Comparative Single-Dose Pharmacokinetics of Sustained-Release and Modified-Release Morphine Sulfate Capsules Under Fed and Fasting Conditions

Alan Broomhead, Raelene West, Lisa Eglinton, Melissa Jones, Rosemary Bubner, Dorota Sienko and Kaye Knox

Drug Studies Unit, Royal Adelaide Hospital, and E.H. Faulding & Co. Limited, Adelaide, Australia

Summary

A randomised, single-dose, open-label, crossover study in 24 healthy male and female volunteers evaluated the pharmacokinetic profile and relative bioavailability under fed and fasting conditions of the 2 oral morphine sulfate formulations, modified-release capsules (MXL™) and sustained-release capsules (Kapanol™). A 60mg dose of study medication was administered 7 days apart after either an overnight fast of 10 hours or after a standard high-fat meal. Blood samples were taken for 48 hours postdose and were analysed for morphine by high-performance liquid chromatography using electrochemical detection. Kapanol™ was bioequivalent fed and fasting, and under fasting conditions Kapanol™ and MXL™ were bioequivalent. In contrast, MXL™ was not bioequivalent under fed and fasting conditions. Although Kapanol™ and MXL™ showed similar oral bioavailability [area under the plasma concentration-time curve (AUC) and maximum plasma drug concentration (Cmax)], the time to Cmax (tmax) of Kapanol™ was significantly longer than that of MXL™. Food significantly prolonged the tmax of Kapanol™ but had no effect on the extent of absorption or Cmax. In contrast, both the rate and extent of absorption of morphine from MXL™ were significantly reduced with food. In conclusion, Kapanol™ both fed and fasting has a superior sustained-release pharmacokinetic profile for a formulation designed for once-a-day administration compared with MXL™. Because food does not impair the bioavailability of Kapanol™, it can be taken without regard to meals.
Oral opioid analgesics, particularly oral morphine, are the treatment of choice for cancer pain. However, because of the short half-life of immediate-release morphine formulations, tablets or solution must be given every 3 to 4 hours to maintain adequate pain control. Over the last decade, controlled-release morphine formulations have become available, enabling a dosage schedule of every 8 to 12 hours. Although these formulations have simplified dose administration for the patient, the pharmacokinetic profiles show a short time to peak plasma morphine concentration and relatively large fluctuations in plasma concentrations at steady-state.

Kapanol™ (Kadian®, F.H. Faulding & Co. Limited, Adelaide, Australia) is a novel sustained-release formulation of polymer-coated morphine sulfate pellets in a gelatin capsule, designed for dose administration every 24 hours. Kapanol™ has been shown to effectively control pain over a 12- or 24-hour dosage interval in patients with advanced cancer.

MXL™ modified-release capsules (Napp Laboratories, Cambridge, England) are morphine sulfate granules in a gelatin capsule and are indicated for the prolonged relief of severe and intractable pain when administered at 24-hourly intervals. However, there are very few pharmacokinetic or clinical data published on this formulation. One recent abstract has shown reduced bioavailability and a much longer time to reach maximum plasma concentration (tmax) when MXL™ capsules were given with food compared with the same dose given in the fasting state.

The objective of this study was to compare the pharmacokinetic profile and relative bioavailability, under fed and fasting conditions, of the 2 oral morphine sulfate formulations, MXL™ modified-release capsules and Kapanol™ sustained-release capsules when administered as a single 60mg dose.

**Methods**

The study was approved by the Royal Adelaide Hospital Research Ethics Committee and conducted under medical supervision in the Drug Studies Unit, Royal Adelaide Hospital, Adelaide, Australia. The study was conducted in accordance with the Declaration of Helsinki (Hong Kong Amendment 1989), and all volunteers gave written, informed consent before study entry. The requirements of the Clinical Trial Notification scheme of the Australian Therapeutic Goods Administration were met.

**Study Participant Characteristics**

The study was conducted in male and female healthy volunteers aged between 18 and 50 years and weighing within 10% of ideal bodyweight for height and body frame (Metropolitan Life Insurance Company, Statistical Bureau). Study participants were judged to be healthy on the basis of medical history, physical examination and the absence of clinically significant abnormal laboratory values (full blood examination and urinalysis).

Volunteers were excluded if they had participated in an investigational drug study within 30 days prior to the administration of drug in this study, or if they had participated in a study involving an opioid within the previous 6 months; were allergic or hypersensitive to opioids; had a clinically significant illness or predisposing condition that might interfere with the absorption, distribution, metabolism or excretion of drugs; clinically significant nocturnal snoring; blood loss greater than 450ml in the 12-week period before initial dose; abnormal dietary habits; inadequate venous access; a history of abnormal bleeding; positive tests for hepatitis B, C or HIV; a history of drug or alcohol abuse or a positive prestudy urine drug screen; a history of psychiatric illness that would impair the ability to give informed consent; were heavy smokers; might be poor compliers; were pregnant or lactating females or those of childbearing potential not taking adequate contraceptive precautions, excluding oral contraceptives.

Study participants were instructed not to take any prescription medications for at least 14 days or over-the-counter medications for at least 7 days prior to the initial dose of study medication and during the study. In addition, volunteers were