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Rational Use of Sublingual Opioids in Palliative Medicine

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ABSTRACT

The sublingual administration of opioid analgesics has been a mainstay in the pain management of homebound dying hospice patients who are no longer able to swallow. It is also a potentially useful route of administration in other situations in which the oral route is not available and other routes are impractical or inappropriate. Potential advantages of the sublingual route include rapid analgesic onset and avoidance of hepatic first-pass metabolism. Pharmacokinetic and pharmacodynamic studies have yielded widely disparate data on sublingual morphine. Other opioids have been less studied. Available data suggests limited sublingual availability of hydrophilic opioids (e.g., morphine, oxycodone, and hydromorphone) and superior absorption of the lipophilic opioids (e.g., methadone and the fentanils). Buprenorphine, a potent, lipophilic, partial μ-opioid receptor agonist, appears promising but awaits further study.

INTRODUCTION

No class of medications can compete with opioids for the sheer number of routes of administration. One such route is the sublingual, which is commonly—and nearly exclusively—endorsed by the hospice and palliative care communities, most often for the control of pain in homebound, dying patients who are no longer able to swallow. More than simply an alternative to the oral administration of morphine, some proponents of the sublingual route have argued for its superiority as defined by rapidity of onset, intensity and duration of analgesia, and lesser magnitude of opioid-related side effects.[1–3]

Certainly, the sublingual route offers several potential advantages relative to non-oral routes in the home setting. These include low cost, noninvasiveness, lack of discomfort, and simplicity and ease of administration by patient and caregiver.[4] In certain circumstances, particularly when the oral route is not available, for example because of obstructing aerodigestive tract tumors, bowel obstruction, dysphagia, odynophagia, frequent nausea and vomiting, or diminished level of consciousness in the dying patient, the sublingual route may be a practical alternative. Thus, when the intravenous route is not readily accessible; when the subcutaneous route is unsatisfactory (due to anasarca, coagulopathy, circulatory insufficiency, or unwillingness of patient or caregiver to accept the modest discomfort or invasiveness); or when the rectal route is impractical (in the settings of diarrhea, constipation, fecal impaction, fissure, or aesthetic unacceptability to patient or caregiver), the sublingual route is a rational choice.

Also, there is a theoretic basis for the potential superiority of the sublingual route. Major short-

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comings of oral opioid administration, especially for the treatment of episodic pain, are an often unacceptably long time to analgesic onset—typically approximately 30 minutes—and extensive first-pass metabolism.[5] The sublingual route addresses both of these limitations. First, the opioid is delivered directly to the central circulation, bypassing gut presystemic elimination and hepatic first-pass metabolism, thereby potentially increasing bioavailability relative to the oral route.[6] Second, more rapid absorption may lead to more rapid analgesic onset.[7]

Disadvantages cited for the sublingual route include unpalatability,[7–9] burning sensation,[7] (rarely) ulceration,[10] and the need to retain the drug sublingually for several minutes.

THE SUBLINGUAL SPACE

In addition to providing a conduit for the introduction of drugs to the gastrointestinal system, the oral cavity offers several *in situ* locations—buccal, gingival, and sublingual mucosae—for drug absorption. The sublingual mucosa comprises a small fraction of the 200 cm^2 of oral mucosa, but it is the most permeable region in the oral cavity.[11] In contrast to the buccal mucosa, which is comprised of 40–50 cell layers and is 500–800 μm thick, the sublingual mucosa comprises fewer cell layers and is only 100–200 μm thick. And unlike the gingival mucosa, the sublingual mucosa is nonkeratinized, thus eliminating an important barrier to drug absorption.[12]

In nonkeratinized mucosa the outermost epithelial layers pose the major barrier to drug absorption. Lipophilicity of drugs has long been considered to be of primary importance for transmucosal absorption. Indeed, this is an advantage for passage across lipid-rich epithelial cell membranes. Paracellular (or intercellular) passage, however, is an important route for hydrophilic drugs. Drug absorption often involves a combination of these two avenues of ingress.[12]

Salivary pH also plays a role in drug absorption. Normal pH of saliva is 6.5 ± 3, but is influenced by a number of factors including mouth-breathing, nutritional status, age, recent beverage consumption, vomiting, chemotherapy, stomatitis, and decreased salivary flow rate.[9,12,13] Even within an individual oral cavity, there is significant pH variation among the sublingual, buccal, and gingival microenvironments.[13]

SPECIFIC OPIOIDS

Morphine

This most widely used opioid has also received the most research attention. Early anecdotal reports on its sublingual use touted its efficacy and, indeed, even its superiority relative to the oral route.[2,14,15] Pharmacokinetic data, however, were equivocal. Some concluded that poor absorption made morphine unsuitable for sublingual administration.[16] Coluzzi[17] reviewed the use of sublingual morphine, concluding based on published reports up to 1997 that morphine is relatively poorly absorbed through the oral mucosa, with resulting delays in time to peak plasma concentration. Little data on morphine have been published since that review. We will briefly examine the available pharmacokinetic and pharmacodynamic data.

