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THERAPY IN PRACTICE

Options for Treating Pain in Cancer Patients with Dysphagia

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Abstract Patients with chronic pain often develop dysphagia during the course of an advanced disease such as cancer. Opioids are the cornerstone of the management of cancer pain and are commonly administered orally. However, the oral route does not suit patients with dysphagia, who require alternative methods to administer analgesic drugs. Opioids given by parenteral or transdermal routes provide adequate pain control, being at least as efficacious as the oral route, but knowledge and experience in conversion ratios are mandatory when using these routes of administration. For breakthrough pain, transmucosal fentanyl preparations should be the preferred option and these can be given as needed due to the route of absorption. In addition, a new class of opioid formulations has been developed for use in dysphagic patients that are administered via nasogastric or enteral tubes while maintaining their sustained-release properties.

Key Points

The oral route is often not available for opioid administration in cancer patients due to dysphagia and thus alternative methods should be offered.

Opioids administered via transdermal and parenteral routes may provide efficient analgesia.

New technologies may be effective for administration of drugs, even in patients who have difficulties swallowing.

1 Introduction

Dysphagia is a swallowing disturbance associated with many neuromuscular conditions and the consequences of systemic weakness. It is a difficulty in swallowing and trouble passing food or liquid down the throat. Some people may gag, cough, or choke when trying to swallow, while others may feel like food is stuck in their throat. Difficulty swallowing means more time and effort to move food or liquid from the mouth to stomach and, in some cases, swallowing may be impossible. Persistent dysphagia may indicate a serious medical condition requiring treatment. Dysphagia can occur at any age but is more common in older adults [1] and the causes of swallowing problems vary. Esophageal dysphagia refers to the sensation of food sticking or getting hung up in the base of throat or in the chest after starting to swallow. The causes of esophageal dysphagia include the following [2]:

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(a) Acalasia: the lower esophageal sphincter doesn't relax properly, causing a food back-up into the throat. Esophageal muscles may also be weak. This condition tends to worsen over time.
(b) Diffuse spasm: poorly coordinated contractions of the esophagus after swallowing produce multiple high-pressure muscle contractions, also affecting the involuntary muscles in the esophageal wall.
(c) Esophageal stricture: a narrowed esophagus, due to tumors or scar tissue often caused by gastroesophageal reflux disease, can trap large pieces of food.
(d) Tumors: difficulty swallowing tends to get progressively worse due to muscular disturbances or stenosis.
(e) Foreign bodies: food or objects can partially block the throat or esophagus. People who have difficulty chewing, particularly older patients, are more likely to have a piece of food lodged in the throat or esophagus.
(f) Eosinophilic esophagitis: related to a food allergy, and is caused by an infiltration of eosinophils in the esophagus.
(g) Scleroderma: involves the development of scar-like tissue, causing stiffening and hardening of tissues and weakening of the lower esophageal sphincter, facilitating acid to back up into esophagus and causing frequent heartburn.
(h) Radiation therapy: this cancer treatment can lead to inflammation and scarring of the esophagus.

Dysphagia is often associated with other signs and symptoms, including pain while swallowing (odynophagia), a sensation of food getting stuck in the throat or chest, drooling, being hoarse, regurgitation, heartburn, food or stomach acid back-up into the throat, losing weight, coughing or gagging when swallowing, and the need to cut food into smaller pieces or avoid certain foods because of trouble swallowing. Thus, dysphagia has a severe impact on nutritional status [3]. Several conditions can interfere with the process of swallowing, including multiple sclerosis, muscular dystrophy, and Parkinson's disease. Sudden neurological damage, such as from a stroke or brain or spinal cord injury, can also affect the ability to swallow [2, 4]. Pharyngeal diverticula produce a small pouch collecting food particles in the throat, often just above the esophagus, leading to difficulty swallowing, gurgling sounds, bad breath, and repeated throat clearing or coughing. With the exception of dysphagia caused by stroke, for which there can be a marked improvement, dysphagia from other causes is stable or progressive and the prognosis depends on the underlying cause, its tendency to progress, the availability of therapy, and the response to therapy. Even dysphagia caused by a malignant obstruction can be palliated with endoscopic resection of part of the tumor and/or stenting. However, progressive neurologic and skeletal muscle diseases are the most difficult to treat and carry the worst prognosis. Some diseases are more likely to produce dysphagia as a result of local involvement and reactions to systemic and local treatments, including surgery and radiotherapy [4].

