Series on nursing pharmacology and medicine management

Part 3:

Drug dosage forms and the routes of drug administration

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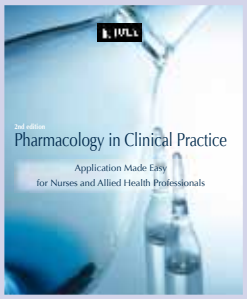
Abstract

In this, the third in a series of articles on practice-related aspects of pharmacology, drug therapy, and applied nursing pharmacology, we focus on the role of the nursing practitioner in administering prescribed medication to patients in their care. Specific emphasis is placed on different dosage forms, as well as the more commonly encountered routes of drug administration. This series uses excerpts and diagrams with permission from the 2nd edition of *Pharmacology in Clinical Practice: Application Made Easy for Nurses and Allied Health Professionals,* and is compiled and expanded upon by the author.



Introduction

As explained in part 1 of this series, in pharmacotherapy an important aspect of the interaction between nursing practitioners and their patients is the administration of prescribed medication. This includes preparing medicines for administration and monitoring the response to therapy, including the effects and possible adverse reactions. Nursing practitioners need to understand what the prescriber is aiming to achieve with the treatment, what the medication may do to the patient, and how it should be administered for optimal effect.[1]

There are several different routes of drug (medication) administration, and a wide variety of dosage formulations to suit each one of them. Therefore, nursing practitioners should have an understanding of the applied pharmacological principles that underlie the safe and effective administration of medication.

Dosage formulations

Drugs usually require specially formulated preparation to make them suitable for administration to the human body. This process usually involves the addition of inactive substances that are required to make up a dosage form, such as a tablet, capsule, mixture, emulsion or suppository. While a drug will be the active pharmaceutical ingredient (API) of a medicine, the inactive substances added are known as excipients. Excipients may be used as preservatives, flavourings, colorants, antioxidants, thickeners, emulsifiers, etc. Table I shows examples of commonly encountered dosage forms in clinical practice.[2]

Table I: Examples of commonly encountered dosage forms in clinical practice[2]

Aerosols	Pastes
Capsules	Pessaries (vaginal suppositories)
Creams	Powders
Elixirs	Skin patches for transdermal administration
Emulsions	Solutions
Gels	Sponges impregnated with drugs
Granules	Suppositories
Lotions	Suspensions
Mixtures	Syrups
Ointments	Tablets
Ophthalmic and aural preparations	Volatile liquids and gases
Parenteral preparations for injection	

A few notes on drug disposition in the body

The effective administration of a specific dosage form is dependent on a number of different factors:[3-6]

- The severity of the patient's condition determines the *urgency* with which the onset of action is required.

E.g. should a rapid onset of action be desired the intravenous route may be selected.

- The *nature* of the dosage form, since the preferred drug for a given symptom or condition may only be available is a specific dosage form, thus, requiring a route of administration that suits the formulation (e.g. a parenteral drug formulation that is only suited to intramuscular injection). The pharmacokinetic profile of a specific drug will usually determine the number of available options in terms of drug delivery systems and dosage forms. E.g. a very high rate of presystemic elimination with poor bioavailability, acid lability or physicochemical characteristics that do not allow for effective absorption from the gastrointestinal tract (GIT), could preclude the use of oral formulations.
- The *pathophysiological processes* that underlie the patient's symptoms or condition, and which may alter the patient's ability to respond to the treatment, as well as to absorb, distribute, metabolise and excrete the drug. The pharmacodynamic and pharmacokinetic profile of the drug may be altered due to illness, or any other relevant anomaly in body physiology. A patient suffering from severe nausea and vomiting may not be able to retain and absorb any orally-administered drug formulation. Similarly, diarrhoea may preclude the rectal route of drug administration, while extensive burn wound trauma will exclude the intramuscular route of drug administration.
- The *proficiency* with which the drug is prepared and administered to the patient, in addition to the suitability of the handling and storage conditions prior to being dispensed and subsequently administered to the patient. It is of vital importance that the medication is handled and stored in accordance with the manufacturer's specifications as well as good dispensing practices, in keeping with the Good Pharmacy Practice requirements.[7] Furthermore, the nursing practitioner who prepares and administers the medication to the patient will need to ensure that this procedure is executed in a safe, proper and professional manner.
- The patient's *ability* to accept or comply with a particular route of drug administration, which may be linked to one or more of the aforementioned factors, or be an independent factor to consider. E.g. the patient may be unable to swallow tablets whole (which is especially relevant in the case of tablets, such as enteric-coated ones, that cannot be broken or crushed), or may be unable to receive any type of oral drug formulation owing to being unconscious, or simply be unwilling to use a rectal suppository.

