Chapter 8
Pharmaceutical Aspects of Drugs

Pauline Siew Mei Lai

Abstract Drugs can be obtained from many sources such as plants, animals, minerals or microorganisms. However, most drugs are synthetically produced in the laboratory, as they can be produced on a larger scale, in a more cost effective manner and be of higher quality. It is important to know the sources of drugs as patients can develop hypersensitivity reactions to certain drug source. Some patients (based on their religious beliefs) also prefer not to use drugs obtained from bovine or porcine sources. Drug development and trials in animals and humans is a long and costly process. This process is essential to determine that the new drug is safe for human consumption. Drugs should be packaged in a manner that protects the active ingredient from deterioration due to external factors. Drugs should also be labeled with sufficient information to enable the determination of the exact content of the active ingredient, its storage conditions and manufacturing details.

Keywords Drug sources • Drug development • Clinical trial • Packaging • Labelling

Introduction

Drugs can be obtained from many sources, such as plants, animals, and minerals. Today, most drugs are synthetically manufactured in laboratories, or produced by microorganisms. Most drugs have undergone several years in the developmental stages where intensive research, drug trials and safety testing on them had been done on the generic form. After they have been cleared for human consumption through all these testing and post testing surveillance, the company that has invested in the research would commission for its production and registration with national and international drug registries. Drugs as it is available to the patients are also packaged in such a way that the original drug is protected from the many agents that can contribute to its deterioration.

P.S.M. Lai, B.Pharm., Ph.D. (✉)
Department of Primary Care Medicine, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia
e-mail: plai@ummce.edu.my

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Sources of Drugs

Plants as Sources of Drugs

Plants have been used as drugs as far back as 2700 B.C. Drugs can be sourced from most parts of a plant. Atropine and caffeine are obtained from leaves; castor oil and strychnine are extracted from seeds; hyoscine and quinine are extracted from barks; morphine and vincristine are extracted from flowers; ipecacuanha and reserpine are extracted from roots; tubocurarine is extracted from stems; and anthracene and physostigmine are extracted from fruits.

Today, plants are no longer used in the raw form. Instead, their active ingredients are extracted and identified for its pharmacodynamics and pharmacokinetic properties. This is performed to ensure that a precise and constant dosage is available for therapeutic use. Scientists will also look into the possibility of chemical synthesis for sustainability. Active ingredients obtained from plants can be grouped according to their physiochemical properties.

Alkaloids

An alkaloid is defined as a "basic nitrogenous compound of plant origin which produces salt when combined with acid, and is physiologically active in the plant and animal". Alkaloids are a white crystalline substance, bitter and insoluble in water. Its salt preparation however, is highly soluble in water. Alkaloids can be classified according to their plant source. For example: belladonna (atropine), cinchona (quinine), cocaine, ergot (ergotamine), opium (morphine), rauwolfia (reserpine), vinca (vincristine), and xanthine (caffeine). Names of alkaloids end in ". . .ine".

Glycosides

Glycosides are non-nitrogenous, colorless, crystalline solids. They can be split into sugar and non-sugar parts with the addition of an acid or enzyme. They do not form salts. Some glycosides are poisonous. The non-sugar part of glycosides (called aglycone) is responsible for its pharmacological activity. Chemically, they are similar to bile acid, sterol and steroid hormones. When sugar is combined with aglycone, the lipid/water partition coefficient, potency, and pharmacokinetic properties are modified. Glycosides can be classified as glucoside, galactoside, fructoside according to the presence of these sugars. Glycosides are found in the bark, seed and leaf of a plant. An example is Digoxin, which can be isolated from the leaves of the purple foxgloves, Digitalis purpurea.

Oils

Fixed oils are a mixture of glycerol esters (such as palmitic, stearic, and oleic acid). They are not volatile, are lighter than water, are insoluble in water, but are soluble in chloroform and ether. They are not dissipated by heat. Olive oil and castor oil are examples of fixed oils. Metabolites of castor oil irritate the mucosa of the gastrointestinal tract, which promotes peristalsis and gut evacuation. Olive oil is edible. It can also be used as an emollient.

