Prevention of Opioid Side Effects

T. Declan Walsh, MSc
Department of Hematology and Medical Oncology, Cleveland Clinic Cancer Center, Cleveland, Ohio

Abstract
Physician education in cancer pain management is seriously deficient. Many problems occur with opioids simply because of therapeutic ignorance. Opioid side effects are best prevented by using morphine as the drug of first choice for severe pain. Anticipation and prevention of opioid side effects avoids most problems. Physicians need to be aware of how to transfer patients from one opioid to another or from one route of administration to another. Side effects common in clinical practice are constipation, nausea/vomiting, dry mouth, and sedation. The importance of the issues of tolerance, dependence, and respiratory depression have been exaggerated. J Pain Symptom Manage 1990;5:362-367.

Key Words
Opioid, morphine, side effects, nausea/vomiting, sedation, constipation, dependence, tolerance, respiratory depression

Correct Use of Opioid and Nonopioid Analgesics

Prevention of drug side effects in cancer pain management is best achieved, as in any other area of therapeutics, by using a small number of drugs for specific indications. This allows the prescriber to become familiar with the common side effects, their prevention, and the management of those unwanted effects that could not be prevented or were unforeseen. Prevention of opioid side effects is thus best achieved by a three-pronged approach: first, ensure that the medication chosen is employed correctly; second, anticipate common, predictable side effects and advise the patient and family about how best to deal with these; and third, bear in mind common drug interactions that may precipitate side effects in a given therapeutic setting.

An important question that must be considered first is whether use of an opioid is appropriate in a given situation. Many cancer patients can have their pain managed for at least some period of time by nonopioid analgesics, e.g., nonsteroidal antiinflammatory drugs. While it is true that the nonsteroidal antiinflammatory drugs have their own unwanted effects and specific contraindications, these are different than those associated with the
prevent the use of opioids altogether and consider an alternative agent in a given individual. This is particularly important to consider in those with a history of previous intolerance, e.g., nausea and vomiting, to opioids.

Many patients do not have confidence in simple analgesics, such as acetaminophen (Tylenol). This is usually because these medications are available as over the counter (OTC) preparations. Patients must be reassured that these are indeed effective analgesics, provided they are used correctly, and the correct use of these agents in terms of frequency of dosing and dosage must be explained carefully. Once this is done, administration of an opioid may be able to be deferred, or the daily opioid dosage reduced, by the use of a simple analgesic. If added to an opioid, these nonopioid analgesics can either be given regularly as an adjuvant or as needed for "breakthrough" pain.

If an opioid is indicated for the treatment of chronic cancer pain, many problems can be avoided by choice of the best drug. In the author's view, morphine is the single best agent. The reasons for this do not lie in the fact that morphine is intrinsically a superior analgesic, but in the flexibility of dosage, formulations, and routes of administration available. Morphine may be given orally in liquid or sustained release tablets, sublingually, by suppository, by intramuscular/intravenous/subcutaneous injection, by continuous infusion (either subcutaneous or intravenous), and occasionally by epidural, intrathecal, and intraventricular administration. Alternatives to morphine, including hydromorphone (Dilaudid), and levorphanol (Levodromoran), have no apparent advantage over morphine in routine clinical practice. There is also less systematic clinical experience in their use, and fewer formulations are available.

There is extensive clinical experience in the use of morphine. Units in North America and Europe that specialize in the care of patients with advanced cancer have demonstrated a consistent preference for morphine, for the reasons described earlier. The correct use of morphine when given by mouth is well established and is summarized in Table 1.

Critical to the prevention of opioid side effects is the education of the patient and family in the correct use of the drug. Implicit in this process is the assumption that the physicians, nurses, and pharmacists involved are themselves familiar with the correct principles and practice of pain control in advanced cancer. Unfortunately, this is often not the case. Curiously, many cancer specialists have little or no training in pain control or symptom management. Nursing staff are often more concerned with the potential side effects of opioids than methods to achieve efficacy, so that even if orders are correctly written by the physician, nurses may be unwilling to carry them out because of fears of problems such as respiratory depression. Pharmacists are often excessively concerned with the legal and administrative requirements involved with opioid prescribing and are reluctant to dispense the "large" doses of morphine that some cancer patients require.

The prevention of opioid side effects is also aided by the avoidance of certain drugs in the treatment of cancer pain. These are the antagonist/opioids, such as pentazocine, which are associated with an unacceptable incidence of psychotomimetic side effects and do not produce analgesia superior to the agonist agents. In addition, codeine (constipation) and meperidine (short-acting and associated with a toxic metabolite) are best avoided for routine purposes. Codeine appears in the World Health Organization's (WHO) "analgesic ladder" as a recommended intermediate choice before use of morphine, and the recommendation to avoid it may be controversial; its selection by the WHO appears to have been based on factors other than its efficacy or toxicity profile.