PHARMACOKINETICS

Pannuti et al.[1] compared the pharmacokinetics of morphine hydrochloride solution administered by the intramuscular ($n = 8$), oral ($n = 5$), rectal (n = 8), and sublingual ($n = 8$) routes to patients with advanced cancer. In the sublingual group, patients were instructed to retain the opioid (10 mg [20 mg/mL]) sublingually for 10 minutes. Blood samples were collected periodically for quantitative serum morphine determination by radioimmunoassay (RIA). The intramuscular route displayed higher peak serum levels than all other routes at 15 minutes. There appeared to be no statistically significant differences between the sublingual, oral, and rectal routes over the initial 4 hours. The authors apparently permitted patients to swallow the sublingual opioid after the retention period, thereby permitting gastrointestinal absorption and confounding the interpretation of their data.

McQuay et al.[10] examined the pharmacokinetics of morphine sulfate solution by the intravenous (10 mg) and sublingual (10 mg, concentration unspecified) routes in a crossover study of pain clinic patients on chronic opioid therapy ($n = 5$). In the sublingual arm, participants were instructed to retain the opioid for 5 minutes. This study measured both the opioid recovered in the expectorant ($n = 4$) and opioid plasma levels ($n = 5$). The mean absorption determined by measur-

ing morphine in the expectorant was 51%, while the mean bioavailability determined by serum RIA was 61% (range, 10%–100%), with a mean T_{max} of 138 minutes.

Weinberg et al.[7] examined the pharmacokinetics of several sublingual opioids, including morphine sulfate, 5 mg (5 mg/mL) in healthy volunteers ($n = 10$). Participants were instructed to retain the opioid sublingually for 10 minutes, after which the expectorant was collected and quantitative morphine measured by high-performance liquid chromatography (HPLC). Mean absorption was determined to be 22%. In a separate arm of the study, healthy volunteers ($n = 7$) were administered sublingual morphine sulfate, 15 mg (tablet), with blood samples collected serially and serum morphine measured by RIA, with apparent bioavailability of 9.0% ± 11.9% (mean ± standard deviation [SD]) and a range of 0%–31%. In this arm, the authors specified neither the sublingual retention time nor the fate of the morphine-rich saliva.

Osborne et al.[8] examined morphine sulfate administered by a variety of routes in a crossover study of healthy volunteers ($n = 10$). In the sublingual arm ($n = 8$), participants were administered morphine (11.7 mg tablet) and instructed to retain it until dissolution (0.18 ± 0.06 hour). The authors did not specify whether saliva was subsequently expectorated or swallowed. Blood samples were collected at intervals and serum assayed by HPLC. Bioavailability of sublingual morphine was 21.9% ± 6.0%, which was not significantly different from that of oral morphine (20.1% ± 8.7%). The sublingual route proved inferior by other indices, including T_{max} (sublingual = 1.75 ± 1.3 hour; oral = 0.84 ± 0.4 hour) and C_{max} (sublingual displayed non-statistically significant reductions relative to intravenous and oral).

Davis et al.[18] performed a crossover study of sublingual, oral, and intramuscular morphine sulfate in patients with cancer pain ($n = 6$). Sublingual retention time was not specified, nor was the fate of the morphine-rich saliva. Blood samples were drawn periodically and serum assayed by RIA. Bioavailabilities of sublingual and oral morphine were 23% and 25%, respectively, a nonstatistically significant difference.

Robison et al.,[9] in a review of sublingual opioids, cited their own submitted (but not published) data of a crossover study of cancer patients ($n = 17$, 10 of which provided usable data). Participants were administered sublingual morphine (dosage unspecified). Neither sublingual retention time nor the fate of the morphine-rich saliva were specified. Blood was collected serially; the assay was not specified. The authors found no statistically significant pharmacokinetic differences between the two routes, but noted great interpatient variability, and a suggestion of higher plasma concentrations with the oral route in 7 of 10 patients.

