ho, 1972). In general, polar drugs are badly absorbed; for example clindamycin (Taraszka, 1970) is absorbed extremely slowly or not at all from the buccal cavity. Drugs with a moderate lipophilicity are well absorbed (Beckett and Moffat, 1969, 1970), while drugs with a very high partition coefficient are too water-insoluble to achieve a sufficiently high concentration in salivary fluids (Gibaldi and Kanig, 1965). The pH of the buccal area is important for the absorption of acid or alkaline drugs (Beckett and Moffat, 1969, 1970), while membrane storage seems to occur for lipophilic drugs such as propranolol (Schürmann and Turner, 1977). In addition, binding of drugs to macromolecules in the mouth interferes with drug absorption (Dearden and Tomlinson, 1971).

The buccal absorption test is a useful tool and easy to perform. It has been shown (Beckett and Triggs, 1967) that this test provides a better indication of the passage of drugs through biological membranes than do simple partition or rate of partition between water and organic solvents.

There are two routes of transport of absorbed drug into the systemic circulation. Absorption of drug occurs into capillaries, but also uptake into lymph may be significant, as has been demonstrated by buccal administration of para-aminosalicylic acid in rabbits (De Marco and Blomsnes, 1974).

Examples of Buccal and Sublingual Drugs

Cardioactive drugs

Nitroglycerin and isosorbide-dinitrate. Nitroglycerin (NG) is a standard example of a drug which is often administered buccally or sublingually. Both NG and isosorbide are used with more or less success in the treatment of angina pectoris, variant angina, congestive heart failure, acute myocardial infarction and peripheral vascular diseases (Elkayam and Aronow, 1982). To evaluate the therapeutic efficacy of the buccal and sublingual route the effects of acute and chronic administration require consideration.

Acute treatment. Sublingual administration is the route of choice when acute therapy is desired. Nitroglycerin is absorbed rapidly following sublingual and buccal (Blumenthal et al., 1977) administration,
resulting in early and relatively high peak plasma concentrations (fig. 6) and consequently, a rapid onset of action. However, the rate of the elimination of nitroglycerin is also rapid. It is metabolized in rats by glutathione organic nitrate reductase (Needelman, Lang and Johnston, 1972) in the liver and also degraded rapidly (76% in 1 h) when incubated in rat serum (Dicarlo and Megler, 1970).

Isosorbide-dinitrate is also absorbed very rapidly following sublingual administration. Peak serum concentrations are reached within 10 min (Spörl-Radun et al., 1980). The rate of elimination following i.v. administration is also rapid with the half-lives of parent drug, 2- and 5-isosorbide-mononitrate, being 30 min, 1.8 h and 7.6 h (Spörl-Radun et al., 1980; Taylor et al., 1980) respectively.

Prophylactic and maintenance treatment. Following oral administration of both nitroglycerin (Blumenthal et al., 1977) and isosorbide-dinitrate (Taylor et al., 1980) substantially higher doses are required to obtain plasma concentrations of the parent drug which are comparable to those following sublingual or buccal administration. Nitroglycerin 2.5 mg in a capsule (orally) is not effective compared with 0.3 mg administered in a tablet sublingually (Blumenthal et al., 1977).

These drugs are subject to considerable presystemic elimination following oral administration and they are not effective unless relatively high doses are given.

A plasma concentration profile similar to that following high-dose oral administration is achieved with nitroglycerin applied in an ointment (Blumenthal et al., 1977). Also, satisfactory results for continuous treatment have been shown following buccal administration of nitroglycerin in a sustained-release tablet (Greengart et al., 1983). Reduction in angina pectoris and increase in exercise duration occurred for more than 5 h.

In summary, it would appear that sublingual and buccal administration of nitroglycerin and isosorbide-dinitrate are effective in the acute treatment of angina pectoris. However, this route is probably less effective and acceptable in maintenance therapy, since the patient is required to take sublingual or buccal preparations frequently and maintain them in situ. Oral administration is to preferred in mainte-
nance treatment with sustained-release dose forms, but a major disadvantage of this route is the very substantial presystemic elimination. It seems, however, that the metabolites of both compounds also have some pharmacological activity and are longer-acting (Stauch, Grewe and Nissen, 1975). For a detailed description of the pharmacological properties and therapeutic use of both drugs, the reader is referred to the recent review of Elkayam and Aronow (1982).

Nifedipine. Nifedipine is a calcium entry blocker used in the treatment of certain types of angina pectoris and in hypertension. Following sublingual administration of a 10-mg tablet it was shown to produce dilatation of the forearm vessels (Robinson, Dobbs and Kelsey, 1980). The antihypertensive effect after sublingual administration of a 10-mg tablet to patients (three women and four men) with essential hypertension was found to last approximately 3 h, while the onset of action was rapid. Peak concentrations were achieved within 1 h (Thibonnier, Bonnet and Carvol, 1980).

Propranolol. The buccal absorption of propranolol has been studied in two male volunteers by Henry and colleagues (1980). They measured the decrease in propranolol concentrations of a 20-ml solution introduced and maintained in the buccal cavity. Recovery was found to be dependent on pH (variation of 5.2–9.2) of the solution and varied from 55.6 to 18.9% respectively. With a variation in residence time of 1–15 min there was an accompanying variation in recovery time of 58.0–36.3%. In a similar study, Ohashi and Turner (1979) found that the pH-dependent absorption of propranolol from the buccal mucosa was 80%.