Absorption

Drug absorption is the movement of drug molecules from their site of administration into the bloodstream. The sites or routes that allow actual systemic administration of the active drug are the transdermal, subcutaneous, intramuscular, enteric and transpulmonary routes. The intravenous route is not included here since it does not require the process of absorption to take place, because drugs are injected directly into the bloodstream (Figure 1).[3-6]

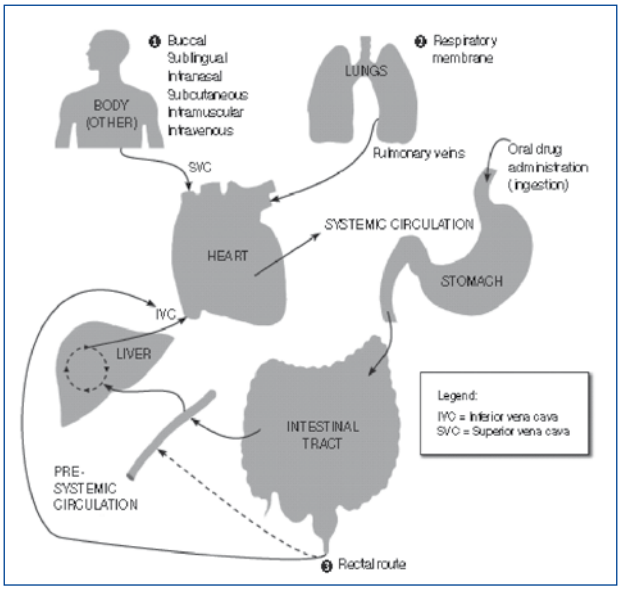


Figure 1: Routes of drug administration that bypass the "first-pass" effect (i.e. hepatic first-pass metabolism)

Therefore, the drug molecules will need to cross a number of biological barriers or membranes, i.e. mucosal layers, capillary endothelia or more specialised physiological barriers. Thus, the more readily the drug molecules cross these membranes or barriers, the better the drug is absorbed (Figure 2).[3-6]

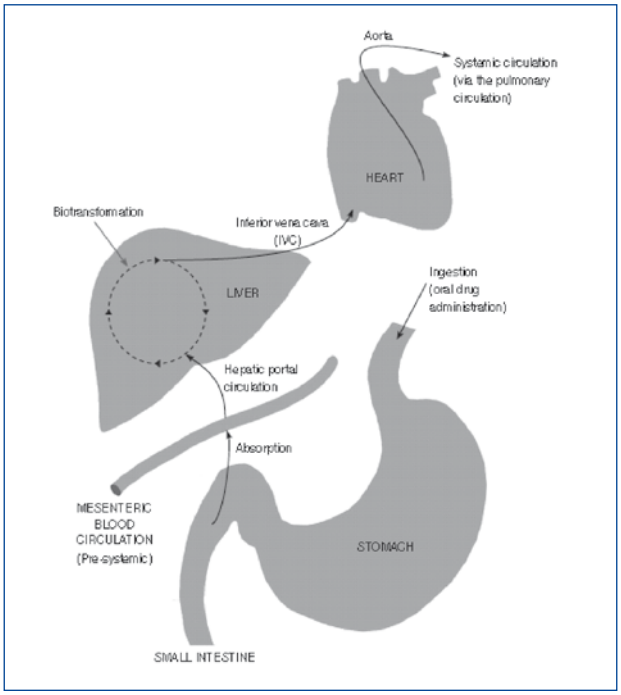


Figure 2: The pathway of drug absorption, from the gastrointestinal tract to the systemic blood circulation