Watson et al.[19] compared the pharmacokinetics of intravenous (0.075 mg/kg) and sublingual (aerosolized) morphine sulfate (9.6 mg) in healthy volunteers ($n = 5$). Neither sublingual retention time nor the fate of the morphine-rich saliva were specified. Serial serum samples were analyzed by HPLC. Results for sublingual morphine included a bioavailability of 19.7% ± 6.7%; time to opioid detection of 7.2 minutes (limit of detection: 1 ng/mL); $T_{max} = 48$ minutes; and $C_{max} = 8.0 \pm 1.9$ ng/mL (compared to 97.6 ± 32.5 ng/mL for the intravenous route).

Pharmacodynamics

Pannuti et al.,[1] in a separate arm of their aforementioned study found that over a period of 5 weeks, patients treated with sublingual morphine (dose titrated to effect and administered every 4 hours as needed) experienced (mean) pain reduction from 7.8 to 2.7 on a 0–10 visual analogue scale. Relative to the oral and rectal routes, the sublingual route exhibited statistically significant advantages in terms of rapidity and intensity of analgesia, and nonsignificant reductions in constipation and vomiting.

Engelhardt and Crawford,[20] compared analgesia in pediatric surgical patients between sublingual ($n = 14$) and intravenous ($n = 15$) morphine sulfate in a double-blinded study. Participants were administered the opioid (0.1 mg/kg solution) and diclofenac (1 mg/kg per rectum) after anesthetic induction for adenotonsillectomy. Pain was scored on a 5–point numerical rating scale; who performed the rating is not specified. Groups were similar in terms of age and weight. Outcomes included time to first analgesic request 324 ± 213 minutes (sublingual), 347 ± 257 minutes (intravenous); and average pain scores 2.3 ± 0.5 (sublingual), 2.5 ± 0.6 (intravenous) over 24 hours. These differences were not statistically significant. The administration of diclofenac to all participants

would appear to confound the interpretation of morphine analgesia.

OXYCODONE

Pharmacokinetics

Weinberg et al.,[7] in a single-dose study of healthy volunteers ($n = 10$), found that sublingual oxycodone, 2.5 mg/mL had a bioavailability of less than 20%.

Kokki et al.[21] compared the pharmacokinetics of buccal ($n = 15$) and sublingual ($n = 15$) oxycodone (0.2 mg/kg [10 mg/mL parenteral liquid]) in a randomized, open-label study of healthy, awake, preoperative children (ages 6 months to 7 years). Neither the mucosal contact times nor the fates of the oxycodone-containing saliva were specified. Blood was drawn serially and serum oxycodone measured by gas chromatography/mass spectroscopy (GC/MS). Twelve of 15 (80%) in each group achieved therapeutic plasma levels (defined by the investigators as 12 ng/mL) that were sustained for comparable periods (sublingual: median = 175 minutes; range, 32–62 minutes; buccal: median = 160 minutes; range, 43–209 minutes). It seems to us that given the young ages of these study participants, the swallowing of significant amounts of the opioid was inevitable.

Al-Ghananeem et al.,[22] in an animal study using a sublingual oxycodone spray, found a bioavailability of 45%. Alkalinization of the oxycodone solution to pH 9 increased the bioavailability to 70%, a difference that was not statistically significant, possibly due to the small number of subjects. Sublingual retention time was not specified.

Pharmacodynamics

We were unable to identify any literature on the pharmacodynamics of sublingual oxycodone.

HYDROMORPHONE

Weinberg et al.,[7] in a single dose study in healthy volunteers ($n = 11$) found that hydromorphone 2.5 mg (1 mg/mL) had a bioavailability of approximately 25%. We were unable to identify any literature on the pharmacodynamics of sublingual hydromorphone.

METHADONE

Pharmacokinetics

McQuay et al.,[10] in a separate arm of their aforementioned morphine study, examined the pharmacokinetics of methadone administered by the intravenous (10 mg) and sublingual (two 5-mg tablets) routes to patients ($n = 7$) on chronic opioid therapy. The tablets were allowed to dissolve sublingually, but neither the retention time nor the fate of the methadone-rich saliva were specified. Serial blood samples were collected and the serum analyzed by RIA. The relative bioavailability of the sublingual methadone was 141% (range, 92%–240%) of the intravenous methadone bioavailability. T_{max} was achieved at a mean of 175 minutes. The authors do not discuss the surprisingly high relative bioavailability of the sublingual methadone; presumably it resulted from the lack of hepatic first-pass metabolism.