Narcotic analgesic drugs

Buprenorphine. Buprenorphine is a long-acting narcotic analgesic, which exhibits a substantial first-pass effect following oral administration, resulting in large inter-individual variations in systemic availability (Bullingham et al., 1981). Following sublingual administration of buprenorphine in tablets to 15 patients undergoing total hip replacement, the initial rate of absorption was fast, but subsequently diminished. Relatively low, but effective plasma concentrations were reached within 3 h (Bullingham et al., 1981). The times of peak plasma concentrations differed considerably (20 min–3 h) and the mean absolute systemic availability up to 3 h was 31%.

Edge, Cooper and Morgan (1979) also found that buprenorphine was effective in sublingual administration for the treatment of acute pain. The analgesic onset time, duration of action and extent of individual variation are not measurably different when buprenorphine is given either sublingually or parenterally for postoperative pain (McQuay et al., 1980). The duration of analgesia is approximately 9 h following a sublingual tablet (0.4 mg), which is comparable to that achieved by parenteral administration of 0.3 mg (Bullingham et al., 1981). In a follow-up study Bullingham and colleagues (1982) measured plasma buprenorphine concentrations over a period of 10 h after administration. The mean peak concentration occurred at 200 min (90–360 min) following doses of 0.4 and 0.8 mg sublingually (tablets, see fig. 7). The ratio of the systemic availabilities of the 0.8-mg group to the 0.4-mg group was 1.8:1, while the absolute systemic availability was 55% for both groups. The uptake from the sublingual site did not increase after 5 h.

In summary, while buprenorphine may be administered sublingually in the treatment of pain, the rate of absorption is relatively slow (in comparison with injection); therefore in acute situations the sublingual route may not be so effective. In contrast, for maintenance therapy administration by the sublingual route seems to provide satisfactory results for treatment of pain (Bullingham et al., 1981, 1982).

Phenazocine. Brown (1966) studied the buccal absorption of phenazocine and found that a dose of 5 mg (tablet) was as effective as 2 mg given i.m. to patients with pain after operation, while the results were considerably better than those with the oral preparation. In addition it was suggested that doses of 10 and 20 mg sublingually given two or three times in 24 h could maintain good analgesia in patients with carcinoma and severe intractable pain over 24 h. This could not be obtained with oral administration of the drug (Brown, 1966).

Hormones

Oestrogens and methyltestosterone. Burnier and colleagues (1981) studied the sublingual absorption of micronized 17β-estradiol (E2, tablet 0.5 mg) in 10 postmenopausal women. With a single dose, a 26-fold increase in serum E2 occurred and a nine-fold
increase in serum estrone (E1) compared with endogenous concentrations. Concentrations of follicle stimulating hormone (FSH) and luteinizing hormone (LH) decreased significantly within 6 h. With a dose of 0.5 mg alternate nights, increased circulating concentrations of oestrogens were obtained.

Rapid absorption of a sublingual dose (micronized E2 2 mg) was found in hypogonadal women and those with a normal cycle (Casper and Yen, 1981). A nine to 41-fold increase in basal E2 serum concentrations was observed within 30 min. Because E1 was the predominant circulating oestrogen it was concluded that the sublingual route is not ideal for E2 replacement.

Methyltestosterone is well absorbed sublingually (Alkaly and colleagues, 1973). The systemic availability of methyltestosterone following oral doses of 25 mg and 10 mg (tablets) and sublingual doses of 10 mg and 5 mg (linguets) relative to an oral solution were 0.90, 0.95, 1.42 and 1.63 (corrected for dose differences) respectively. The higher bioavailability with the sublingual route probably results from avoidance of liver metabolism.

**Vasopressin analogues.** It has been shown that analogues of vasopressin produce adequate therapeutic effects when administered sublingually as tablets (3 x 30 μg day⁻¹). Greater doses were needed than those with the intranasal route of administration (Laczi et al., 1980).

**Oxytocin.** Buccal administration of oxytocin from linguets has been used for the induction of labour (Miller, 1974). Induction was successful in 84% of patients. The doses ranged from 200 to 800 units with 26 patients responding to 1000 units of less. In most instances labour was induced in less than 7 h. Although this method is simple and convenient, a major complication seems to be an increased occurrence of postpartum haemorrhage.

**Other drugs**

**Ergotamine.** The absorption of ergotamine across the buccal mucosa appears to be a passive process, pH-dependent, but independent of ergotamine concentrations and not influenced by simultaneous administration of caffeine. As a result of the low aqueous solubility of ergotamine it is unlikely that therapeutic amounts of the drug are absorbed across the buccal mucosa (Sutherland et al., 1974).
CONCLUSION

Although the rectal and sublingual routes are not used frequently for administration of drugs, both routes may serve as alternatives to oral and parenteral administration. Each route has different limitations which decrease general applicability for drug administration.

The disadvantages of the rectal route include interruption of absorption by defaecation and lack of patient acceptability. The mechanism of drug absorption from the rectum is probably similar to that from the small intestine, despite considerable differences in physiological conditions (e.g. pH, fluid content). Absorption may be extremely fast with solutions. The rectal route is suitable for short-and long-term drug delivery and it is possible partly to avoid hepatic first-pass elimination.

The sublingual and buccal routes of administration are useful when fast action is desired with potent drugs. In addition, first-pass elimination (gut-lumen, gut-wall and hepatic) is avoided. Prolonged residence in the mouth can limit usefulness because of patient intolerance, and for long-term drug administration this route is not convenient when conventional formulations are used.

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SUBLINGUAL AND RECTAL ABSORPTION


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