OPIOIDS AND CHRONIC PAIN: WHY IS THERE A CONTROVERSY?

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In 1988, Ronald Melzack, a psychologist renowned for his description (with Patrick Wall) of the 'gate control' theory of pain, challenged the established wisdom of the day about the use of strong opioids in non-malignant pain states. His paper, delivered to the Congress of the International Association for the Study of Pain, was an indictment of the attitudes to the use of morphine of society in general and the caring professions in particular. He welcomed the initiatives which the pioneers of modern palliative care had introduced – regular dosing schedules, dose escalation and a determination to provide the best possible analgesia for all cancer pain sufferers – but was critical of the slow uptake of such principles in the relief of suffering not due to cancer. Eleven years on, it sometimes seems from the perspective of a general hospital pain clinic that not much has changed. Our armamentarium of analgesics has been increased. The use of anti-depressants has become routine. New anti-convulsants are on the horizon: we are about to take part in a clinical trial of the new agent gabapentin. Novel drugs, like capsaicin, have reduced the morbidity of painful neuropathy, and, we suspect, have spared patients from hospital clinics and pain clinic procedures. We are more confident with the use of drugs which do not have specific product licences for chronic pain. We are bolder with our 'interventions' or injection techniques and have become confident with nerve destruction procedures. We have thought the unthinkable and become involved in the political debate about the licensing of cannabis as a medicine. We have progressed to multidisciplinary working. And yet we have a

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problem with one class of drugs, the opioids. We avoid them. Frankly, we are scared of them. Unless the patient is going to die within a reasonable time, we are terrified that the prescription of morphine or similar will have the effect of opening a Pandora's box of unmanageable problems.

We are, of course, terrified of being responsible for addiction. The spectre of inner city degradation and the problem of the drug culture haunts us. It is a belief shared by the public and the profession that we will create a society of 'junkies' if we use opioids for the control of pain. This belief is reinforced by lessons from history: it is said that Hermann Goering, the Nazi war leader, became a morphine addict as a consequence of treatment for a wound sustained in the 1923 Munich beer hall *putsch*. The implication could be that if only his doctor had used something else, the world might have been spared his malevolence.

The pharmaceutical industry has not eased our worries. Fear of morphine addiction has prompted the search for 'less addictive' drugs. When the manufacturers of tramadol, a moderately strong opioid with a few other interesting actions,

wanted to promote its use for the treatment of chronic pain, it was on the basis that it was 'nonaddictive'. In other words, it was seen as a better choice than an 'addictive' drug. The message we were meant to hear was "this is an ideal analgesic, a rose without thorns", and to support the claim, the manufacturers pointed out that there is no demand for tramadol on the streets. This is useful: tramadol is not subject to the tight controls of morphine, and patients will not be burgled or mugged for their medication. In the light of the story about Goering it is particularly interesting that it was in Germany that tramadol made its name as a 'safe' alternative to morphine. And to support the claim of freedom from addictive potential, naloxone has been given to patients with chronic pain who have taken tramadol for many weeks. An abstinence syndrome is not provoked.

But there is a problem with evidence based on the observed effects of naloxone, which is that none of the work done on the effects of naloxone on chronic opioid users has been done on patients who had taken morphine for the control of chronic pain. All the data we have is based on experience of using naloxone in volunteers or recreational drug users. What we call the 'abstinence syndrome' may be provoked by depriving the street user but there is no compelling evidence that the patient with chronic pain behaves in the same way. Tramadol is an interesting drug and it tells us something about the opioid receptor response in the drug abuser. But it does not make it the ideal analgesic. It remains one of a number of useful intermediate strength drugs, to be considered along with the codeine-containing compounds and other drugs such as buprenorphine. It may be the safest drug to use where the community is afflicted with an addiction problem. On that basis alone it may succeed in the market place where other, safe and better analgesics get a bad name. But that is not a valid clinical reason to deny relief or to inflict unpleasant side effects (and tramadol does produce them) on those who suffer pain.

So what should be our response to the patient who wants 'something stronger' for chronic pain, or our reply to those who are surprised by our 'liberal' use of drugs which society treats with alarm and suspicion? There is a risk that a 'liberal' policy for the prescription is a recipe for confusion and sloppy medical practice. Morphine could quite literally become 'the opium of the people': at best a panacea for pressured prescribers, at worst a refuge for the diagnostically destitute. In the pain clinics of Lancaster, Morecambe and Kendal we have begun to develop a rationale for its appropriate use and here are our thoughts. They are not prescriptions for practice, but suggestions on how to proceed and avoid pitfalls. To those general practitioners who look after our patients with us and who seek our advice we ask that you get back to us if we are missing some vital evidence from the community – we are seeing patients in a very artificial environment.