Weinberg et al.,[7] administered sublingual methadone, 5 mg (0.8 mg/mL or 5 mg/mL) to healthy volunteers, and measured the quantity of drug in the saliva expectorate after 10 minutes. Methadone absorption was 35% at pH 3.5 and 75% at pH 8.5, a statistically significant difference. The absorption of methadone at even the lower pH was significantly greater than it was for morphine, oxycodone, hydromorphone, levophanol, and heroin. Sixty-five percent of the C_{10min} was achieved by 2.5 minutes. Bioavailability was not influenced by the concentration of the methadone solution.

Pharmacodynamics

We were not able to identify any pharmacodynamic studies of sublingual methadone. Fisher et al.[23] reported a relatively rapid onset of action of oral methadone for episodic cancer pain. This provided the rationale for a current pilot study of the pharmacodynamics of sublingual methadone for breakthrough pain in cancer patients (N. Hagen, personal communication).

FENTANYL

Fentanyl's potency, lipophilicity, and clinical efficacy have made it the object of intense interest for a variety of transmucosal applications. It is presently formulated as 200, 400, 600, 800, and

1600 mcg oralets ("lollipops") for transbuccal use, and has been the subject of recent reviews.[24,25] Clinical trials are ongoing for an intranasal spray.[26] A buccal effervescent tablet has recently become commercially available. This delivery system, by generating CO_2 and thereby raising local pH, may enhance transmucosal fentanyl transport.[27] The following discussion will be limited to the sublingual transmucosal administration of fentanyl citrate solution.

Pharmacokinetics

Weinberg et al.[7] examined the pharmacokinetics of sublingual fentanyl in healthy volunteers ($n = 18$). Fentanyl 50 μg (50 μg/mL) was administered, and fentanyl in expectorated saliva was measured by RIA in separate groups at 2.5 and 10 minutes. Mean absorption was 51%; 60% of the T_{max} achieved by 2.5 minutes.

Lennernas et al.[28] conducted a double-blinded crossover study of sublingual fentanyl (100, 200, and 400 μg rapidly-dissolving tablets, not commercially available in the United States) in metastatic cancer patients ($n = 9$). They collected serial blood samples and measured serum fentanyl levels by means of liquid chromatography-mass spectroscopy. They found detectable fentanyl levels within several minutes (100 μg: 10.7 $\pm$ 3.2 minutes; 200 μg: 8.0 $\pm$ 2.7 minutes; 400 μg: 9.0 $\pm$ 4.1 minutes); therapeutic and linear C_{max} (100 μg: 0.24 $\pm$ 0.14 ng/mL; 200 μg: 0.41 $\pm$ 0.16 ng/mL; 400 μg: 0.91 $\pm$ 0.3 ng/mL), and reasonable T_{max} (100 μg: 39.7 $\pm$ 17.4 minutes; 200 μg: 48.7 $\pm$ 26.3 minutes; 400 μg: 56.7 $\pm$ 24.6 minutes). The authors also noted relatively small interpatient variability.

Pharmacodynamics

Gardner-Nix[29] published a case series of sublingual fentanyl in chronic pain patients ($n = 3$ malignant; $n = 3$ chronic nonmalignant). Doses of 2.5–20 μg (50 μg/mL) administered every 2 hours as needed reduced pain by more than 40% within 5–10 minutes in all patients.

Zeppetella (2001)[4] prospectively examined sublingual fentanyl doses of 25–150 μg (50 μg/mL) for episodic pain in hospice inpatients ($n = 11$) on a wide range of baseline opioid doses (20–200 morphine equivalents per day). Dosing began with 25 μg and was increased in increments of 25 μg until pain was controlled or the limit of 150 mcg was reached. The effective dose was then used for five consecutive episodes of episodic pain. At 10 minutes 6/11 (55%) noted analgesia; at 15 minutes 9/11 (82%) noted analgesia. Analgesia was rated as good in 3/11; fair in 6/11; and poor in 2/11. The 9 patients with good or fair responses rated the medication as better or the same as their usual rescue opioids. Our examination of the data showed that one of the two patients with poor analgesia ratings was on morphine 200 mg/day and that the 150 μg fentanyl for episodic pain was likely an insufficient analgesic dose.

