How Cancer Pain is Treated

Appendix 1, Appendix 2 and Appendix 3

(A Supplement to the Print Version)

Note: This content is already included in the Onscreen Reading Version – it is published separately here for the convenience of readers of the Print Version

First published in 2011 by Wanterfall eBooks, Sydney

Second Edition 2013 by Wanterfall eBooks, Sydney

The work may also be read as a series of web pages, starting at www.wanterfall.com/Myths-and-Facts-about-Cancer-Pain.htm

Paper copies are best made by downloading the printable PDF file available at http://www.wanterfall.com/downloads.htm (Booklet mode printing on A4 paper gives the best results.)

Please note that printed copies of the parent booklet may be ordered at cost (currently less than A$1 [1 AUD] per booklet, plus postage) by sending an email to sales@wanterfall.com

Alternatively, the full version of How Cancer Pain is Treated may be read online, or downloaded as a PDF file for offline reading or printing, at http://www.wanterfall.com

CONTENTS

(If you are reading this booklet onscreen, open the Bookmarks pane to browse to any heading.)

APPENDICES 1, 2 & 3

(A SUPPLEMENT TO THE PRINT VERSION OF HOW CANCER PAIN IS TREATED)

DISCLAIMERS

These appendices, written by a senior medical practitioner with considerable experience in palliative medicine and hospice care, are offered purely for educational purposes. Nothing in them should be taken as therapeutic advice for any particular patient. Mention of any trade (brand) name should not be taken as an endorsement of the brand or its manufacturer.

CAUTIONS

If you read these appendices and their parent booklet carefully, and think about the information, in relation to a particular pain management problem affecting you or someone you love, you may sometimes be able to think of modifications to the current treatment which might be expected to improve the situation.

However, it is very dangerous to make changes to a patient's medication without first discussing them with the prescribing doctor. The doctor must always know *exactly* what the patient is taking, as virtually all medications can cause unwanted side effects and interact in various ways with other medications.

Importantly, this also applies to "natural", "alternative" or "complementary" therapies, many of which have significant interactions with prescribed medications. Therefore, even if you feel that the current pain management is not optimal, never make any changes without first discussing them with the doctor.

INTRODUCTION

Most patients with advanced cancer experience severe pain if they do not receive good pain management, but their pain can almost invariably be relieved if it is managed correctly.[1, 2] Patients whose cancer has been cured or is in remission may also need treatment for pain in some cases.

The principles of cancer pain management are well established[1], and indeed they have changed very little since I summarised them for a medical readership a quarter of a century ago[2]. However, there have been a number of useful practical developments, which have made treatment more convenient, reduced associated side effects, or, in some cases, provided better solutions to previously difficult problems.

Cancer pain can be relieved by treating the cancer itself; by inhibiting the mechanisms by which cancers can give rise to pain stimuli; by interrupting the "pain pathway" which carries pain stimuli to the brain; or by inhibiting the perception of pain stimuli which reach the brain, either by the use of medications or by non-drug interventions. All of these methods are discussed fully in the parent booklet available from www.wanterfall.com.

The information in these appendices (which were omitted from the print version of the booklet in order to keep costs down) is intended for a general readership. Therefore, although the issues discussed are complex, and many medications will be named, no medical or nursing knowledge will be assumed.

---

[1] World Health Organization. 1996. Cancer Pain Relief: with a Guide to Opioid Availability - 2nd ed. Geneva: WHO Publications.

[2] Coates, GT, "Management of cancer pain. A practical approach", Med J Aust 1985 vol. 142, pp. 30-35.

APPENDIX 1:
USE OF OPIOIDS IN RENAL FAILURE

Much of the information under this heading is not of direct relevance to patients and their carers, as the problems discussed will be addressed by the doctor. However, I have decided to provide the information in non-technical terms for the sake of completeness.

The metabolic products of most opioids are normally removed by the kidneys. They therefore tend to accumulate when renal function is reduced. Many of these metabolic products become toxic as their concentrations rise, causing muscle twitching and confusion, and in extreme cases convulsions, coma or even death.

It is not uncommon for patients who need opioid analgesia to also have some degree of renal failure, either as a result of their cancer, its treatment or some other illness. It is then necessary to watch carefully for the adverse effects caused by accumulation of toxic opioid metabolites. If they become significant, it may be necessary to change to an opioid which is better tolerated in renal failure.

