EDITORIAL

Methadone for Neuropathic Pain: A New Use for an Old Drug?

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"For the easing of neuro-traumatic pain we tried, in turn, the whole range of medicines known as narcotics, such as conia, hyoscyamus, daturia, atropia, and morphia. None of them, save the last, seemed, when singly used, to be of the slightest value and one by one they were laid aside until, in the vast mass cases the salts of morphia alone were employed… The morphia salts…… are invaluable". Silas Weir Mitchell 1872[1]

More than 130 years ago, Silas Weir Mitchell observed that the only drug that relieved nerve injured Civil War soldiers was morphine. We are only now again beginning to use opioids for neuropathic pain, after over a century of opioid phobia. Several randomized controlled trials now support this approach.[2-6] However, even the use of a variety of opioids of short and long duration, and in high doses, fails to relieve a proportion of these sufferers.

Moulin et al[7] have reported in a case series the use of methadone in very refractory neuropathic pain patients with long duration severe pain who would not be expected to improve spontaneously, and who had been treated aggressively with antidepressants, anticonvulsants and other opioids. Twenty-two of 50 (44%) had moderate or better relief with methadone with tolerable side effects and improved quality of life in 14 (28%) over a long period of follow-up (mean duration 21.3 months), including three of seven with central neuropathic pain considered to be even more refractory than peripheral neuropathic pain. In this population, these are very good results. A comparative randomized controlled trial will be necessary to conclusively determine that methadone is superior to other opioids for neuropathic pain, however, the design of such a study will have its difficulties.

The authors review the theoretical advantages of methadone in terms of its actions as an opioid agonist, an NMDA (N-methyl D-aspartate) antagonist and its effect on monamines such as serotonin and noradrenaline, the latter being the putative action of the antidepressant analgesics such as amitriptyline.

Methadone was discovered by German scientists during World War II who were looking for a synthetic opioid which would replace morphine, as they were concerned that the availability of this would be threatened by the war. It was originally called dolophine hydrochloride. It is not clear as to the origin of the name, but it has been suggested that it was named after Adolph Hitler and also that it was derived from the Latin word dolor meaning pain. In the 1970's it began to be used to treat drug addiction, where it was useful because of its long duration of action and lack of euphoria, although it replaced the abused opioid with another also with addictive properties. Psychological dependency (addiction), is however, not a major issue in treating chronic pain patients.

Should neurological clinicians use methadone for neuropathic pain patients who are refractory to first-line drugs such as antidepressants, gabapentin and other opioids? Certainly neurological clinicians are singularly suited to diagnose and treat neuropathic pain (which is often misdiagnosed) and waiting lists for pain clinics are very long. Moulin et al[7] have indicated that some education regarding methadone is necessary. They point out that methadone is more difficult to use than other opioids, however, published guidelines are available[8] and one guideline with particularly good suggestions for commencing or changing to methadone should be available at the time of the publication of this journal issue.[9] Prescribing opioids for neuropathic pain does require, however, a commitment to ongoing care with early frequent monitoring to determine the appropriate dose as the drug is titrated. However, following that, patients may be seen every three months or so or possibly referred back to an interested, knowledgable and experienced primary care physician.

A proportion of neuropathic pain patients will only respond to chronic opioid therapy and perhaps only to methadone as the Moulin[7] report suggests. If we offer only codeine (which is a poor choice for moderate to severe pain), we will do little to improve the lot of these patients. It is not difficult to start using conventional opioids and we are blessed with several choices of short and long term preparations. A "start low and go slow approach" is reasonable with slow dose titration. Tables of equianalgesic doses for the different opioids are readily available from a number of sources.[10] One can simply replace for example codeine – acetaminophen preparations with equianalgesic oxycodone by itself, oxycodone/acetaminophen or with morphine or hydromorphone, determine the total daily dose required and switch to a long acting preparation of the same or equianalgesic dose of another long-acting opioid such as transdermal fentanyl, routinely prescribing a stool softener and often an antinauseant. Tolerance does not occur to constipation, but does to other opioid side effects, such as drowsiness and nausea. As mentioned psychological dependency and also tolerance are not significant issues in these patients although some inquiry or screening for a history of drug seeking behaviour is prudent.

Although a special knowledge and licence is needed for methadone, these are not difficult to acquire and methadone may be a useful additional arrow in the quiver for these truly terrible conditions.

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