Cancer and anti-cancer treatments often cause a variety of adverse effects or complications. One of the most frequent causes of dysphagia is cancer, especially mouth, throat, or esophageal cancers as cancer growing in these areas may narrow the passages. Head and neck cancer is a relevant risk factor for dysphagia, as is a low Karnofsky level, possibly as an expression of generalized weakness, involving most muscles, particularly in the last weeks of life. Difficulty swallowing also occurs after some anti-cancer treatments, including radiation therapy, surgery, and, less commonly, chemotherapy [5]. Such treatments may cause swallowing difficulties with different mechanisms:

– Physical changes to the mouth, jaws, throat, or esophagus due to surgery.
– Fibrosis (scarring or stiffness) in the throat, esophagus, or mouth (particularly occurring after surgery).
– Mucositis, which is soreness, pain, or inflammation in the throat, esophagus, or mouth, often associated with chemotherapy.
– Dry mouth, also called xerostomia, frequently occurring after radiation therapy or chemotherapy, or associated with concomitant use of drugs with anticholinergic activity [6].
– Infections of the mouth or esophagus, often occurring after radiation therapy or chemotherapy.
– Swelling or narrowing of the throat or esophagus, which occurs after surgery or radiation therapy.

2 Cancer Pain

Pain is one of the most prevalent, burdensome, and feared symptoms among cancer patients. The prevalence of pain in the cancer population has been estimated to be high, and rises according to the stage of disease. Moreover, chronic pain in cancer survivors affects approximately 33% of patients [7]. Pharmacologic treatment, particularly with opioids, is the foundation of cancer pain management.

The most common route of opioid administration for the management of moderate to severe chronic cancer pain is by mouth; oral medications are preferable in patients with advanced cancer because of its ease of administration. The oral route is simple, safe, inexpensive, and effective [8]. However, treatment of chronic pain in dysphagic patients poses serious problems. Regardless of its etiology,

dysphagia compromises the ingestion of fluids and/or solids, including oral medications. The combination of chronic pain with dysphagia presents a challenge to physicians and patients alike when oral opioid analgesia is needed to control pain but patients are unable to swallow solid, oral dosage forms [9]. Patients with cancer pain may experience difficulty swallowing, in part due to worsening disease, co-morbid conditions, iatrogenic etiology, or age. The presence and severity of dysphagia compromise the ingestion of fluids and liquids in a large number of patients, half of whom require alternative routes of drug administration [10]. This population often alters their oral medications by crushing or chewing them in an attempt to make them easier to swallow [11].

3 Management of Cancer Pain

Alternative drug administration routes are often used along the disease course for different reasons, including poor analgesic response or poor availability due to low intestinal absorption. In the presence of dysphagia, it should be mandatory to provide analgesic drugs through a non-oral route [12]. In a study by Pergolizzi et al. [13], pain physicians indicated that 5–20% of their patients had difficulty swallowing. Until recently, the treatment of chronic pain consisted of transdermal fentanyl, immediate-release or extended-release (ER) opioids, and methadone syrup. However, these currently available treatment options were reported to be unsatisfactory by physicians. On the other hand, 29% of dysphagic patients with pain had trouble swallowing or disliked swallowing pills. Interestingly, in 80% of cases, physicians did not ask patients about their ability to swallow solid, oral dosage forms. To circumvent swallowing problems, a minority of patients (16%) crushed their medication, most of whom (65%) were unaware that altering tablets could potentially change the drug release of the tablet, possibly leading to serious adverse events [13]. Liquid solutions of opioids may still be ingested in some patients with some forms of dysphagia; however, they are not recommended, particularly in some non-medical environments or in unstable patients whose clinical condition may change to one that definitely precludes the use of the oral route, unless a nasogastric tube or gastrostomy is present.