Weak opioids

Weak opioids, if they are ever used at all, should not be administered to patients with a significant degree of renal failure. This is partly because their ratio of wanted to unwanted effects is relatively low to start with, and partly because that ratio deteriorates further as metabolic products which are normally removed by the kidneys accumulate in the bloodstream.

Pethidine

Pethidine (meperidine, demerol etc) is also completely unsuitable in renal failure (as it is in most other situations) because its metabolites are particularly toxic. Other strong opioids vary in their suitability for patients with renal failure, or for those undergoing renal dialysis, as discussed below.

Morphine, Oxycodone and Hydromorphone

Morphine is chiefly metabolised in the liver, and the resulting metabolites[3] are then excreted by the kidneys. They naturally accumulate in the bloodstream in renal failure, when they cause drowsiness, muscle twitching, hallucinations, and, at higher concentrations, convulsions, coma, and ultimately death.

Therefore, although morphine can be used cautiously in the presence of mild renal insufficiency, it often becomes unsuitable for continued use as renal function deteriorates. This is especially likely to be the case when the glomerular filtration rate[4] (GFR) is 10 ml/minute or less. Continued opioid analgesia will then usually need to be provided by a different opioid, as discussed later.

The hepatic metabolites of **oxycodone** and **hydromorphone** are probably somewhat better tolerated than those of morphine, but they also become toxic if their concentrations rise too much as a result of renal failure. When this occurs, these two opioids must also be replaced by an alternative opioid in order to maintain satisfactory opioid analgesia.

In the case of patients undergoing **renal dialysis**, morphine, oxycodone, hydromorphone and their metabolic products are usually reduced in concentration after each episode of dialysis. However, the degree of clearance varies with different dialysis systems, and is difficult or impossible to predict accurately.

In some cases, dialysis might cause failure of pain control, or even precipitate opioid withdrawal symptoms. In other cases, a reduction in opioid dosage might be necessary. Therefore,

---

[3] The most important hepatic metabolites of morphine are morphine-3-glucuronide, morphine-6-glucuronide and normorphine.

[4] Glomerular filtration rate (GFR) is usually the best measure of renal function. A fairly accurate estimate of the GFR can be derived from a simple blood test, though its exact measurement is more difficult.

unless a dialysis patient's condition remains entirely satisfactory, one of the opioids discussed below may need to be substituted.

Fentanyl

Fentanyl is removed from the bloodstream mainly by being metabolised in the liver. Its metabolic products appear to be virtually inactive, as their accumulation in renal failure does not usually cause any clinically significant problems.

In most cases, fentanyl is therefore the ideal opioid for patients in whom renal failure is severe enough to result in side effects from the accumulation of toxic metabolic products of other opioids, such as morphine, oxycodone or hydromorphone.

Fentanyl is not removed by most dialysis filters, so failure of pain control, or an opioid withdrawal syndrome, does not usually occur as a result of renal dialysis. However, close monitoring of the patient is always essential, as dialysis systems vary, and information about drug clearance is limited.

Buprenorphine

Buprenorphine is well tolerated in renal failure and during renal dialysis, as its hepatic metabolites are virtually inactive and are also excreted into the bile. However, in view of the low concentrations achieved by the currently available patches, it would usually need to be administered by continuous infusion. Its ability to precipitate opioid withdrawal must, of course, also be taken into account by the prescribing doctor in patients who were recently, or are currently, taking another opioid.

Methadone

Methadone also has the advantages of having well tolerated hepatic metabolites, and of hepatic excretion of its metabolites into the bile. However, as discussed under Strong Opioids, methadone should only be prescribed by clinicians with considerable experience in its use because its duration of action is variable and unpredictable, even in healthy people.

APPENDIX 2:
USE OF OPIOIDS IN HEPATIC FAILURE

Much of the information under this heading is not of direct relevance to patients and their carers, as the problems discussed will be addressed by the doctor. However, I have decided to provide the information in non-technical terms for the sake of completeness.

It is not uncommon for patients who need opioid analgesia to also have some degree of liver failure, either as a result of cancer in the liver or because of some other illness affecting it. As most opioids are removed from the body chiefly by being metabolised in the liver, an increased amount of the parent drug, and a decreased concentration of its metabolites (which sometimes provide part of the analgesic effect), is the usual result when hepatic function is significantly reduced. (Fentanyl is an exception to this rule, as discussed below.)

