AN OVERVIEW OF HOW DRUGS ARE DESIGNED AND DEVELOPED

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ABSTRACT Gallimore, D. (2006) An overview of how drugs are designed and developed. Nursing Times; 102: 47, 30–31. Medications have traditionally come from natural sources. Recent advances in biology and chemistry have revolutionised the way in which drugs are designed and developed. This article discusses drug discovery and the subsequent testing process.

A drug is sometimes defined as a chemical that can affect living processes but this can be true of any substance if administered in large amounts (Aschenbrenner and Venable, 2006). In medicine it is generally accepted that a drug is a chemical that has some therapeutic action for a particular condition (Dawson, 2002). The identification and development of a new drug costs an estimated £950m (Tonkens, 2005). It can take between five and 10 years to develop, and marketed a new drug (Aschenbrenner and Venable, 2006).

TRADITIONAL DRUG DEVELOPMENT

Historically, drugs have been developed from natural sources, such as plants and animals. Elements such as mercury have also been used (Waller et al, 2001). However, other chemicals in the plant may be taken along with the therapeutic chemical and the exact dose can be difficult to measure. It is difficult to develop drugs from natural sources as there has to be local knowledge of which plants or animals can be used to treat specific conditions.

SCIENTIFIC DRUG DEVELOPMENT

Since the 1950s there has been a revolution in drug development (Berkowitz, 2004). It is possible to manufacture new compounds – thought to number in the hundreds of thousands – artificially (Dawson, 2002). The process of testing every chemical used to be laborious but it has since been automated. Despite this, it is an inefficient process that needs a lot of resources and produces only a small number of potentially therapeutic chemicals. Another line of development is the modification of existing drugs to make them more effective, to reduce side-effects and to find easier methods of administration.

RATIONAL DRUG DEVELOPMENT

Rational drug development uses our understanding of the disease process and the way drugs work. It is relatively recent and advanced significantly in the 1980s (Liang, 2002). We now understand that most drugs act primarily by attaching to receptors in the body (Golan, 2004). We also have a more detailed understanding of the disease process in the human body. Identification of the specific causes of diseases and the changes in normal body functioning assist in developing drugs for specific medical conditions. Modern scientific discoveries, such as the sequencing of the human genome, have aided this process.

One way of developing a new drug is to identify the receptors that are important in a specific disease and design a chemical that has the correct shape to bind to it.

DRUGS APPROVAL

The discovery of a potential new drug is only the first stage of the process that results in its use by patients. Mechanisms have been developed to ensure the safety of patients. In the UK the Medicines Act 1968 regulates the use of therapeutic products and is overseen by bodies coordinated by the MHRA (www.mhra.gov.uk). Its role is to evaluate safety, quality and efficacy (Grahame-Smith and Aronson, 2002). The testing process is split into a number of distinct phases: preclinical studies, pre-marketing clinical studies (phase 1–3); and, post-marketing surveillance (phase 4) (Waller et al, 2001) (Box 1).

PRECLINICAL STUDIES

This is the transitional stage between the identification of a new compound and its use on humans. The aim is to identify how the chemical interacts with living tissues, for example, how the drug is absorbed into the body, how it is broken down and what chemicals are produced by this process (Grahame-Smith and Aronson, 2002).

Other important information gleaned is the therapeutic dose and if the chemical has

<table>
<thead>
<tr>
<th>Phase</th>
<th>Main aims/means of investigation</th>
<th>Subjects/average duration</th>
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</thead>
<tbody>
<tr>
<td>Preclinical</td>
<td>Pharmacology, Toxicology</td>
<td>Animals, Laboratory tests, At least 2–3 years</td>
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<tr>
<td>Phase 1</td>
<td>Clinical pharmacology and toxicology, Drug metabolism, Evaluation of safety</td>
<td>Healthy individuals and/or patients, Small numbers (20–80), Approximately one year</td>
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<tr>
<td>Phase 2</td>
<td>Initial treatment studies, Evaluate effectiveness of treatment</td>
<td>Small numbers of patients (usually under 200), Around two years</td>
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<tr>
<td>Phase 3</td>
<td>Large randomised controlled trial, Comparing new to old treatments, Evaluate safety and efficiency</td>
<td>Large numbers of patients (several thousand), Can take 3–5 years</td>
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<td>Phase 4</td>
<td>Post-marketing study, Monitoring of long-term issues, Yellow Card scheme</td>
<td>All patients prescribed the drug, Continuing process</td>
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LEARNING OBJECTIVES

- Understand how the development of new drugs has been influenced by scientific innovations
- Outline the different phases in the testing of a new drug
- Explain the process of drug testing and development
- Recognise the importance of continued monitoring of adverse reactions in new drugs

any toxic effects on living tissue. Most of this is done on cultures of cells and tissue in a laboratory but there is a requirement for testing of new drugs on animals, mainly for screening of toxic reactions and testing the effects on the reproductive system and foetal development (Waller et al, 2001).

PHASE 1 STUDIES

The aim of a phase 1 study is to establish the safety of the drug. Testing is done on between 20 and 80 volunteers (Craig and Stitzel, 2004) – often young, healthy males but sometimes patients with the disease the new drug has been designed to treat.

The initial dose given is generally much lower than that which is thought to have a therapeutic effect. This is increased over time. There is a chance the drug will react unpredictably, such as in the recent trial at Northwick Park hospital (Mayor, 2006).

PHASE 2 STUDIES

These typically involve 30 to several hundred volunteers (Tonkens, 2005). It is the first time the drug is given to patients with the condition it was designed to treat.

PHASE 3 STUDIES

The aim here is to find out how effective the drug is. This is done in large, randomised, controlled trials in a number of countries over several years, costing from £25m to £50m (Tonkens, 2005). Comparisons are often made between patients taking the new drug and a similar looking tablet with no active ingredient (placebo), or a previously well-established medication for the condition (Waller et al, 2001).

The number of participants is much larger than before but small when compared with the total population likely to take the new drug. At the end, it may have been taken by 2,000 to 3,000 people. The number taking the drug for six months or more may only be a few hundred (Katzung, 2004).

PHASE 4 – POST-MARKETING

Following successful phase 3 studies the drug is approved for use but monitoring continues in order to identify side-effects and problems. To identify a one in 10,000 chance of a reaction, the drug would have to be taken by several hundred thousand patients (Katzung, 2004). Most reactions are minor, although in 25 years almost 3% of drugs have been withdrawn due to side-effects found during this phase (Lee, 2006).

The Committee on Safety of Medicines (CSM) can require that adverse reactions are monitored for a specified number of patients (Graham-Smith and Aronson, 2002). There is also a voluntary Yellow Card system in which healthcare professionals and the public can report suspected adverse reactions. The information can be supplied on a postage-prepaid card or online (www.yellowcard.gov.uk).

FUTURE OF DRUG DEVELOPMENT

New approaches are under investigation. Possibly the most interesting is pharmacogenetics, based on the knowledge that not all drugs work equally well in all patients because we have slight variations in our genetic composition. Research is looking at modifying drugs to adapt to the patient's own genetic profile.

GUIDED LEARNING

- Outline your place of work and why you were interested in this article
- Write about the different phases of testing new drugs
- Detail how you would report an adverse drug reaction
- Explain how you intend to disseminate what you have learnt among your colleagues

REFERENCES