Although oral opioid administration is preferable in most cancer patients with pain, alternative modes of administration, including transdermal or parenteral routes, should be considered when the oral route is not feasible. The transmucosal route of administration may be helpful to treat patients who are unable to swallow in some particular circumstances, such as for the management of breakthrough pain. However, ER formulations usually lose a substantial proportion of their properties when ground or crushed and some oral morphine preparations are used off-label, with patients opening the capsules. More recently, a microsphere-in-capsule abuse-deterrent formulation designed to retain its ER properties following tampering or misuse (e.g., chewing, crushing) has shown clinical advantages such as the possibility to administer the drug via an enteral tube or by sprinkling it onto soft food, allowing its use even in patients with swallowing difficulties.

3.1 Transdermal Administration of Opioids

Patients who have malignancies of the head and neck region or of the gastrointestinal tract frequently present with symptoms—such as dysphagia, severe nausea and vomiting, or constipation—that require parenteral or non-oral administration of opioids [12]. The transdermal administration of opioids provides a simple, non-invasive alternative that produces stable blood drug concentrations comparable with those achieved with continuous infusion. For patients who are unable to swallow, transdermal opioids are an effective, non-invasive means of opioid delivery [14]. Unlike morphine, which is highly polar and does not easily penetrate human skin, the low molecular weight, high potency, and lipid solubility of fentanyl and buprenorphine make them suitable for delivery via the transdermal therapeutic system. Transdermal fentanyl and buprenorphine delivery systems enable a slow increase of drug plasma concentrations, with very long apparent half-lives (several days) and a long latent period before pharmacological steady states are reached. The amount of drug released per hour is proportional to the surface area of the patch on the skin. At the start of transdermal treatment, a depot accumulation of the drug results in a significant delay between the time that the initial patch is applied and the time that clinically relevant plasma drug concentrations are achieved [15]. For these reasons, cancer patients using transdermal preparations require concomitant use of short-acting opioids during the titration period. The initial analgesic effect can be observed after 12 h, but this delayed onset of action is not problematic with repeated dosing. Dry skin and thickness of the subcutaneous tissue is often observed in older patients and may limit the effective use of transdermal drugs. In addition, the transdermal route is likely to be less useful in patients with generalized edema because absorption is unpredictable. Moreover, increased skin temperature may cause drugs to be absorbed too rapidly. The slow pharmacokinetics of transdermal systems make them appropriate only for patients with a relatively stable pain condition. Therefore, patients who have unstable pain, require rapid titration of the analgesic dose, or need frequent dose changes are not candidates for

transdermal systems, unless an intravenous route is used to achieve pain control and then converted to transdermal therapy once clinical stabilization is achieved. High dosage requirements are a limiting factor in cachectic patients with poor peripheral circulation [12].

3.1.1 Fentanyl

Additional fentanyl delivery systems are available commercially. With the transdermal therapeutic system (TTS), the amount of fentanyl released per hour is proportional to the surface area of the patch on the skin. Commercial dosing systems provide delivery rates of 12, 25, 37, 50, 75, and 100 μg/h. However, the availability of these dosages is not uniform across different countries. The pharmacokinetics of this system suggest that serum concentrations of fentanyl can be maintained long enough to provide constant analgesia for 72 h, with small fluctuations in the serum concentration after the second application [15]. Due to dermal depot accumulation of fentanyl, the serum half-life is longer than 16 h. In terms of efficacy, there is no overall difference in the adverse effect profile among transdermal opioids, including buprenorphine and fentanyl, with slow-release morphine in moderate to severe cancer pain [16]. Constipation was less problematic in patients treated with transdermal fentanyl [17]. Cutaneous reactions to the patch, including erythema and itching, are generally rare, mild, and transient [18]. This suggests that in some cases, for example when they are unable to swallow, transdermal opioids are appropriate and effective even in patients who have not previously received step III opioids. The European Association for Palliative Care (EAPC) expert group provided a weak recommendation that either drug (transdermal buprenorphine or fentanyl) may be the preferred step III opioid for some patients. Along the disease trajectory there is a time at which the oral route is no longer available and a switch to the transdermal route is advisable. However, controversy exists regarding how to safely and effectively switch from oral morphine to fentanyl TTS. Conversion from oral morphine to transdermal fentanyl has been demonstrated to be effective and safe [19], and patients with a stable, low level of cancer pain could be switched from oral morphine to transdermal fentanyl using a 100:1 ratio. For some patients, however, concerns regarding limited cross-tolerance, advanced age, or sensitivity to opioids should also be addressed.