SUFENTANIL

Sufentanil is 5–10 times as potent an analgesic as fentanyl by the intravenous route.[30] It has been used by a variety of routes including intrathecal and epidural for the treatment of cancer pain.[31] There is little published literature on its use by the sublingual route.

Pharmacokinetics

We were not able to identify any pharmacokinetic studies of sublingual sufentanil. We did, however, find a single study of sufentanil administered by another transmucosal route: intranasal. This single-dose study of elective surgical patients demonstrated rapid and effective transmucosal absorption of 15 μg sufentanil, comparing favorably to the same dose administered by the intravenous route. Mean plasma levels of the intranasally administered dose were 36% and 56% of that of the intravenous dose at 5 and 10 minutes, respectively, with identical plasma concentrations after 30 minutes, and area under the curve (AUC) 0–120 minutes of 78% of that after intravenous administration.[32]

Pharmacodynamics

There are a few reports on the use of sublingual sufentanil for breakthrough cancer pain.[29,33,34] Kunz et al.[33] published a case report of a patient with cancer treated with controlled-release morphine sulfate, 600 mg/d, and episodic bone pain. Rescue doses of sublingual sufentanil, 25 μg every 3 minutes as needed (maximum dose of 75 μg) provided "satisfactory" analgesia with minimal transient sedation. Gardner-Nix[29] reported on three patients with cancer pain treated with sublingual sufentanil (50 μg/mL). Doses of 2.5–

7.5 μg, 5–7.5 μg, and 12.5–15 μg, respectively, resulted in 40%–50% pain reduction within 6 minutes and an analgesic duration of 35 minutes. The British Columbia Cancer Agency has been using an episodic pain sufentanil protocol since 2002 (P. Hawley, personal communication). The protocol calls for the administration of sublingual sufentanil (50 μg/mL), 25 μg every 5 minutes as needed, to a maximum dose of 75 μg per episodic pain episode. In unpublished data on 50 patients, they noted an analgesic response in 42 of 50 (84%). Fifteen patients responded to a single 25 μg dose with a mean pain reduction of 4.3 (range, 1–9) on an 11–point numerical rating scale; an additional 18 patients responded to two 25 μg doses with a mean pain reduction of 4.8 (range, 2–8); and a further 9 patients responded to three 25 μg doses with a mean pain reduction of 3.9 (range, 2–8). Hawley reports that most of the patients tolerated the medication well; a few displayed a drop in respiratory rate that did not require pharmacologic reversal.

A potential advantage of sufentanil over most other opioids is its high potency, allowing small volumes to be used in the limited sublingual space. Furthermore, it appears to be safe for use in renal[35] and hepatic dysfunction.[36]

ALFENTANIL

Alfentanil (500 μg/mL), approximately 10%–20% as potent as fentanyl by the intravenous route,[30] is used by the sublingual route by some centers in the United Kingdom. Duncan[37] has noted a faster onset and shorter duration of action relative to fentanyl. Fiona Lisney, M.D., of the National Health Service has suggested an analgesic onset time of 10–15 minutes and an analgesic duration of 30–40 minutes.[38] There exists no pharmacokinetic or pharmacodynamic data on the use of alfentanil by the sublingual route, although clinical trials are reportedly underway.[39]

BUPRENORPHINE

Buprenorphine is a partial μ-opioid receptor agonist, with κ-opioid receptor antagonist properties. It has a high affinity and low-to-moderate intrinsic activity at the μ-opioid receptor.[40] A sublingual wafer was approved by the U.S. Food and Drug Administration in 2002 for opioid substitution therapy in opioid addiction. A parenteral formulation (Reckitt Benckiser Pharmaceuticals, Inc., Richmond, VA) has been marketed as an analgesic in the United States since the 1980s.

The successful sublingual use of buprenorphine in cancer pain dates back to the 1970s.[41] It has subsequently been used by a variety of other routes including epidural,[42–44] subarachnoid,[45] subcutaneous,[46] intravenous,[47] intramuscular,[48,49] transdermal,[50–56] The use of buprenorphine for cancer pain has recently been reviewed.[57]

Buprenorphine in cancer pain—chiefly as a new, transdermal formulation available in Europe and Australia—is acquiring a rapidly expanding evidence base of safety and efficacy.[58] Buprenorphine also illustrates the potential of sublingual opioids for baseline pain. There is a specific sublingual preparation; it is a lipophilic molecule with poor oral bioavailability (approximately 10%),[59] but good sublingual bioavailability (approximately 50%)[60]; potency is high and serum concentrations are linearly related to dose from 1–32 mg.[61] A delayed T_{max}, however,[60,62] makes it a less than optimal choice for episodic pain.