Systemic bioavailability

Only a fraction of a drug dosage will actually reach systemic circulation after oral administration. One reason is that not all of the drug molecules are in fact absorbed from the GIT, as a result of the pharmaceutical characteristics of their dosage form, their molecular size, degree of ionisation and lipid solubility, the quality of mesenteric blood flow, etc. Another important factor is the biotransformation of the drug molecules on their first pass through the liver. The liver may eliminate a significant percentage of the drug molecules before they reach the inferior vena cava. On subsequent passes through the liver, smaller fractions of the absorbed drug will be biotransformed (Figure 2).[3-6]

The systemic bioavailability of a drug is the fraction (*F*) or percentage of the orally administered dosage that actually reaches the systemic blood circulation. For intravenous injections, where absorption does not need to take place at all and the entire dosage is delivered into the circulation, the bioavailability is 100% (i.e. $F = 1.0$). Other routes of drug administration are associated with fractions of less than 1.0. [3-6]

Distribution

Distribution is the second of the four kinetic processes, i.e. absorption, distribution, metabolism and excretion, or "ADME". Once drug molecules reach the systemic blood circulation they are transported to other parts of the body. At capillary level these molecules leave the bloodstream to enter the other fluid compartments of the body. However, the bloodstream transports drug molecules not only to their sites of action (or target areas) but also to their sites of elimination. Drug distribution is the movement of drug molecules from the circulation. Drug molecules are transported either in their free form or bound to plasma proteins. Molecules in their free form are pharmacologically active and able to cross membranes.[3-6]

Almost all drugs are partially bound to plasma proteins, some to a lesser and some to a greater extent, while being transported by the bloodstream. Molecules that are plasma-protein bound are pharmacologically inactive and cannot exit the circulation without being "released" from their bonds first. Certain drugs may compete for binding sites on the same plasma proteins. Warfarin is a good example of a drug that is almost entirely plasma-protein bound (up to 98%).[3-6]

Drug molecules are not distributed in equal quantities to all tissues and organs around the body. Rather, those organs that receive larger percentages of the total cardiac output will initially receive larger percentages of the absorbed drug dosages as follows:[3-6]

- The lungs receive 100% of the right ventricle output.
- At rest, 80% of the left ventricle output is distributed among organs that are particularly vascular (blood-vessel rich). These are the brain, myocardium, adrenal glands, thyroid gland, liver and kidneys. The kidneys receive 25% of the entire left ventricle output.
- During the later stages of pregnancy the uterus and placenta may be included in the list above.
- Distribution to other tissues occurs in the following order: skeletal muscle tissue, then skin and adipose tissue and finally the avascular structures (lacking blood vessels) such as ligaments, tendons and cartilage.

The extent of a drug's distribution in the body may be expressed as the drug's apparent volume of distribution (V_d). This is the volume into which the specific drug dosage will need to be dissolved for it to reach the same concentration as it does in the plasma. Drugs that penetrate the intracellular fluid compartment therefore have larger apparent volumes of distribution, whereas drugs that are largely plasma-protein bound exhibit much smaller volumes of distribution.[3-6]

Routes of drug administration

Drugs are usually either administered systemically or applied topically. Various routes may be used for the systemic administration, the most convenient and acceptable of these being the oral route. Topical delivery of drugs is their application to specific body surface areas, where they exert localised effects. For instance, a cream or lotion, may be applied to the skin, or an ophthalmic preparation instilled into the eye. These drugs do not require absorption into the systemic blood circulation to be effective.[3-6]