3.1.2 Buprenorphine

The buprenorphine patch has been approved for use in most European countries since the 1990s, in doses of 35, 52.5, and 70 μg/h (patches containing buprenorphine 20, 30, and 40 mg, respectively), with patch application every 3–4 days. More recently, low-strength patches (5, 10, and 20 μg/h) that are changed weekly have become available for clinical use, with possible indications for frail patients or children. The available buprenorphine patches (35, 52.5, and 70 μg/h) have been found to be useful in opioid substitution for reliable equipotent ratios, even at medium high doses of oral morphine equivalents [20, 21]. The use of low doses of buprenorphine in opioid-naïve cancer patients was shown to be effective and well-tolerated, as were other opioids, when used as a step II drug [22]. Some studies have shown that doses can be further increased (up to 140 μg/h; two patches of 70 μg/h), producing a proportional increase in the analgesic effect [23]. It has been shown that stable cancer patients receiving relatively high doses of opioids, oral morphine, or transdermal fentanyl can be switched safely to transdermal buprenorphine using a ratio of 70:1 (for morphine) or 0.6:0.8 (for fentanyl), confirming that the passage from or to other opioids is feasible without important consequences [21]. Other beneficial properties include the compound's favorable safety profile, particularly in elderly patients and those with renal impairment [24, 25], and its lack of effect on sex hormones and the immune system [26]. These issues suggest that in the presence of dysphagia, oral opioids could be switched to transdermal buprenorphine to maintain pain control.

3.2 Parenteral Opioids

In addition to being indicated for patients with nausea and vomiting, or those who are at the end of their life who are unable to continue with oral analgesics because of weakness or debility, parenteral opioid administration is often necessary for patients who cannot swallow. Dysphagia is the main indication for using the subcutaneous route, as are vomiting, bowel obstruction, comatose state, breakthrough pain, and initial opioid dose titration requiring frequent dose changes [27]. Intravenous and subcutaneous infusions can be used to achieve optimum pain control in patients unable to achieve adequate analgesia with oral and transdermal administration. Techniques for patient-controlled analgesia can be adopted for subcutaneous and intravenous opioid infusions in patients who are able and willing to be in control of rescue doses. Before beginning this approach, patients and caregivers need to consider the choice of pump, drug, mode of infusion, dosing schedule, family and community healthcare system resources, and cost [28]. Some patients may require a change in the route of administration because they are no longer able to swallow oral medications. An oral-to-intravenous relative potency ratio of 1:2 to 1:3 in patients with cancer pain receiving long-term morphine treatment has been used commonly [29].

When opioids are administered by a parenteral route, there is a short time to the peak analgesic effect, which

facilitates a more rapid dose adjustment. The subcutaneous route has been shown to be equianalgesic to intravenous administration of morphine when administered as a continuous infusion [30]. Pharmacokinetic studies have demonstrated that identical doses of subcutaneous and intravenous infusions provide satisfactory analgesia with comparable adverse effects. The absorption at higher doses may differ, however, and this may account for the possible need for dose increases with subcutaneous infusions [31]. In a randomized trial comparing subcutaneous and intravenous morphine dose titration in patients with uncontrolled cancer pain, boluses of morphine were calculated on the basis of the previous oral dose and given every 5 or 30 min intravenously and subcutaneously, respectively. An improvement in pain intensity was observed with both routes with mean morphine intravenous and subcutaneous doses of approximately 18 and 56 mg, respectively. Subcutaneous morphine titration required more time and higher doses than intravenous titration, although no differences were observed after 24 h [32]. These findings suggest that intravenous morphine titration allows timely analgesic activity.