There are three major potential limitations of buprenorphine in the setting of severe pain:

1. Its purported analgesic ceiling. Preclinical studies of buprenorphine indicated that it exhibits an analgesic ceiling or even a bell-shaped dose-response curve, wherein doses exceeding the maximal analgesic dose were associated with decreased analgesic efficacy.[63] More recent work has found such dose-response curves in some pain models but not in others.[64] Moreover, some of these animal studies show maximal efficacy at doses of approximately 1 mg/kg, doses far exceeding those used in human studies.[59,64] Neither we nor others have been able to find published evidence of an analgesic ceiling for buprenorphine in humans.[59,64–66] It has been asserted that incremental analgesia is seen between 1 and 32 mg/d of sublingual buprenorphine,[57,67] but this appears to be a serious misreading of a study that examined nonanalgesic subjective responses to buprenorphine in opioid addicted volunteers.[61] Most studies in cancer pain used relatively low doses of buprenorphine—generally from 0.2–0.8 mg per dose.[41,68–70] The maximum recommended dose for the transdermal formu-

lation (two 70 μg/h patches) is 3.4 mg/d.[67] Two pharmacodynamic studies on the use of buprenorphine for acute pain, however, found no analgesic ceiling at more than double this dose.[71,72]

2. Its potential to precipitate a withdrawal syndrome in patients physically dependent on pure μ-opioid receptor agonists. Buprenorphine-induced opioid withdrawal is dependent on the buprenorphine dose, the previous opioid dose, and time since administration of the previous opioid.[73] In the context of its use as an analgesic, these parameters remain largely undefined. Several studies, conducted with (non-pain) opioid-dependent volunteers, suggest that buprenorphine can be safely administered to patients taking low- to moderate-dose opioids.[40,74–78]
3. Its ability to block or attenuate the effects of subsequently/concurrently administered opioids. Multiple studies have demonstrated that chronic administration of buprenorphine can block the nonanalgesic subjective effects of pure μ-opioid receptor agonists in opioid-dependent individuals,[79] but we were unable to identify any studies demonstrating the capacity of buprenorphine to block the analgesic effects of subsequently administered pure μ-opioid receptor agonists. To the contrary, recent work combining fentanyl[58] and morphine[80] with buprenorphine suggest that buprenorphine can be combined safely and effectively with pure μ-opioid receptor agonists for episodic pain.

Another important, and as yet unresolved, issue with buprenorphine concerns equianalgesic determinations. Recent data suggests that transdermal buprenorphine is between 75[81] and 150[82] times as potent as oral morphine. Assuming approximately equal bioavailabilities by the sublingual and transdermal routes,[67] 30 mg oral morphine might be approximately equianalgesic to 0.2–0.4 mg sublingual buprenorphine within the tested analgesic range of 0–1.6 mg/d of buprenorphine.

Potential advantages for buprenorphine include effectiveness in neuropathic pain states[58]; possible anti-hyperalgesic properties[83]; lower ceiling for respiratory depression than for analgesia[65,84]; relatively low incidence of constipation[41,65]; and safety in renal insufficiency with no need for dosage adjustment.[85]

DISCUSSION

Sublingual opioids have long been used in the hospice and palliative care settings because the route is often well-suited to home patients with advanced terminal illnesses. Anecdotal reports of morphine administration by the sublingual route remarked on its superiority over the oral route. Studies of the pharmacokinetics and pharmacodynamics of morphine and other opioids administered by the sublingual route have provided sometimes widely conflicting data. For example, studies of sublingual morphine have found mean bioavailabilities ranging from a low of 9% to a high of 61%, with ranges of 0% to 100%.[7,10] There are several possible reasons for these discrepancies, including: (1) most studies employed small numbers of participants; (2) interstudy variability in drug formulations (e.g., morphine sulfate versus morphine hydrochloride), forms (liquid versus tablet), dosages, concentrations, and volumes; (3) different sublingual retention times (e.g., 2.5 minutes, 5 minutes, 10 minutes, "until dissolved," and unspecified); and (4) different methodologies, including choice of analysate (saliva vs. serum), eventual disposition of sublingual opioid (swallowed or expectorated), and assays for calculation of drug concentrations. Nevertheless, the preponderance of available data does not support assertions of clinical superiority of the sublingual route over the oral or other routes of administration for the most commonly used opioids for breakthrough pain: morphine, oxycodone, and hydromorphone.[5]