However, systemic drugs need to be administered in a way that allows them to be absorbed into the systemic blood circulation (as explained in the previous section). This will provide them with an effective "carrier" that will transport their molecules to target areas around the body. Some drugs do not require such transport if they may be administered directly to their target areas. The bronchodilator salbutamol, for example, may be inhaled directly into the lower respiratory tract. The respiratory membrane of the lungs will also allow absorption into the pulmonary circulation, but its primary site of action will be the bronchial smooth muscle itself.[3,5,6]

Many different routes of drug administration are used in clinical practice. The various routes all have their indications, advantages and disadvantages. Table II lists the routes of drug administration most often encountered in clinical practice.

Other areas into which drugs may be injected include the vitreous humour of the eye (i.e. intravitreal injection),

Table II: Routes of drug administration[3]

Aural (into the ear) Buccal (applied to the inside of the cheek, between cheek and gums) Intra-arterial (into an artery) Intra-articular (into a joint space) Intracutaneous (intradermal, into the skin) Inhalation (into the lower airway) Intramuscular (injection into skeletal muscle tissue) Intraosseous (into the bone marrow cavity) Intrathecal (into the spinal canal) Intravenous (into a vein)	Nasal (into the nose/nasal passages) Ocular (into the eye) Oral (per mouth) Per rectum (into the rectum) Per vaginam (into the vagina) Subcutaneous (hypodermic, i.e. just beneath the skin) Sublingual (placed under the tongue) Topical (applied to surface areas, e.g. the skin or the surface of a wound) Transdermal (applied to the skin for systemic absorption through it)

cutaneous and subcutaneous lesions, nerve tissue and the left ventricle of the heart (intracardiac injection). The last-named, previously reserved for the emergency cardiac resuscitation drug adrenaline, is no longer considered to be an acceptable, safe and effective route for drug delivery into the systemic circulation. During epidural anaesthesia the local anaesthetic agent is injected into the epidural space (a potential space that allows for injection of the drug onto the dura mater).[3,5,6]

Note that certain routes of drug administration, such as the epidural, intra-articular, intrathecal, intra-arterial, intravitreal and intraosseous routes, as well as injections into lesions and nerve tissue, should only be reserved for specialist intervention by an appropriately qualified healthcare practitioner.

The oral route (per mouth, per os, PO)

The kinetic process of absorption is best introduced by using the oral route of administration as an example. The oral route is generally considered to be the most convenient and acceptable way of administering medication, since swallowing is the natural way of ingesting food and drink. Most laypersons also do not require the assistance of a healthcare professional when taking medicines per mouth.[3-6]

Once the drug has been ingested, a number of processes and events determine the actual absorption of the drug molecules into the bloodstream:[3-6]

- Oral drug formulations (oral dosage forms) are designed to allow the active drug to dissolve in the lumen of the GIT. Most of these dosage forms will disintegrate and dissolve inside the stomach, unless they have been specifically formulated to disintegrate and dissolve further down in the alimentary canal. Enteric-coated tablets are designed to dissolve in the alkaline environment of the small intestine instead of the acidic environment of the stomach itself. Liquid dosage forms are the best absorbed oral formulations.
- The stomach cannot be regarded as an absorptive organ but may allow some of the dissolved drug molecules to enter into the bloodstream. The small intestine with its vast absorptive surface, is the primary site of the absorption of drugs that have been orally administered.
- Having been absorbed from the stomach and small intestine, drug molecules will have to cross a series of biological membranes and barriers to reach the hepatic portal circulation.
- Blood entering the portal circulation moves through, in order, the portal vein, liver, inferior vena cava, the right side of the heart, the pulmonary circulation and left side of the heart before finally entering the systemic circulation, from where the absorbed drug molecules will be distributed to other parts of the body (Figure 2).