Weak Opioids and Pethidine

As in the case of renal failure, neither weak opioids nor pethidine should be used in patients with hepatic failure, as their combination of a weak analgesic effect and plentiful, sometimes serious, side effects leaves very little room for manoeuvre.[5] Other opioids vary in their suitability for patients with hepatic failure, as discussed below.

Morphine, Oxycodone and Hydromorphone

Morphine, oxycodone and hydromorphone can usually be used cautiously in hepatic failure by means of downward adjustment of the dose and/or upward adjustment of the interval between

[5] This may be particularly important in the case of codeine, and possibly also dihydrocodeine, as some of their hepatic metabolites (especially morphine, in the case of codeine) may contribute significantly to their analgesic effect. However, the metabolism of codeine and dihydrocodeine remains very incompletely understood at the time of writing.

doses. However, dosage adjustment can be expected to become more difficult as liver function deteriorates further.

Fentanyl

Although fentanyl is metabolised in the liver, its metabolism appears to require very little residual liver function. Markedly reduced hepatic blood flow can interfere with the metabolism of fentanyl, but hepatic failure itself rarely results in fentanyl accumulation. For this reason, fentanyl, which is usually the opioid of choice in the presence of renal failure, is also, in most cases, the opioid of choice when hepatic failure is severe enough to preclude the safe and effective use of morphine, oxycodone or hydromorphone. In many cases, it is not even necessary to use reduced doses of fentanyl in the presence of hepatic failure, but, of course, this should not discourage frequent review of the patient's response.

Buprenorphine

Buprenorphine is metabolised in the liver, and its metabolites are excreted into the bile. (They are also, to a lesser extent, excreted by the kidneys.) There are some reports of acute liver toxicity associated with buprenorphine in the presence of liver disease, but information about its use in this situation is otherwise quite sparse. At the time of writing, I would suggest that buprenorphine, if it is ever used at all, should not be used in the presence of significant liver disease unless all other strong opioids are contra-indicated.

Methadone

Methadone, which is very difficult to use safely at the best of times, should not be used in the presence of significant hepatic failure unless absolutely no alternative exists. This is simply because the risk of excessive blood levels of methadone developing will be greater, and more unpredictable, than ever.

APPENDIX 3:
SPECIAL MEDICATION DELIVERY SYSTEMS

Much of the information under this heading is not of direct relevance to patients and their carers, as the problems discussed will be addressed by the doctor. However, I have decided to provide the information in non-technical terms for the sake of completeness.

Syringe Drivers

Syringe drivers are very useful for delivering medication by continuous infusion, often via a "butterfly" needle which is sited subcutaneously somewhere convenient, such as the anterior surface of the chest or abdomen. If a single analgesic medication is being infused continuously, extra doses of a predetermined size can be added to that infusion by the patient or nursing staff if breakthrough pain occurs, or if incident pain is expected, simply by pressing a button on the device.

A syringe of suitable size is filled with the medication which is to be administered, placed in the device, and connected to a butterfly needle by a flexible tube. After expelling air from the system, the butterfly needle is inserted subcutaneously at the chosen site and covered with sterile adhesive film, which keeps it in place and also protects the entry point from contamination.

The plunger of the syringe is then moved along very slowly by the drive mechanism of the device, over a number of hours, at a rate set by the doctor, nurse or pharmacist. This rate is, of course, calculated so that the medication in the syringe will be administered exactly as fast as is necessary in order to provide that particular patient's baseline analgesia.

Although this sounds simple, the end result depends on quite a number of steps, each of which must be carried out correctly in order to achieve the desired effect. Therefore, anyone who is responsible for the use of this type of medication delivery

system must obviously be familiar with the particular device in use, as well as the general principles involved, and must have received suitable training and supervised experience.

The devices themselves can be quite temperamental. There have been some welcome advances in their engineering in recent decades, but they are still far from foolproof, so close monitoring of their function is essential. If, for example, the plunger jams and therefore fails to advance at the set rate, baseline analgesia will fail, and the patient's pain will return. Alternatively, if the rate is set incorrectly high, the patient will receive a progressively worsening overdose of the medication.

