Clinical Pharmacokinetics of Meloxicam
A Cyclo-Oxygenase-2 Preferential Nonsteroidal Anti-Inflammatory Drug

Neal M. Davies¹ and Neil M. Skjodt²

¹ Department of Pharmaceutics, School of Pharmacy, College of Health Sciences, University of Sydney, Sydney, New South Wales, Australia
² Respiratory Research Group, Faculty of Medicine, University of Calgary, Calgary, Alberta, Canada

Abstract

Meloxicam [4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide] is a nonsteroidal anti-inflammatory drug (NSAID) of the oxicam class which shows preferential inhibition of cyclo-oxygenase-2.

Meloxicam has a plasma half-life of approximately 20 hours, making it convenient for once-daily administration. Meloxicam is eliminated after biotransformation to 4 pharmacologically inactive metabolites, which are excreted in urine and faeces. Meloxicam and its metabolites bind extensively to plasma albumin. Substantial concentrations of meloxicam are attained in synovial fluid, the proposed site of action in chronic inflammatory arthropathies.

Neither moderate renal nor hepatic insufficiency significantly alter the pharmacokinetics of meloxicam. Dosage adjustment is not required in the elderly. Drug-drug interaction studies are available for some commonly co-prescribed medications. Concentration-dependent therapeutic and toxicological effects have yet to be extensively elucidated for this NSAID.
Meloxicam [4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide] is a nonsteroidal anti-inflammatory drug (NSAID) that inhibits prostaglandin synthesis via relatively selective inhibition of cyclo-oxygenase-2 (COX-2), imparting analgesic, antipyretic and anti-inflammatory properties. Meloxicam is a zwitterion in the pH range 1 to 4 and an anion above pH 4. Meloxicam is currently marketed in more than 30 countries worldwide. Therapeutic doses of meloxicam have proven to be equally effective compared with other commonly used NSAIDs in the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and other rheumatological conditions. The good tolerability profile of meloxicam in basic, clinical and epidemiological studies has been attributed to its COX-2 selectivity.

General review articles are available describing the pharmacological properties, therapeutic uses, selectivity for COX-2 and pharmacokinetics of meloxicam. In this article, the clinical pharmacokinetics of meloxicam and its metabolites are updated and reviewed.

1. Pharmacokinetic Properties

1.1 Absorption

Meloxicam is most often administered orally, with conventional regular-release tablets being commercially available. Meloxicam has also been administered as an intravenous or intramuscular solution and as a rectal suppository. Tables I and II show the pharmacokinetic properties of meloxicam when administered in different formulations and in different disease states.

Parenteral, oral or rectal doses of meloxicam are almost completely absorbed with an absolute bioavailability of 89%. There were no detectable differences in bioavailability when meloxicam was given following food. Maximum plasma concentrations (Cmax) were achieved 9 to 11 hours (tmax) after 30mg of meloxicam was given orally. Rectal administration produced similar tmax values. In a crossover study, 30mg of 14C-labelled meloxicam was given to 4 healthy men as a 15-minute intravenous infusion and as an oral solution. After intravenous administration, tmax was 1 to 1.5 hours with an absolute median bioavailability of 97%. The area under the concentration-time curve (AUC) is proportional to dose in the range 7.5 to 30mg.

Because of its long half-life (22 to 24 hours), steady-state blood concentrations of meloxicam are not achieved for 3 to 4 days with oral administration of meloxicam. Assessment of clinical utility should account for this delay. Tablets, capsules and rectal suppositories are bioequivalent.

For situations requiring rapid analgesia (such as acute mechanical lower back pain, sciatica and acute flares of osteoarthritis) a parenteral form of meloxicam has been developed. Meloxicam is rapidly and completely absorbed after intramuscular administration with a mean absolute bioavailability of 102%. In 32 non-obese healthy adults, intravenous infusion of meloxicam 15mg over 1 minute resulted in mean plasma concentrations 3 minutes after the start of intravenous injection (C3 min) of 2.99 ± 0.75 mg/L, higher than the mean peak concentrations (Cmax) observed after intramuscular administration of the same dose (1.62 ± 0.20 mg/L).

1.2 Distribution

The apparent volume of distribution (Vd/F) determined after oral administration is between 10 and 15L in humans (0.1 to 0.2 L/kg), approximates to the extracellular fluid volume, and is consistent with that of other similar oxicams. Meloxicam is strongly bound to serum albumin (>99%) and thus has a small mean steady-state volume of distribution (Vss) of 0.2 L/kg after intravenous administration. Since meloxicam is essentially confined to the actual distribution volume of albumin, its tissue binding is far less important than its plasma binding in determining Vss.

The synovium is the proposed primary site of action for NSAIDs in chronic inflammatory arthropathies. Meloxicam readily penetrates into...