Movement of drug molecules from their absorption site in the GIT through the hepatic portal circulation is referred to as their "first pass" through the liver. This first pass produces the so-called first-pass effect, or presystemic elimination of certain drugs. Figure 2 gives a diagrammatic representation of the relationship between the hepatic portal circulation and drug absorption. Under normal circumstances gastric emptying may take up to four hours, and transit time through the small intestine may take another six hours to complete.[3-6]

Rectal route (per rectum, PR)

Indications for using this relatively unpopular and uncomfortable route of administration include unconsciousness, nausea and vomiting, febrile (feverish) and convulsive states and other situations where the danger of aspiration exists, or where oral administration is undesirable owing to gastric irritation, dysphagia and other clinical problems. The active drug is formulated into a rectal suppository, or may be available as a rectal enema.[3-6]

The absorptive surface of the rectum is small, due to the absence of intestinal villi, which explains the relatively slow rate of absorption. Anatomically, venous blood from the distal portion of the rectum is drained by the inferior and middle rectal veins, while blood from the proximal rectum drains into the hepatic portal system via the superior rectal vein. The inferior and middle rectal veins directly enter the inferior vena cava via the hypogastric vein, effectively bypassing the hepatic portal system. There is a rich anastomosis system between the three rectal veins, making this an important area of portacaval anastomosis (one of the sites where the hepatic portal circulation may be significantly bypassed), and is therefore of clinical significance (Figure 1).[3-6]

Diazepam and metronidazole are absorbed particularly well from the rectal mucosa. Many antipyretics, anti-inflammatory drugs, antiemetics and anticonvulsive drugs, and also the nonselective bronchodilator aminophylline, are available as rectal suppository formulations. Suppositories should be carefully inserted into the distal rectum, just above the internal anal sphincter and the anorectal ring.[3-6]

Buccal and sublingual (SL) routes

The mucous membranes of the oral cavity have a very rich blood supply, thus providing a highly vascular absorptive surface. Lipid-soluble drugs may be rapidly absorbed directly into the systemic circulation, since venous return to the heart is via the superior vena cava, thus bypassing the hepatic portal circulation (see Figure 1).[3-6]

Buccal administration implies spraying or placing the drug formulation between the cheek and gums. For sublingual drug administration, the formulation is placed under the tongue. Drugs administered via these routes need to be soluble in saliva and should be active in very small concentrations. The sublingual route is popular for the administration of glyceryl trinitrate during attacks of angina pectoris or in the event of acute myocardial infarction. Certain tablets may also be allowed to dissolve sublingually after they have been chewed.[3-6]

Other mucous membranes used for drug absorbtion

Nasal mucous membranes are relatively inefficient as absorptive surfaces for drug molecules, since large percentages of the applied dosages often go to waste. However, the nasal mucous membrane provides an effective and convenient route of administration for small peptide molecules such as desmopressin, a synthetic analogue of vasopressin (i.e. antidiuretic hormone) used in the treatment of diabetes insipidus. Nasal preparations, used for their localised effects in allergic rhinitis and sinusitis, are also sprayed into the nasal passages via the nostrils (Figure 1).[3-6]

The respiratory membrane (the combined alveolar and capillary membranes) measures approximately 0.5 μm in thickness, making it almost 100 times thinner than the skin. Per minute, the pulmonary circulation receives cardiac output equivalent to the entire output received by the rest of the body. In total surface area, the alveolar surface of the lungs, which is in the region of 160 to 200 m^2, is comparable to that of the small intestine. The respiratory membrane forms the functional air-blood barrier between the pulmonary circulation and the atmospheric air that enters and exits the respiratory units of the lungs. The respiratory gases (oxygen and carbon dioxide) diffuse through this barrier.[3-6]

