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Alternatives to Oral Opioids for Cancer Pain: Page 3 of 3

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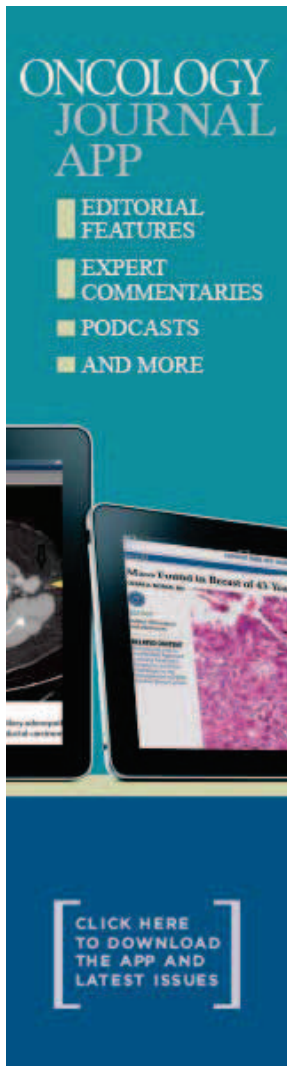
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By Sebastiano Mercadante, MD and Fabio Fulfaro, MD

Oral Transmucosal Route

The mouth has three areas for potential transmucosal delivery: sublingual, buccal, and gingival. Drug permeability appears to be highest in the sublingual area and lowest at the gingival site.[54]

The sublingual route has been proposed as a good route for the delivery of drugs because the sublingual space is highly vascular and because this route avoids first-pass elimination. Sublingual morphine has demonstrated very little kinetic advantage, however. Notable limiting factors include the number of tablets that must be placed in the mouth as dose requirements increase, slow dissolution



and absorption of the tablets, and dry mouth.[26,55] Transmucosal routes are not useful in patients with severe cognitive failure or those in comatose states.

Variations in Bioavailability

Morphine is not readily absorbed in the mouth because of its low lipid solubility. The time to maximum concentration was significantly delayed after sublingual and buccal administration of morphine.[56] The bioavailability of sublingual morphine was 18%.[57]

Compared to intravenous morphine, sublingual and buccal morphine resulted in delays in absorption and in the attainment of peak morphine and metabolite levels.[56] Sublingual morphine also produces a bitter taste.[58] Local toxicity, including rubor of the mucosa with pruritus and a burning feeling, was reported when a concentrated morphine solution was used to prevent swallowing and, hence, the first-pass effect.[59]

Opioids with high lipid solubility, such as buprenorphine, fentanyl, and methadone, are absorbed to a significantly greater extent than morphine when administered sublingually.[60] Buprenorphine has a systemic bioavailability of about 50% after sublingual administration and is effective for long-term pain management.[61] Methadone bioavailability was 38% with an increase up to 75%, when the oral cavity was buffered to a pH of 8.5 by adding bicarbonates.[57]

Sublingual fentanyl has been used as a rescue medication in doses of 25 mg (0.5 mL). The effect was achieved within 1 minute and lasted 20 to 30 minutes. Fentanyl has an unpleasant taste, however, and increased fluid volume was a limiting factor because larger amounts were swallowed before sublingual absorption. The sublingual use of a more potent opioid, such as sufentanil, is effective unless the volume of fluid becomes too great and patients have problems retaining the necessary volume of fluid in their mouth for some minutes.[60,62]

Oral transmucosal fentanyl citrate (Actiq) is a fentanyl-containing matrix that dissolves when rubbed against the buccal mucosa. When the matrix dissolves, approximately 25% of the total fentanyl is absorbed almost immediately through the buccal mucosa and enters the bloodstream with no first-pass metabolism, producing a rapid effect. The remaining 75% is swallowed, thus undergoing first-pass metabolism. About one-third of this amount is bioavailable, achieving a total bioavailability of about 50%.[60]

Transmucosal fentanyl provides a rapid onset of pain relief within 5 to 10 minutes and a short duration of effect, even though it takes more than 20 minutes to achieve peak plasma levels with this route.[63] These characteristics make transmucosal fentanyl appropriate for treating breakthrough pain

episodes.[64] and this formulation was recently approved by the FDA for this purpose in adult cancer patients.

Intranasal Analgesic Device

A device for patient-controlled intranasal analgesia was recently reported to provide a rapid onset of action and an analgesic effect equivalent to intravenous administration. The high bioavailability after the intranasal application of lipophilic opioids seems to be due to the fact that the venous outflow of the nasal mucosa enters the systemic circulation, bypassing the liver.[65]

Theoretically, intranasal morphine is an attractive way of rapidly delivering analgesic agents through the highly vascular areas of the nasal cavity. No studies exist, however, to support this route for analgesia. In addition, serious local toxicity has been reported.[59]

Inhalational Route

Nebulization is an inefficient way of administering drugs, as bioavailability has been shown to be very low.[66] Since the airways have been shown to contain opioid receptors, a local mode of action has been proposed for nebulized opioids. Nebulized therapy has been used to administer several drugs exerting a local action in the airways. The rationale for using morphine by this route is that it acts locally and directly on afferent nerve endings in the lung to reduce dyspnea, rather than systematically.

The effects of nebulized therapy have been described in different groups of patients, including those with cancer, using different opioids at varying dosages. Extremely ill patients, those in comatose states, or those suffering from asthma and feelings of claustrophobia caused by wearing a mask to inhale the drugs, cannot use this route. An acute respiratory depression requiring

ventilation was recently reported after 4 mg of nebulized morphine was administered to a dyspneic patient receiving chronic opioid morphine.[67]

Conclusions

Although the oral administration of analgesic agents to manage cancer pain is generally preferred because of its ease and reliability, many patients require alternate routes during the course of their illness. These alternative routes are likely to be useful for patients unable to use the oral route because of bowel obstruction, severe vomiting, dysphagia, cognitive failure, or comatose states. Pharmacokinetic data and clinical experience also suggest that, in some clinical situations, routes of opioid administration other than the oral route have potential advantages.

Table 1 summarizes some of the potential clinical applications of the different alternative routes.

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