Volatile oils are the odorous part of a plant. They are sometimes called essential oils, as they represent the essence of a plant. When fresh, volatile oils are colorless. When exposed to the environment, they turn dark. They can evaporate. They can also be oxidized and resinified. Hence, volatile oils should be stored in a cool, dry place, tightly closed in an amber glass container. Peppermint oil and spearmint oil are examples of volatile oils. Menthol is the active ingredient of peppermint oil. These oils are used as solvents and flavors in the compounding of preparations.

Gums and Mucilage

Gum is a secretory hydrocarbon product which originates from plants. When hydrolysed, it produces sugar. Gum dissolves in water easily, whilst mucilage forms a slimy mass. Agar is an example of gum. When swallowed, gum absorbs water to form bulk, thereby exerting its laxative effect. Tragacanth is an example of mucilage. It is most commonly used as a suspending agent for insoluble powder in mixtures, an emulsifying agent for oil and resin, or as an adhesive.

Carbohydrate and Related Compounds

Sucrose is used as a demulcent and nutrient. Concentration of sucrose of more than 65 % is bacteriostatic and acts as a preservative. Dextrose is a nutrient, which may be given orally or intravenously. Fructose is used in food, particularly for patients with diabetes. Alcohol at 70 % concentration is used as an antiseptic.

Animals as Sources of Drugs

Insulin was initially extracted from the pancreas of cows (bovine) or pigs (porcine). Heparin is extracted from porcine intestinal mucosa or bovine lung. Human menopausal gonadotropins are isolated from the urine of postmenopausal women. However, animals as sources of drugs are frequently associated with hypersensitivity reactions. Some patients may also prefer not to have drugs obtained from porcine or bovine sources.

Minerals as Sources of Drugs

Clay, kaolin and activated charcoal are used for diarrhea. Iodine is used for the treatment of goiter. Gold is used for arthritis. Externally, sulfur is used for treating skin diseases. Most antacids contain aluminum hydroxide and magnesium trisilicate. To relieve constipation and to control eclamptic seizures, magnesium sulphate can be used.

Laboratory as Sources of Drugs

Today, most drugs are artificially synthesized as it is safer, and more effective than extracting drugs from plants or animals. Drugs produced in laboratories are of high quality and less expensive. They can be produced on a large scale within a short period of time. Examples are digoxin and insulin.

Microorganisms as Sources of Drugs

Drugs produced by microorganisms include amphotericin and chloramphenicol.

Clinical Correlation – Implications of Sources of Drugs

Some drugs (especially those sourced from animals) are frequently associated with hypersensitivity reactions. Before administering the drug, it is necessary to ascertain that the patient does not have any allergy to animal sources. Viper venom antiserum for example, is produced in horses (equine).

For religious reasons, some patients may also prefer not to have a drug from a porcine (relevant for Muslims patients) or bovine (relevant for Hindu patients) source. Alternative drug sources will need to be found for these patients.

Drug Development

Drug development is defined as the process of bringing a new drug to the market once a compound has been identified as potentially being able to impact a particular physiological/pharmacological process in the body. There are two phases to drug development.

The Pre-clinical Phase

Compounds that emerge from the process of drug discovery are called new chemical entities (NCEs). They will have some promising activity against a biological target, in a certain disease. However, little is known about the safety, toxicity, pharmacokinetics and metabolism of this compound in humans. Hence, these parameters will need to be assessed prior to human clinical trials. The dose and frequency of dosing will also need to be determined. The physicochemical properties of this new chemical entity (its chemical makeup, stability, solubility) will need to be established. Production on a large scale to different pharmaceutical formulations (known as chemistry, manufacturing and control [CMC]) will also need to be performed.

