Exhibit 1011

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

ONCOLOGY
Review Article | February 01, 1999 | Palliative and Supportive Care
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.

REFERENCES

1. Lombard DJ, Oliver DJ: The use of opioid analgesics in the last 24 hours of life of patients with advanced cancer. Palliat Med 3:27-29, 1989.

2. Mercadante S, Genovese G, Kargar JA, et al: Home palliative care: Results in 1991 versus 1988. J Pain Symptom Management 7:414-418, 1992.

3. Expert Working Group of the European Association for Palliative Care: Morphine in cancer pain: Modes of administration. Br Med J 312:823-826, 1996.

4. Cherny NJ, Chang V, Frager G, et al: Opioid pharmacotherapy in the management of cancer pain: A survey of strategies used by pain physicians for the selection of analgesic drugs and routes of administration. Cancer 76:1288-1293, 1995.

5. Bruera E: Alternate routes for home opioid therapy. Pain Clinical Updates 1:1-4, 1993

6. Coyle N, Cherny NI, Portenoy RK: Subcutaneous opioid infusions at home. Oncology 8:21-27, 1994.

7. Bruera E, Ripamonti C: Alternate routes of administration of opioids, in Patt RB (ed): Cancer Pain, pp 161-184. Philadelphia, JB Lippincott, 1993.

8. Nelson KA, Glare PA, Walsh D, et al: A prospective, within-patient, cross-over study of continuous intravenous and subcutaneous morphine for chronic cancer pain. J Pain Symptom Management 13:262-267, 1997.

9. Moulin DE, Kreeft JH, Murray-Parsons N, et al: Comparison of continuous subcutaneous and intravenous hydromorphone infusions for management of cancer pain. Lancet 337:465-468, 1991.

10. Waldmann CS, Eason JR, Rambohul E, et al: Serum morphine levels: A comparison between continuous subcutaneous infusion and continuous intravenous infusion in postoperative patients. Anaesthesia 39:768-771, 1984.

11. McDonald P, Graham P, Clayton M, et al: Regular subcutaneous bolus morphine via an in-dwelling cannula for pain from advanced cancer. Palliat Med 5:323-329, 1991.

12. Drexel H, Dzien A, Spiegel RW, et al: Treatment of severe cancer pain by low-dose continuous subcutaneous morphine. Pain 36:169-176, 1989.

13. Devulder JE: Subcutaneous morphine is superior to intrathecal morphine for pain control in a patient with hypernephroma. J Clin Anesth 10:163-165, 1998.

14. Kalso E, Heiskanen T, Rantio M, et al: Epidural and subcutaneous morphine in the management of cancer pain: A double-blind cross-over study. Pain 67:443-449, 1996.

15. Bruera E, MacEachern T, Ripamonti C, et al: Subcutaneous morphine for dyspnea in cancer patients. Ann Intern Med 119:906-907, 1993.

16. Wolff T, Samuelsson H, Hedner T: Concentrations of morphine and morphine metabolites in CSF and plasma during continuous subcutaneous morphine administration in cancer pain patients. Pain 68:209-216, 1996.

17. Tiseo PJ, Thaler HT, Lapin J, et al: Morphine-6-glucuronide concentrations and opioid-related side effects: A survey in cancer patients. Pain 61:47-54, 1995.

18. Singer M, Noonan KR: Continuous intravenous infusion of fentanyl: Case reports of use in patients with advanced cancer and intractable pain. J Pain Symptom Manage 8:215-220, 1993.

19. Paix A, Coleman A, Lees J, et al: Subcutaneous fentanyl and sufentanil infusion substitution for morphine intolerance in cancer pain management. Pain 63:263-269, 1995.

20. Mercadante S, Caligara M, Sapio M, et al: Subcutaneous fentanyl infusion in a patient with bowel obstruction and renal failure. J Pain Symptom Management 13:241-244, 1997.

21. Brenneis C, Michaud M, Bruera E, et al: Local toxicity during the subcutaneous infusion of narcotics (SCIN): A prospective study. Cancer Nurs 10:172-176, 1987.

22. Bruera E, Faisinger R, Moore M, et al: Local toxicity with subcutaneous methadone: Experience of two centers. Pain 45:141-143, 1991.

23. Warren DE: Practical use of rectal medications in palliative care. J Pain Symptom Manage 11:378-387, 1996.

24. Campbell WI: Rectal controlled-release morphine: Plasma levels of morphine and its metabolites following the rectal administration of MS-Contin, 100 mg. J Clin Pharm Ther 21:65-71, 1996.

25. De Conno F, Ripamonti C, Saita L, et al: Role of rectal route in treating cancer pain: A randomized crossover clinical trial of oral versus rectal morphine administration in opioid-naive cancer patients with pain. J Clin Oncol 13:1004-1008, 1995.

26. Gorman DJ: Opioid analgesics in the management of pain in patients with cancer: An update. Palliat Med 5:277-294, 1991.

27. Maloney CM, Kesner RK, Klein G, et al: The rectal administration of MS Contin: Clinical implications of use in the end stage of cancer. Am J Hosp Care 6:34-35, 1989.

28. Babul N, Darke AC, Anslow JA, et al: Pharmacokinetics of two novel rectal controlled-release morphine formulations. J Pain Symptom Management 7:400-405, 1992.

29. Kaiko RF, Fitzmartin RD, Thomas GB, et al: The bioavailability of morphine in controlled-release 30 mg tablets per rectum compared with immediate-release 30 mg rectal suppositories and controlled-release 30 mg oral tablets. Pharmacotherapy 12:107-113, 1992.

30. Babul N, Darke AC: Disposition of morphine and its glucuronide metabolites after oral and rectal administration: Evidence of route specificity. Clin Pharmacol Ther 54:286-292, 1993.

31. Leow KP, Smith MT, Watt JA, et al: Comparative oxycodone pharmacokinetics in humans after intravenous, oral, and rectal administration. Ther Drug Monit 14:479-484, 1992.

32. Ripamonti C, Zecca E, Brunelli C, et al: Rectal methadone in cancer patients with pain: A preliminary clinical and pharmacokinetic study. Ann Oncol 6:841-843, 1995.

33. Bruera E, Watanabe S, Faisinger RL, et al: Custom-made capsules and suppositories of methadone for patients on high-dose opioids for cancer pain. Pain 62:141-146, 1995.

34. Mercadante S: Pain treatment and outcome in advanced cancer patients followed at home. Cancer, 1999 (in press).

35. Portenoy RK, Southam M, Gupta SK, et al: Transdermal fentanyl for cancer pain: Repeated dose pharmacokinetics. Anesthesiology 78:36-43, 1993.

36. Lehmann KA, Zech D: Transdermal fentanyl: Clinical pharmacology. J Pain Symptom Management 7(3;suppl):S8-S16, 1992.

37. Grond S, Zech D, Lehmann KA, et al: Transdermal fentanyl in the long-term treatment of cancer pain: A prospective study of 50 patients with advanced cancer of the gastrointestinal tract or the head and neck region. Pain 69:191-198, 1997.

38. MacDonald N: Commentary. J Pain Symptom Management 8:320-321, 1993.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.