PAIN AS A DISEASE, NOT A SYMPTOM

Recommendations should be based on known physiology. What does morphine do as an analgesic? What sort of pain does it help? What happens to the central nervous system after chronic opioid use? And more fundamentally, what happens to the central nervous system in chronic pain? The answers to these questions depend on the clinical situation. In the case of cancer, there is progressive tissue destruction and nerve damage. In the case of other chronic pain syndromes, however, the pathological process is static. Damage has been done but is not progressive. There may be crises; for example, the patient with renal stone formation or sickle cell disease, or even relapsing lumbar disc problems, but the exacerbations are limited in time even though acutely very painful.

The central nervous system behaves abnormally in chronic pain. I find that this is a useful explanation for the patient who

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is distressed by the failure of conventional medicine to deal with the pain. It is a more sympathetic explanation than a psychological/psychiatric diagnosis which risks labelling the patient a fraud. In the case of a neuropathic pain, such as

post-herpetic neuralgia or phantom limb pain, this is not a difficult concept to explain to the patient. For apparently nociceptive pain (for example, back pain or fibromyalgia) it is, in my experience, more difficult to persuade the patient to think in these terms.

There are two important consequences of grasping the concept of chronic pain being a disorder of the pain processing system, a disease rather than a symptom. Firstly, since it is known that opioid receptors are found throughout the central nervous system, there is a legitimate target for analgesic actions. Secondly, if chronic pain is a chronic disorder of the central nervous system it follows that medication (whether it be anti-depressant, anti-convulsant or opioid) should be taken on a regular basis and not ‘as required’. I use the analogy of ‘damping down’ a fire to give a reason for regular analgesia. There may be a requirement for the action of opioid at the molecular level, in the same way that there is for insulin in the diabetic. Administration is not conditional on the presence of unbearable pain, and the dose not determined by the intensity of discomfort.

That at least is my argument. It raises many questions. What about dependency and tolerance? When should one start opioids? Are there risks in maintaining people on opioids long term?

DEPENDENCY, ADDICTION AND TOLERANCE

Dependency is a syndrome derived from the ‘street’ user. Psychological and physical aspects of dependency have been studied in the addict, but not as far as I know in the patient with pain. The abstinence syndrome can be provoked by removal of drugs or the use of naloxone, and it is well described. On the other hand, those with cancer pain can be weaned off morphine within a very short time if the pain is relieved by, for example, a nerve block of the coeliac plexus. There are inevitably some minor, predictable and even troublesome side effects such as ‘flu-like’ symptoms and gastrointestinal upset, but the patient does not indulge in drug-seeking behaviour.

Tolerance is a normal phenomenon of opioid administration. There are several explanations for tolerance and they are understood in terms of conventional pharmacology. For example, morphine is metabolised by the liver to a number of compounds with different actions. The derivative

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morphine-3-glucuronide has opposite effects to the morphine itself. A consequence of the accumulation of morphine-3-glucuronide is, therefore, a reduction in the efficacy of morphine. There are other possible mechanisms such as an alteration in the number and behaviour of the opioid receptors in the central nervous system. The important thing about tolerance, however, is that it is predictable and of no great clinical significance. In fact tolerance to the side effects of opioids develops, so with time, the side effects become less troublesome. In practice the onset of tolerance means that the patient does need an increase of dose. But it appears that tolerance develops only to a finite extent and a patient with a chronically painful condition may ultimately stabilise on a particular dose of opioid. This is clearly not the same as ‘addiction’.

PAIN ASSESSMENT

Any assessment of the patient with chronic pain should seek out the mechanism of the pain and the impact of the pain on the total suffering. Where there is an obvious nociceptive (tissue damage) source for the pain, then it is appropriate in the first instance to use an analgesic appropriate to the degree of pain. General practitioners and specialists will usually have tried codeine and possibly tramadol, but may have baulked at the idea of progressing to morphine. The question we have to ask is “is this a pain that is likely to respond to morphine?”. In the case of an obviously nociceptive cause it is clearly indicated but occasionally it is worth considering the use of opioid in a neuropathic case, for example following a spinal cord injury. In both cases, but particularly in the latter where dose requirements may be very high, it is a question of whether the drug will be effective without the patient being too inconvenienced by nausea, constipation or drowsiness. The question is best answered by a short therapeutic trial. This can mean either a few weeks in the outpatient setting or a hospital admission for an intravenous trial with a more rapid answer. We recently tried the injection of the new short-acting opioid remifentanyl to assess a patient who had had an arm amputated following a brachial plexus injury. The patient complained of two pains: a ‘stump’ or nociceptive pain and a phantom or neuropathic pain. We found that both pains responded to an infusion of opioid, but the dose needed to control the phantom pain was far higher than that needed for the stump pain. It answered our question that it would be reasonable, if other measures failed, to push the opioid dose higher to treat the neuropathic pain.