Many aspects of drug development are to satisfy regulatory requirements of drug licensing authorities to ensure safety. A number of tests need to be conducted to determine major organ toxicities of the new compound prior to its use in humans. Some tests can be performed using in vitro methods. However, many tests still require the use of experimental animals, to examine the complex interplay of metabolism and effects of exposure to toxicity.

Information obtained from the pre-clinical phase and CMC is submitted to regulatory authorities as an Investigational New Drug (IND) application. If the new drug is approved, development moves to the clinical phase assessing the efficacy and safety of the drug.

Clinical Phase

The process of drug development continues even in human clinical trials (Table 8.1). Long-term or chronic toxicities are determined, as well as its effects on fertility, reproduction and other systems, and its cancer causing effects if any. If the compound has an acceptable toxicity and safety profile, and the desired effect

Table 8.1 The various phases of drug trials through human subjects

Phase of drug trial	What is being done
Phase I trials	Conducted in healthy volunteers, to determine safety and dosing
Phase II trials	Used to get an initial reading of efficacy and further explore safety in a small numbers of sick patients
Phase III trials	Large, pivotal trials to determine the safety and efficacy in patients
Phase IV trials (optional)	Post-market surveillance studies, to assess the safety and efficacy of the drug after its release to the market

in clinical trials, it will be submitted for marketing approval. The drug then becomes ready for registration and distribution to pharmacies. However, most new compounds fail these tests. The success rate for a new chemical entity to successfully complete Phase I-III clinical trials to the point of registration is low.

Drug Packaging

Packaging is defined as the "collection of different components which surround the pharmaceutical product from the time of production until its use". The quality of the packaging of the pharmaceutical products plays an important role. It must

1. Protect against all adverse external influences that can alter the properties of the product (moisture, light, oxygen and temperature variations)
2. Protect against biological contamination
3. Protect against physical damage
4. Have the correct information and identification of the product

The packaging of materials used must be chosen so that the packaging does not have an adverse effect on the product and vice versa. Written labels on the packaging must include the following information: the international non-proprietary name (INN) of the active ingredient, the dosage form and trade name, information on storage and the batch number. Packaging and labeling allows compliance with the Code of Good Manufacturing Practice.

Clinical Correlation – Importance of Proper Storage Conditions for Drugs

Drugs may need special storage conditions to prolong their shelf life and require special packaging.

Co-amoxiclav has two active components: amoxicillin and clavulanic acid. Amoxicillin is sensitive to dehydration, whilst clavulanic acid is sensitive to moisture. An imbalance in dryness or moisture can deactivate one or the other of the active components of the drug, thereby, affecting potency of the components of the drug. The packaging of co-amoxiclav needs to be specially designed to maintain the efficacy of the two active ingredients that require contrasting protective needs. The innovator pharmaceutical company of co-amoxiclav has packed the drug in a desiccated pouch with material that helps maintain just the right amount of moisture ideal for both components during transport and storage.

The generic companies may not consider this fact in their packaging and this may explain the reduced potency of the drug from these companies.

Key Concepts

- Drugs can be obtained from many sources. However, presently, most drugs are manufactured synthetically in laboratories.
- Drug development consists of two phases: preclinical and the clinical phase.
- The preclinical phase determines the physicochemical properties of the compound, possible production to a large scale, and its toxicity profile.
- The clinical phase involves clinical trials on humans to determine its safety profile.
- Packaging should protect against all adverse external influences that can alter the properties of the product, biological contamination and physical damage.
- Packaging should also carry the correct information and identification of the product.

Summary

It is important to know the source of a drug, as animal sources of drugs are frequently associated with hypersensitivity reactions. For religious reasons, some patients may also prefer not to have a drug from a porcine or bovine source. Drug development is a slow and costly process. It takes several years before a new chemical entity passes successfully through all the stages of clinical trials and is registered with the relevant authorities for sale in a country. Good drug packaging is required to protect the drug from the environment, and to protect the environment from the drug. All packaging has to be labeled appropriately according to the Code of Good Manufacturing Practice.

Further Reading

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