

FAST FACTS AND CONCEPTS #166 ONCE-DAILY ORAL MORPHINE FORMULATIONS

Drew A Rosielle MD

Background There are two once-a-day long-acting oral morphine formulations available in the US: Kadian and Avinza. These formulations have unique properties which are important for their safe and effective use. To prevent confusion due to similar generic names, this *Fast Fact* will use trade-names for Kadian and Avinza, and “ER-morphine” to describe extended-release formulations which are usually dosed q12 hours (e.g. MS Contin).

Kadian capsules contain tiny granules of morphine layered with an inert polymer which releases morphine slowly within the gastrointestinal tract. Its t_{max} (time to maximum serum levels after consumption) of ~9.5 hours is the longest of any long-acting morphine preparation. For example, most ER-morphine products have a t_{max} of 2-3 hours. Despite this, some patients do seem to require q12 hour dosing, although for most q24 hour dosing is adequate. Kadian cannot be taken with alcohol due to more rapid dissolution of the granules.

Avinza capsules contain tiny granules which are a mixture of immediate-release and delayed-release morphine such that therapeutic serum levels are achieved rapidly (~1/2 hour) and then maintained for 24 hours. In its steady-state there is essentially no peak-trough phenomenon. Avinza contains fumarate, limiting total daily doses to 1600mg to prevent fumaric acid toxicity. As with Kadian, alcohol, including alcohol-containing medications, cannot be taken with Avinza as this can lead to a rapid dissolution of the granules and release of morphine.

Clinical Use Head-to-head studies of Kadian and Avinza with ER-morphine suggest they can be used as if they were bioequivalent (e.g. ER-morphine 45mg q12 hours = 90mg once a day of Avinza). Curiously, the Kadian prescribing information makes the claim that Kadian can be dosed 1:1 with other oral morphine formulations, but also says that Kadian is not bioequivalent to other extended-release morphine preparations and suggests caution when converting. The basis of this warning cannot be identified as the AUC for Kadian and ER-morphine are very similar. No studies have shown that either is safer, more effective, or has fewer side effects than ER-morphine. Theoretically, patients will have less end-of-dose failure (“rebound” pain due to serum morphine levels dropping prior to a patient’s next scheduled dose) with these longer-acting preparations, but this effect has not been shown to be clinically meaningful in trials. Because of their long duration of action, dose titration should not be more frequently than every 2 days.

Both Avinza and Kadian capsules can be opened and the granules sprinkled onto applesauce for patients who have trouble swallowing pills. Care should be given that the granules are not chewed, crushed, or dissolved. Kadian granules can also be suspended in water and administered down a large bore ($\geq 16F$) gastrostomy tube (the pellets become lodged in smaller tubes which include most nasogastric tubes). Neither of these dosing techniques is safe with ER-morphine or ER-oxycodone. It is not clear whether administering Avinza down a gastrostomy tube is safe; this has not been described in the literature, nor is it part of its manufacturer’s prescribing information. The average wholesale price of a month’s supply of 60mg daily of either formulation is approximately \$300-600 USD (www.drugs.com, August 2015).

Recommendations Avinza and Kadian are the only long-acting oral morphine products that can be used with individuals who cannot swallow pills (or for people with gastrostomy tubes in the case of Kadian). Their expense and lack of superiority to other long-acting oral opioid formulations limits recommending their use beyond this indication.

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Version History: This *Fast Fact* was originally edited by David E Weissman MD and published in October 2006. Re-copy-edited in April 2009; web-links updated. Current version updated in August 2015.

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