3.2.1 Subcutaneous Route

Subcutaneous administration is a simple method that allows administration of parenteral opioids in settings such as hospices, nursing homes, or homecare. The advantages of subcutaneous administration consist of small needles, the ability to use multiple injection sites, easy insertion of the needle, and close supervision being unnecessary. A plastic cannula can easily be inserted in the patient's anterior chest or abdomen to avoid multiple injections. Subcutaneous infusion is a cost effective, simple technique for providing analgesia similar to that achievable with the intravenous route, particularly in poorly developed countries [27]. In most other cases, the subcutaneous route should be considered the standard alternative systemic route.

In a survey of cancer patients followed at home, the preferred alternative route to oral administration of opioids was the subcutaneous route, while the intravenous route was most often used in patients who already had central vascular access. Although continuous subcutaneous infusion offers stable blood drug concentrations, it has not been shown to control pain more effectively than intermittent administration, which is a very simple technique that does not require infusers or pumps. During the steady-state administration of subcutaneous morphine, there is a large inter-individual variation in plasma morphine concentrations, with a poor relationship to the daily administered dose [12].

The limited capacity of subcutaneous tissue to absorb fluid is a relevant advantage when patients need very high doses of opioids. The use of the subcutaneous route is problematic in patients with coagulation disorders, severe immunosuppression, fluid retention at the infusion site, or low skin perfusion [14].

3.2.2 Intravenous Route

The intravenous route allows patients to receive a continuous infusion of opioids. However, since this route requires prolonged venous access and close supervision, it may prevent many patients from returning home. On the other hand, a growing number of cancer patients are implanted with a permanent venous access, for example port systems or peripherally inserted central catheters. The intravenous route may continue to have a role in cases in which large volumes of opioids are administered or in specialized settings [27]. Intravenous infusion should be considered when subcutaneous administration is contraindicated (e.g., because of peripheral edema, coagulation disorders, poor peripheral circulation, and a need for high volumes and doses) [14]. Intravenous administration should also be used for opioid titration when rapid pain control is needed. The relative potency ratio of oral to intravenous morphine in patients receiving long-term treatment for cancer pain was approximately 1:3 [33]. Subcutaneous and intravenous administration of opioids have been compared and a similar efficacy and tolerability with both types of administration, as well no difference in the dose used, were found. However, analgesia was achieved faster with the intravenous route [33].

3.3 Transmucosal Route for Breakthrough Cancer Pain

The mouth has three areas for potential transmucosal delivery: sublingual, buccal, and gingival mucosa. Similarly, the nasal cavity offers a large surface for absorption of lipophilic substances. While morphine is not readily absorbed in the mouth because of its low lipid solubility, opioids with high lipid solubility, such as buprenorphine, fentanyl, and methadone, are absorbed to a significantly greater extent. Fentanyl is a potent and strongly lipophilic drug that matches characteristics that allow its passage through the mucosa and then across the blood–brain barrier to provide fast analgesia. Transmucosal administration of fentanyl has grown in popularity in recent years due to the rapid effect clinically observable 10–15 min after drug administration, obtainable using non-invasive forms [34]. The short onset and duration of the analgesic effect of fentanyl preparations make transmucosal fentanyl

appropriate for treating breakthrough pain episodes, but not for chronic pain, due to their rapid absorption and short analgesic duration. Different technologies have been developed to provide fast pain relief with fentanyl delivered by non-invasive routes. Invariably, all of these preparations may be administered in pain patients with dysphagia. Fentanyl availability ranges from 25 to 90%, depending on the existing delivery systems, which include oral transmucosal fentanyl citrate, fentanyl buccal tablet, sublingual fentanyl, intranasal fentanyl, fentanyl-pectine nasal spray, and fentanyl buccal soluble film. All studies performed with fentanyl products, also known as rapid-onset opioids, have recommended that these drugs be administered to opioid-tolerant patients receiving doses of oral morphine equivalents of at least 60 mg. Their efficacy was superior and more rapid than oral opioids [35].