Morphine, oxycodone, and hydromorphone are strongly hydrophilic drugs.[7] Lipophilic drugs tend to be absorbed best through the sublingual mucosa.[7] Lipophilicity, however, is only one of several variables—including degree of ionization at salivary pH; molecular size and shape; and degree of protein binding—that determine drug movement across biological membranes.[86] Potency is another important variable because of the limited volume and surface area of the sublingual space. In these regards, methadone, sufentanil, and buprenorphine hold promise due to high degrees of lipophilicity and potency, and availability in concentrated forms.

SPECIFIC CONSIDERATIONS

First, are other routes available? The World Health Organization endorses the oral route as

the preferred route, due to considerations of safety, non-invasiveness, cost, practicality, and effectiveness.[87] The transdermal route is becoming an increasingly important non-invasive alternative to the oral route, particularly for stable pain states. Parenteral administration remains the route of choice for severe and unstable pain situations, particularly in institutional settings. Limitations in volume/surface area of the sublingual space and unresolved pharmacokinetic and pharmacodynamic issues make the sublingual route a rational choice when other routes are not available or not clinically appropriate.

Second, what is the purpose of the sublingual opioid—is it for episodic pain, baseline pain, or both? For episodic pain—in response to spontaneous pain or in anticipation of movement- or procedure-related pain—an opioid with rapid onset and short- to intermediate- duration is optimal. Morphine and oxycodone have been the traditional opioids for this purpose, but data supporting rapidity of onset is not robust and these agents present potency limitations (see below). Sufentanil and alfentanil may prove to be superior agents for episodic pain. For baseline pain, duration of analgesia is a primary concern. Methadone and buprenorphine might function well in this capacity, but their full sublingual potential remains unexplored.

Third, what is the degree of the patient's opioid tolerance? While the absorption of the traditional sublingual opioids—morphine and oxycodone—is not good, they may still be acceptable and potentially useful when other agents are not available, other routes are not practical, and, most importantly, when the patient's opioid requirements are modest. In patients who are tolerant to moderate- to high-dose opioids, however, the relatively poor sublingual absorption of morphine and oxycodone, coupled with their relative lack of potency, limits their usefulness in the small sublingual space. Thus, for example, the administration of 1 mL of sublingual morphine sulfate solution (20 mg/mL)—assuming 20% bioavailability—provides the equivalent of 4 mg of parenteral morphine. Oxycodone, also available in a 20 mg/mL concentration, may be moderately more potent than morphine. These agents may be adequate for patients maintained on up to 30–60 mg/d of oral morphine equivalents, but are unlikely to provide adequate analgesia for patients on higher opioid doses. Instilling greater volumes—2 mL and certainly 3 mL—will likely result in leakage out of the sublingual space,[4] with uncertain pharmacokinetic and pharmacodynamic consequences.

Fourth, as would be a consideration with patients taking opioids by any route, what is the patient's hepatic and renal function? Morphine and possibly hydromorphone can be problematic in the face of renal failure due, in large part, to the accumulation of the neurotoxic 3-glucuronide metabolites. Fentanyl, sufentanil, and methadone appear to be safe in renal failure.[35] The fentanils appear to be safe in hepatic failure.[36]

DIRECTIONS FOR FUTURE RESEARCH

What is the role of salivary alkalinization for increasing sublingual opioid absorption? Preliminary data indicates a role for alkalinization for fentanyl,[27] methadone,[7] levorphanol,[7] oxycodone,[22] and possibly buprenorphine,[88] but not for hydromorphone.[7] Would the use of anticholinergics to decrease saliva production improve the absorption of liquid sublingual analgesics?

What is the potential of sublingual buprenorphine in severe cancer pain? Where is the analgesic ceiling located? How well will buprenorphine—sublingual or otherwise—work as a baseline analgesic? And is it feasible to use with rapid onset, short duration pure μ-opioid receptor agonists for episodic pain? The integration of a long-acting baseline opioid such as buprenorphone or methadone with a rapid-onset, short duration opioid such as a fentanil raises the intriguing possibility of total sublingual analgesia.

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