The assessment of the pain sufferer must look for concomitant depression and anxiety resulting from the pain, as well as any ‘illness behaviour’. One concern is that opioids cause a sense of euphoria which may be misleadingly taken as an indicator of success if used on a patient with pain and profound anxiety. The skill in assessment lies in defining that part of the total presentation that will respond to opioid. Issues of depression and anxiety and illness behaviour need other measures. So do patients with a history of opioid use for recreational purposes or who give a history of an apparent ‘dependence’ on opioids following previous prescription. Some colleagues would extend their caution to patients with a

habit of using benzodiazepines, alcohol or tobacco on the basis that such patients have an 'addictive' personality. It is difficult to know how far to extend this caution. Should one, for example, regard a compulsive gambler as a poor risk for the use of opioids?

GUIDELINES FOR PRESCRIPTION

So, how should we go about using strong opioids, assuming that it is felt that the pain is likely to respond and that there is not an obvious contraindication? The technique involves the use of regular dosing of a long-acting preparation. There is a good choice: morphine sulphate slow release, transdermal fentanyl and methadone are currently available, although at the time of writing not all are licensed for this use. Other drugs which might soon be available include oxycodone and hydromorphone. The trick is to avoid using the drug as an 'as required' analgesic. In contrast to the person with cancer presenting in acute uncontrolled pain, there is probably not much advantage in titrating up with rapid release formulations. Those suffering chronic pain will know within a few days of starting a slow- release preparation whether relief has been obtained, and changes can be made over several days or weeks. It is important that the sufferer understands that the drug is not being given to provide total pain relief, merely to 'dampen down' symptoms so that normal activities can be undertaken again. Regular assessment is necessary, and in this process the message can be reinforced and dose increases can be made if it becomes clear that tolerance is preventing a sustained benefit.

Pethidine is not on my list of suitable drugs, firstly because of the short duration of action and rapid result that can be obtained from injection, and secondly because of the metabolise norpethidine. Unfortunately its use has been thought appropriate for the acute treatment of ureteric and biliary stones because of a relaxant effect on smooth muscle. The patient who forms renal calculi and is given pethidine for the immediate treatment of acute symptoms is a desperately difficult problem to manage in the longer term. One such patient has been admitted to hospital with convulsions that we have attributed to norpethidine toxicity. Methadone is on my list, but there is a problem. Methadone is used as a drug for the detoxification of addicts, and the patient who is prescribed methadone may be mistakenly tarred with the same brush. My patient with the norpethidine toxicity was prescribed

methadone 'to get him off pethidine'. Unfortunately he was then, in accordance with the usual practice for the management of substance abuse, inappropriately prescribed a reducing dose.

What about the long term? Follow-up must be regular and there is a requirement to ensure that the patient is complying with the spirit of the original prescription. At present we suggest that one doctor prescribes and one pharmacist dispenses a limited amount of drug. That way it is easier to keep account of the actual amount of drug dispensed and regular attendance at follow-up clinics is ensured. Some colleagues enter into a formal contract with the patient that explains the purpose of the prescription and includes an agreement to use the drug for the appropriate purpose. Some have advocated using opioids only where there is a limited life expectancy, but in practice that does exclude some of the most difficult management problems, and in another sense is a denial of all that we have said here.

We may expect a resurgence of interest in opioids for the management of chronic pain. Recent adverse experience with nonsteroidal anti-inflammatory drugs and a realisation of the true morbidity and cost of treating the complications of these drugs has prompted the reappraisal of opioids, as has the timely challenge of Ronald Melzack.

Let us return to history. Hermann Goering was, apparently, off morphine by 1925 and returned to it in the 1940s when he had things on his mind other than pain. One might have to look beyond his medical history to explain his behaviour.

● opioids are not being used for the total control of pain, but for its modification   ● the patient must understand the purpose of the prescription   ● assessment of function and activity is important in evaluating the drug   ● opioids are appropriate for nociceptive pain but can be used for neuropathic pain   ● a short therapeutic trial may be valuable   ● long-acting drugs taken regularly are indicated   ● a 'contract' with the patient may be useful

Table 1 Practice points for the use of opioids in chronic pain