3.4 Pharmacological Manipulation of Oral Opioids

There are new solid, oral-dose opioid formulations that can mitigate the problems associated with swallowing difficulties while still providing practical, effective analgesia, as well as mitigating accidental exposure and abuse liability. The drug release rate of a new, ER, abuse-deterrent, microsphere-in-capsule formulation of oxycodone for patients with chronic pain and dysphagia has recently been investigated via the alternate modes of opening the capsule and sprinkling the microspheres onto soft foods or administration through enteral tubes. The preparation can also be administered directly via enteral tubes without affecting drug release and without clogging enteral tubes [36].

In a randomized, open-label, active-controlled crossover study in volunteers, five oxycodone treatments (40 mg) were administered, including an abuse-deterrent formulation of oxycodone (intact or crushed), traditional ER oxycodone (intact or crushed), and immediate-release oxycodone (crushed). Both the crushed and intact abuse-deterrent formulation of oxycodone resulted in lower peak plasma concentrations (C_{max}) than immediate-release oxycodone. The crushed abuse-deterrent formulation of oxycodone was bioequivalent to the intact abuse-deterrent formulation of oxycodone and exhibited a numerically lower C_{max}. Moreover, the median time to C_{max} (t_{max}) was unchanged by crushing. In contrast, the mean oxycodone C_{max} values for crushed traditional ER oxycodone were significantly higher than intact traditional ER oxycodone and were bioequivalent to immediate-release oxycodone. The t_{max} for crushed traditional ER oxycodone was similar to that of immediate-release oxycodone and significantly shorter than intact traditional ER oxycodone. These pharmacokinetic data suggest that an abuse-deterrent formulation of oxycodone may be less attractive to illicit drug users than existing abuse-deterrent formulations, and may be a safer option for patients who may unknowingly crush their medication, such as those who have difficulty swallowing [37, 38]. The abuse-deterrent formulations of ER oxycodone can be administered either intact, sprinkled onto soft foods, or via gastrointestinal tubes, thereby providing options for treating pain in patients who have difficulty swallowing. No difference in the dissolution profile was found when administered with various soft foods or when mixed with various liquid vehicles and administered via nasogastric or gastrostomy tubes, based on in vitro studies. When sprinkled onto applesauce and administered orally, the microspheres were bioequivalent to the intact oxycodone capsules. When crushed or chewed, the formulation maintained its pharmacokinetic profile; no bolus dose of opioid was released. However, the sprinkle-dose study was limited by the single-dose study design as well as the small sample size [39]. Although no study assessed the efficacy of this formulation in patients with advanced cancer, it is likely that it could also be useful for those in this patient group who have difficulties in swallowing.

4 Conclusion

Many patients with chronic pain develop dysphagia along the course of a chronic and debilitating disease such as advanced cancer. Most of these patients receive opioid therapy, commonly given orally, and thus alternative methods are mandatory to continue the analgesic therapy when dysphagia is present. Parenteral and transdermal routes are at least as efficacious as the oral route for opioid administration, although they require knowledge and expertise in conversion ratios. Transmucosal fentanyl preparations can be given as needed for breakthrough pain in both patients who are able to swallow and those with dysphagia. In addition, a new class of opioid formulations has been developed that can be used in dysphagic patients, which are administered via nasogastric or enteral tubes while maintaining their sustained-release properties.

Compliance with Ethical Standards

Conflict of interest Sebastiano Mercadante has no conflicts of interest to declare.

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