Chapter 7

Principles of Clinical Pharmacology, Randomized Controlled Clinical Trials, and Evidence-Based Medicine in Headache

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The clinical pharmacology of a drug includes both pharmacokinetics—what the body does to the drug—and pharmacodynamics—what the drug does to the body. In this chapter, a brief account of these aspects of clinical pharmacology relevant to migraine and its treatment will be given, which should help the reader to understand the expressions used in later chapters addressing headache therapy. This chapter also includes a section on the evaluation of the quality of the methods and results in randomized controlled clinical trials in migraine in the perspective of the use of evidence-based medicine in clinical practice.

PHARMACOKINETICS

Pharmacokinetics is the aspect of clinical pharmacology dealing with the degree of drug absorption, the time taken to achieve a peak plasma concentration, the degree of binding to plasma proteins, its distribution from plasma to tissue site of action, the extent of its metabolism, and the pattern of excretion. The absorption, distribution, biotransformation, and excretion of a drug all involve its passage across cell membranes (2). Important characteristics of a drug are its molecular size and shape, solubility at the site of its absorption, degree of ionization, and relative lipid solubility of its ionized and nonionized forms.

Absorption

The degree of absorption of a drug depends on its route of administration: oral, sublingual, subcutaneous, rectal, or inhalational. Absorption from the gastrointestinal tract is governed by factors that are generally applicable, such as surface area for absorption, blood flow to the site of absorption, physical state of the drug, and its concentration at the site of absorption. Any factor that accelerates gastric emptying likely increases the rate of drug absorption, whereas any factor that delays gastric emptying probably has the opposite effect, regardless of the characteristics of the drug. During migraine attacks, gastrointestinal stasis may impair the absorption of aspirin and tolfenamic acid, and the absorption can be normalized by administering the antiemetic metoclopramide, which promotes gastrointestinal motility (4,32,33), but the neuroleptic-type antiemetic thiethylperazine does not have this effect (33).

The *bioavailability* of a drug is an estimate of the amount of intact drug entering the systemic circulation after administration by the intended route and therefore is determined by absorption, and first-pass metabolism. The bioavailability after a certain route of administration is calculated by comparing the area under the drug plasma concentration curve (AUC) with that of the AUC after intravenous administration, expressed as a percentage. That bioavailability is not the same as the amount of a drug absorbed can be exemplified by ergotamine. Sixty-six percent of ergotamine is absorbed after oral administration, but the bioavailability is less than 1%, as a result of extensive first-pass metabolism in the liver (see Chapter 51). If the concentration of a drug in plasma is plotted against time after administration, a curve is outlined, the peak height (C_{max}) and the time taken to reach the peak (t_{max}). Their values depend on absorption, but less obviously, elimination.