<table>
<thead>
<tr>
<th>Correct Use of Morphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administer by mouth</td>
</tr>
<tr>
<td>Give every 4 hr, not &quot;prn&quot;</td>
</tr>
<tr>
<td>Review dose every 24 hr</td>
</tr>
<tr>
<td>Titrate dose against the pain (2.5–15 mg)</td>
</tr>
<tr>
<td>Use a breakthrough dose of 10%–25% of 4-hr dose</td>
</tr>
<tr>
<td>Use 3:1 dose ratio (mg) when transferring from PO to IV/IM/SC</td>
</tr>
<tr>
<td>Use 1:1 dose ratio (mg) when transferring from oral liquid (every 4 hr) morphine to oral sustained release tablets (every 12 hr)</td>
</tr>
<tr>
<td>Titrate dose down when morphine no longer needed</td>
</tr>
</tbody>
</table>
Methadone is a potentially dangerous agent in this patient population. In the author's view, it is associated with unacceptable toxicity because of its tendency to cumulate in patients with renal and hepatic impairment, and it should be abandoned except for specialist use.

**Incorrect Use of Opioids**

The major unwanted effect of incorrect use of opioids is, of course, poor pain control. While this is almost never the intention of the prescribing physician, it is unfortunately often the end result. In addition, by exposing the patient to hazards from opioid side effects caused by incorrect prescribing practices, the physician may indeed impair rather than improve the quality of life for that patient.

Among the common errors in the use of opioids is the use of "prn" prescribing. This is commonly done on the assumption that prn usage will reduce the opioid dose requirements in terms of total dosage required per 24 hr, thereby reducing the risk of problems like dependence. In truth, the reverse is often the case, as prn dosing creates a "see-saw" effect that may result in a rapidly escalating opioid dosage to achieve good pain control. Initial relief of the pain is followed by pain recurrence, and along with it, anxiety that lowers the pain threshold. A further, often larger, dose of medication is then required to reestablish pain control. The pain then returns, and the sequence is repeated.

Use of prn prescribing may be accompanied by failure to recommend an every 4 hr dosing schedule. Most opioids appropriate for routine cancer pain management, e.g., morphine, oxycodone, hydromorphone, are best given on this schedule, although it is unclear why this time interval is so universally effective. Use of opioids at inappropriately long intervals, e.g., every 6 hr, is associated with the same problems produced by prn dosing.

The concept of a "breakthrough" dose is essential to optimal use of opioids. Failure to do this results in inadequate assessment of pain severity, with resultant failure to titrate and individualize the dosage (also a major bedrock of therapy). Medication for pain breakthrough does not have to be an opioid if opioid side effects are a concern and pain breakthrough is mild.

**Formulations and Routes of Administration**

Using the wrong route of administration is common. Whenever possible, opioids should be given by mouth. It is commonplace for patients with advanced cancer who have chronic pain to receive intravenous morphine sulfate infusions without a prior trial of oral medication. The dose of the infusion is often ill-defined and inappropriately determined. Use of such infusions is associated with an unacceptably high incidence of side effects when administered by physicians or nursing staff ignorant of the correct use of opioids. Overdosed patients become restless, sweaty, agitated, and confused. Many of these patients will tolerate oral medications provided they are used correctly.

A common cause of opioid side effects is inappropriate adjustment of dosage when one is transferring from one route of administration to another, from one opioid to another, or from one formulation to another of the same opioid. Many physicians are unaware that equianalgesic doses must be considered when one is changing from one opioid to another or from one route of administration to another. Tables of equianalgesic dosages (Table 2) are available and provide a general reference guide suitable for practical purposes. The use of such tables avoids serious underdosing or overdosing. An appropriate knowledge base by the prescribing physician is essential in this area. For example, the clinician should be aware of the 3:1 ratio when transferring patients from the oral or parenteral route of administration for morphine.

**Table 2**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>MG every 4 hr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>PO</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>IM/SC/IV</td>
<td>10</td>
</tr>
<tr>
<td>Codeine</td>
<td>PO</td>
<td>120</td>
</tr>
<tr>
<td>Dihydrocodeine</td>
<td>PO</td>
<td>60</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>PO</td>
<td>30</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>PO</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>IM/SC/IV</td>
<td>2</td>
</tr>
<tr>
<td>Methadone</td>
<td>PO</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>IM</td>
<td>10</td>
</tr>
</tbody>
</table>

*During repeated administration; doses are approximate.*
(i.e., 3 mg by mouth = 1 mg by injection). This ratio applies to intermittent bolus injections, continuous intravenous, or continuous subcutaneous infusions. Another example is the necessity of using a milligram per milligram conversion when one is switching from morphine to one of the sustained release morphine preparations (MS Contin or Roxanol SR). Failure to do this will result in underdosing (pain breakthrough) or overdosing (morphine side effects).

