# Pharmacokinetics

## Introduction

A major component of clinical pharmacology is pharmacokinetics, popularly known as “what the body does to a drug.”

This section covers the three major processes involved in pharmacokinetics, and describes the key pharmacokinetic attributes and advantages of NSAID X in the treatment of arthritis.

## Learning Objectives

After completing this section, you should be able to:

- Identify characteristics of the bioavailability of NSAID X.
- Identify the time required in NSAID X therapy to reach onset of action, peak plasma concentration, and steady state.
- Explain why multiple dosing of NSAID X does not lead to drug accumulation.
- Describe ways in which the metabolism of NSAID X differs from that of most NSAIDs.
- Explain the term *dual pathways of elimination.*
- Identify the relationship between enterohepatic recirculation and the likelihood of drug accumulation.

## Pharmacokinetic Processes

After an oral drug is taken, it enters the general circulation, is carried to its site of action, and is eliminated from the body. These three major processes —

- absorption
- distribution
- elimination (metabolism + excretion)

make up the drug's pharmacokinetic profile.

Although discussed separately in this program, the three pharmacokinetic processes occur simultaneously. For example, molecules of a drug are being absorbed while others are being excreted.

Pharmacokinetic properties affect how much drug enters the circulation, how much is present in the blood and tissues at a given time, how quickly the drug begins to act, what dosage is required, and how long the drug remains in the body.

Key considerations of the pharmacokinetic processes are the time required for absorption, the extent of the drug's distribution in the body, the way in which the drug is metabolized (processed), and the mode of the drug's excretion.

As discussed below, and in later sections of this manual, pharmacokinetic characteristics are important factors in determining a drug's efficacy, its safety in a variety of patient populations, its tolerability, and its acceptance by patients and physicians.

## Absorption

In the first pharmacokinetic process, called **absorption**, a drug given orally enters the general circulation. Some drugs are absorbed more rapidly and more extensively than others. These characteristics, known respectively as the rate and extent of

absorption, influence how quickly a drug will act (known as its onset of action) and how much drug will be available (the concentration in the plasma at different times).

Several factors may affect the rate or extent of absorption of an oral drug:

- the dosing form (eg, a drug given orally is absorbed more slowly than one given intravenously)
- the presence of food in the stomach
- the rate at which the stomach empties
- the acidity of the stomach and intestine
- the drug's **first-pass metabolism** in the liver
- the design of the drug's delivery system
- the coadministration of other drugs

A key factor in absorption is first-pass **metabolism**. After absorption, and before reaching the general circulation, a drug given orally is transported to the liver and is acted upon by liver enzymes. If drug metabolism is extensive, only a small portion of the drug ever reaches the general circulation.

NSAID X undergoes very little first-pass metabolism. Consequently, it has a very high **bioavailability**: About 95% of the dose is available for use by the body. This means that a high proportion of the active ingredients are made available in the general circulation, capable of exerting therapeutic effects.

***Half-life.*** A drug's **half-life**, the time in which its blood concentration is reduced by half, is another key consideration in pharmacokinetics.

A drug that is slowly metabolized and slowly excreted has a relatively long half-life. This means that compared with a drug with a short half-life:

- it is present in the blood for a much longer time
- its levels in the blood do not fluctuate as much
- its effects can be longer lasting

Half-life may be prolonged in patients with liver disease or kidney disease. Liver disease reduces the rate of drug metabolism, and

kidney disease reduces the rate of drug excretion. (The needs of specialized patient types with pre-existing conditions will be discussed in Section 4 of this module.)

The onset of action of NSAID X is relatively slow: it begins to act 1 to 2 hours after administration. **Peak plasma concentrations** — the highest concentrations reached — are achieved 3 to 5 hours after a single dose is taken. Analgesic relief is achieved with a single dose; full analgesic/anti-inflammatory actions are not realized for several days.

After several days of therapy, plasma concentrations of NSAID X reach a plateau (eg, steady state), and remain within **therapeutic range**, producing their clinical effect.

To achieve a faster onset of action, a one-time **loading dose** of NSAID X may be prescribed. For example, a patient who will be maintained on 1200 mg/day may be given a loading dose of 1800 mg. This dose would speed the onset of action of NSAID X to within 1 hour after administration, and shorten the time needed to achieve full therapeutic response.

The long half-life of NSAID X provides several advantages:

- Once-daily dosing
- Less risk that a missed dose will disrupt steady-state blood levels
- Better maintenance of steady-state blood levels

But the long half-life can also be *perceived* as a disadvantage for the following reason.

Because of the long half-life of NSAID X, it takes more than a day for a dose to be eliminated from the body. Thus, it would *seem* that several days of once-daily dosing would raise blood levels of NSAID X, resulting in overaccumulation and associated toxicity.

Overaccumulation *does not* occur, however, because of the **increased clearance** of the “excess” unbound drug, as described in the next section.