When necessary, multiple medications can be combined in a single subcutaneous infusion, though more frequent re-siting of the subcutaneous needle is then usually necessary. Morphine sulphate, hyoscine, haloperidol, metoclopramide, promethazine and midazolam are usually compatible together in a syringe.

Importantly, when there is more than one medication in the syringe, extra opioid doses for breakthrough or incident pain cannot be given from that syringe, as an extra amount of each other medication in the syringe would be received by the patient, as well as the desired extra dose of opioid.

Some medications, such as diazepam and prochlorperazine, cause irritation when infused subcutaneously. Morphine tartrate (which has the sometimes considerable advantage of greater solubility than morphine sulphate) is inclined to form a precipitate when mixed with various other useful medications. The assistance of a pharmacist is therefore invaluable when more than one medication is to be loaded into the syringe.

Patient-Controlled Analgesia Pumps

Although Patient-Controlled Analgesia (PCA) is primarily used for post-operative pain management, usually by the intravenous or epidural route, the same type of pump can be used as an

alternative to a syringe driver when baseline analgesia is being provided by continuous subcutaneous infusion.

In addition, PCA itself is sometimes used as a temporary measure when a patient is admitted to hospital for the purpose of achieving rapid control of pain and then determining a suitable maintenance regimen. In this case, the intravenous route is often used initially, converting to a more suitable route for long term use when the correct dosage has been established.

As mentioned in the text of the booklet itself, the longer term use of intravenous opioids should be avoided whenever possible, partly because of the inevitable complications associated with venous cannulae, and partly because there is anecdotal evidence of excessive dose escalation when extra doses are frequently given intravenously.

Neuraxial Delivery Systems

Neuraxial administration usually means injection or infusion near the spinal cord, either inside (intrathecal) or just outside (epidural) its membranous coatings. However, the term can also be applied to an infusion into the cerebral ventricles (inside the brain).

Neuraxial delivery systems are sometimes used for the intrathecal administration of opioids, local anaesthetics and various other medications. The opioid most often chosen for intrathecal delivery is morphine. The local anaesthetic usually chosen for intrathecal delivery is bupivacaine. Two other agents which have an established role in intrathecal analgesia are the alpha-2 adrenergic receptor antagonist clonidine, and the $GABA_B$ receptor agonist baclofen. Various other medications, such as ketamine, midazolam and ziconotide, are also being evaluated for possible use as intrathecal analgesics.

The last agent mentioned, ziconotide, which is marketed under the trade name Prialt, is rather interesting. It is a synthetic analogue of a substance found naturally in a marine snail called *Conus magus*. Its therapeutic action is the result of selective

blockade of a neuronal transmission channel called the N-type voltage-sensitive calcium channel, so it is the first example of a new class of analgesics called N-type calcium channel blockers (NCCBs). Ziconotide could provide another option for patients whose pain has not been satisfactorily controlled by the methods currently in regular use, but it is too early to predict how often, or how effectively, it might come to be used.

However, it should be remembered that intrathecal infusions and other neuraxial delivery methods are only very occasionally appropriate in the management of cancer pain. They have the potential to provide very powerful analgesia with minimal drug side effects, but they also have risks of their own, some of which can be serious, so they should not be used if less invasive alternatives are available and effective.

When neuraxial analgesia really is necessary, a catheter can be tunnelled under the skin to a convenient site and connected to a suitable infusion pump. Totally implanted systems (with a subcutaneous portal for the addition of medications to a reservoir) are probably the only satisfactory way of providing long term neuraxial analgesia.

DECLARATION OF INTEREST

None

NOT COPYRIGHT

The work may also be read as a series of web pages, starting at www.wanterfall.com/Myths-and-Facts-about-Cancer-Pain.htm

Paper copies are best made by downloading the printable PDF file available at http://www.wanterfall.com/downloads.htm Booklet mode printing on A4 paper gives the best results.

Please note that printed copies of the parent booklet may be ordered at cost (currently less than A$1 [1 AUD] per booklet, plus postage) by sending an email to sales@wanterfall.com

Alternatively, the full version of How Cancer Pain is Treated may be read online, or downloaded as a PDF file for offline reading or printing, at http://www.wanterfall.com

COMMENTS

If you have any comments about this booklet, please send an email to cancerpain@wanterfall.com