Many opioid side effects can be altered by simply using a different route of administration. Patients intolerant of oral opioids because of severe nausea can be transferred to the same medication given by continuous subcutaneous infusion. This may result in eradication of side effects with continued good analgesia. Likewise, particular patient populations may present specific problems. For example, those with advanced cancer of the esophagus may be unable to swallow oral medication, and substitution of the same medication by the sublingual route or by suppository can deliver satisfactory analgesia without any unwanted effects.

**Common Opioid Side Effects in Clinical Practice**

Constipation is undoubtedly the most common opioid side effect. This is predictable, and its frequency and severity mandates the prescription of a laxative regimen, at the same time a prescription is written for a regular opioid analgesic. It is important to remember that tolerance to this effect of opioids occurs very slowly, if at all, and that so long as an individual is taking a regular opioid, constipation may be inevitable. It is noteworthy that this effect seems more pronounced and more specific with codeine than other agents.

A laxative regimen implies the routine use of a stool softener, along with an osmotic laxative such as milk of magnesia. Provided a stool softener is taken on a daily basis and started at the time that the opioid is begun, most patients do not become constipated. Patients must be carefully instructed to take a dose of milk of magnesia last thing at night, should their bowels not move as expected. The combination of the two types of agents almost invariably ensures bowel function.

Those in whom there are difficulties with the above or who are already constipated because of previous analgesic and insufficient laxative use should be advised to use a daily stimulant laxative, such as bisacodyl (Dulcolax) in suppository or tablet form. If constipation is unresponsive to these measures, then some degree of fecal impaction is present and must be managed vigorously by use of these same measures, in addition to daily use of stimulant laxatives, enemas, and, if necessary, manual disimpaction under sedation.

Nausea and vomiting are often considered common problems with opioids, and some physicians automatically prescribe an antiemetic along with the initial doses of an opioid. This may be an indication of the tendency to blame the opioid for any new symptoms that may occur. Patients given these medications have many reasons to be nauseated, and this must be borne in mind in assessing the problem. Nausea and vomiting induced solely by opioids, even when given by mouth and in regular dosing, are uncommon. Most patients report only mild nausea and/or anorexia after initiation of regular opioid medication. The nausea is transient and will subside within 2–3 days. Patients should be warned concerning the possibility, informed that it is usually transient, and instructed to take appropriate action should severe nausea or vomiting ensue. Those patients who have a history of opioid gastrointestinal intolerance should always be given a routine prophylactic antiemetic.

It is unclear if opioid-induced nausea is centrally or peripherally mediated. Prochlorperazine (Compazine) or metoclopramide (Reglan) seem to work equally well. A small number of individuals given oral opioids develop intractable large volume emesis. This is more common in women. Clinically, this resembles the vomiting seen in pyloric obstruction and occasionally will respond dramatically to metoclopramide, suggesting a peripheral mechanism of opioid induced vomiting in these particular individuals.

Sedation is also a common problem. Fortunately, it too is often transient and subsides with continued opioid use. Patients should be warned of the possibility, and it is important to advise the patient and family against the risks of driving, using machinery, etc. The sedation is usually manifested by transient periods of sleepiness and lack of concentration. In a mi-
nority, these symptoms persist despite regular opioid use and in the absence of any recent changes in dosage. In these individuals, a decision must then be made about the level of pain control that has been achieved. It may be that some reduction in opioid dosage is possible, in which case the dosage should be reduced in a stepwise fashion similar to that by which it was increased. It is also important to review the patient's breakthrough medication to ensure that it is not contributing to these symptoms. All medication that the patient is taking should be reviewed and sedative, but nonessential medications should be eliminated from the patient's regimen. Among individuals in whom it proves impossible to reduce their opioid dose because of recurrence of pain, addition of a stimulant, e.g., methylphenidate, should be considered.

Confusion may be a side effect of opioids. It is often a sign of relative opioid overdose caused by excessively frequent changes in dosage or inappropriately large increases in dosage. In persons with advanced cancer, there are many other causes of confusion, including cerebral metastases, hypercalcemia, dehydration, sepsis, etc. Among those individuals in whom the confusional state is indeed due to overdose, this will clear as the opioid dosage is reduced in a stepwise fashion. In the absence of a threat to life and in the presence of a secure airway, the use of naloxone should be avoided. Administration of naloxone in this situation can precipitate a severe massive pain breakthrough that is a horrifying experience for these patients. Naloxone should only be used in these situations where there is a clear threat to life caused by coma or respiratory depression in an individual with an otherwise reasonable prognosis.