The combination of the thin respiratory membrane, the vast alveolar surface area and the good pulmonary blood supply makes the pulmonary mucous membranes exceptionally good absorptive surfaces. The emergency cardiac resuscitation drugs adrenaline, atropine and lignocaine may therefore be administered via endotracheal tubes, utilising the massive alveolar surface area for absorption into the systemic circulation. Drugs that act on the lung tissue itself may also be administered directly into their site of action. In premature infants surfactant is administered via the same route. For optimum utilisation of this route of administration the drug particles need to be small enough to remain suspended as they pass through the lower airway (Figure 1).[3-6]

Injectable drugs

Intravenous (IV) injection

Injecting drugs into the peripheral veins of the upper extremities, or through central venous catheters that provide direct entry into the pulmonary and systemic circulation via the superior vena cava, obviates the need for drug absorption altogether. It is very useful for drugs that have short elimination half-lives and those that require very careful titration of their dosages, therefore necessitating continuous intravenous infusions. This route also provides the best possible control over the dosage being administered to the patient. When tissue absorption is compromised in any way (e.g. in burn trauma victims, hypovolaemic patients and patients in severe cardiac failure), or when a patient's condition necessitates an immediate response, this route of administration is extremely useful. It takes less than a minute (as little as 20 seconds when cardiac functioning is optimal) for the administered dosage to mix sufficiently with the circulating blood volume (Figure 1).[3-6]

Intramuscular (IM) and subcutaneous injection (SC)

These routes utilise blood supply to subcutaneous adipose and skeletal muscle tissue for the absorption of drug molecules. Because skeletal muscle tissue receives more blood supply than subcutaneous fat does, absorption via the intramuscular route is more rapid than absorption after subcutaneous injection. Depot formulations may be injected into muscle to extend the duration of the drug action over hours, days or weeks. Severe vasoconstriction or hypoperfusion will delay the absorption of drug molecules from these tissues. [3-6]

Other injectable routes

- *Intradermal (intracutaneous) injection:* The injected volume must be very small (less that 0.2 ml) and is administered into the skin.

- *Intra-articular injection:* Joint spaces may be injected with drugs for a localised effect in arthritic conditions.
- *Intra-arterial injection:* When the localised effect of a drug is wanted in a specific organ only, the drug may be injected into the supplying artery. Antineoplastic or chemotherapeutic agents are sometimes administered this way.
- *Intrathecal injection:* Drugs may be injected directly into the subarachnoid space to bypass the blood-brain barrier, i.e. the specialised barrier that separates the extracellular fluid of the brain and cerebrospinal fluid compartments from the intravascular compartment.[3-6]

The transdermal route

The drug is applied to the skin for absorption into the circulation. A transdermal patch is usually attached behind the pinna of the ear or in a comfortable position on the trunk. Note that the postauricular skin (behind the ear) is much more permeable (up to ten times as much) than that of the thigh or trunk.[3-6]

Topical administration

Drugs may be applied to body surfaces to exert localised effects in the area of application only. Aural preparations may be administered into the external auditory canal of the ear, or ocular preparations instilled into the eye. Other examples include preparations for application to the skin (e.g. creams and lotions for sunburn), the nose (e.g. vasoconstrictors for rhinitis), the mouth (e.g. an antiseptic mouthwash for stomatitis), the throat (e.g. lozenges that contain local anaesthetic agents to alleviate a sore throat), the vagina (e.g. antifungal preparations for vaginal thrush) and the anorectal area (e.g. haemorrhoid preparations).[3-6]

Conclusion

The nursing practitioner should be aware of the importance of the applied pharmacological principles to enable them to administer medication safely and effectively to the patients in their care. Many different routes of drug administration are used in clinical practice. The various routes all have their indications, advantages and disadvantages. Special circumstances and unique situations may determine which route is the most suitable for a certain patient at any given time.

Part 4 of this series will consider some of the practical aspects pertaining to drug administration in the ward or healthcare unit, including the timing of dosages, drug interactions, adverse drug reactions and the impact of ward routine.

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