**Common Misunderstandings About the Use of Morphine**

A number of misunderstandings have arisen in clinical teaching about the use of opioids. This has adversely affected the education of physicians, nurses, and paramedical staff involved in caring for patients with chronic pain caused by advanced cancer. While many studies have been conducted to examine the clinical pharmacology and pharmacokinetics of opioids, it is unfortunate that the results of these studies have been often misinterpreted, or misapplied, to patient populations who were not objects of the study. The result has been undue apprehension among prescribing physicians concerning the problems of tolerance, dependence, and respiratory depression. Principally, these concerns have been reflected in physicians' confusion about the best choice and method of administration of opioids, and excessive concern about dosage and frequency of dosing. This has resulted in inadequate control of cancer pain, which has been amply documented.

**Fear of tolerance** is reflected in the concern that increasing dosages of morphine may result in persistently inadequate pain control. That is, once a physician initiates the use of regular opioids, there is a concern that there will be a relentless increase in opioid requirements to maintain adequate, or indeed inadequate, pain control. In truth, provided that regular dosing is adhered to and the concept of the use of breakthrough analgesics is employed vigorously, along with a commitment to individualization of dosage, tolerance is an unusual phenomenon in the cancer patient.

Opioids have specific indications in the treatment of different types of pain, and a poor diagnostic approach to the cancer pain problem may cause an increase in opioid dosage that is simply due to using an inappropriate agent for a particular problem (e.g., a syndrome that might be best treated with radiation therapy). There are specific pain syndromes, e.g., brachial plexopathy, wherein a suboptimal response to opioids is often demonstrated. It is unclear if these pains are simply partially opioid unresponsive or if there is a true tolerance phenomenon. It must be emphasized that tolerance is not solely associated with opioids but is a pharmacologic phenomenon common to many different drugs.

The tolerance issue has been addressed repeatedly in the literature that deals with the opioid addict population. This population is an inappropriate model for the cancer pain population. In the majority of cancer patients, increase in dosage requirements is associated with increase in extent of disease and is not a problem in those with relatively stable disease.

**Dependence** is another pharmacologic phenomenon associated with opiates and other drugs. Ignorance about the correct use of opioids can create self-fulfilling prophecies concerning "addiction." Drug seeking behavior,
i.e., addictive behavior, is rare in patients given opioids for chronic cancer pain.\textsuperscript{14} Data derived from street addicts is also entirely inappropriate to this population. While there is no doubt that those given opioids on a regular basis by whatever route of administration will become physically dependent, this does not imply addictive behavior patterns.

Because of the concern about tolerance and dependence, it is common for patients who request extra opioids (simply because they have been prescribed inadequate doses of the drug to begin with) to have their dosage reduced because of these inappropriate concerns. This, of course, worsens the pain and induces a vicious circle of pain complaint, dosage reduction, etc.

In the author's experience, when oral opioids are used, and withdrawal of opioid occurs (often in error), withdrawal symptoms are not severe and consist of mild-to-moderate anxiety, tremulousness, and sweating. This is so even in those taking large doses. Withdrawal in this setting does not have the dramatic picture associated with the addict "cold turkey" withdrawal syndrome. These symptoms can be avoided entirely, if withdrawal of opioids is indeed appropriate, by stepwise reduction of the opioids at 24-hr intervals in a fashion analogous to the initial dosage titration phase or to withdrawal of corticosteroids.

Respiratory depression rightly concerns many physicians. It is an intrinsic feature of many drugs (including opioids) that are central nervous system (CNS) depressants. Studies that have examined this area restrospectively\textsuperscript{8} and prospectively\textsuperscript{19} have concluded that, provided oral opioids are used correctly, the risk of respiratory depression is small. It is noteworthy, too, that opioids have been used in experimental and clinical practice to relieve the symptoms associated with chronic obstructive pulmonary disease and in dyspnea caused by advanced cancer.

It is rare to produce a respiratory depression with oral opioids in the absence of the following: simultaneous use of other CNS depressant drugs, rapidly changing respiratory status (e.g., pneumonia), or inappropriate increases in dosing or frequency of dose. Appropriate caution is indicated, as with any other drugs acting on the CNS, but excessive concern is misplaced. In the terminally ill patient, checks on respiratory rate and adjustment of opioid dosage accordingly are inapprpriate. The priority in the dying patient is relief of distress, not monitoring of the respiratory rate, and this practice, which is commonplace, should be abandoned.

References

15. Walsh TD. Opiates and respiratory function in advanced cancer. Recent Results Cancer Res 1984;89:115-117