

Pain Relief Connection

The Pain Information Newsletter

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"We interrupt our usual programming . . ."

NOTE: We are interrupting our series on [WHO Analgesic Ladder](#) Step 1 Analgesics, because a "teachable" moment has arisen: This month nursing practice at MGH changed to permit RNs to administer hydromorphone (Dilaudid®) via IV push. This seems like an opportune time to review hydromorphone.

Clinical Focus: Dilaudid® vs Morphine

INTRODUCTION

Hydromorphone is a potent WHO Step 3 opioid agonist that binds with the mu opiate receptor, and is indicated for moderate to severe pain. Hydromorphone is a semisynthetic opioid in the same chemical family as morphine, but milligram for milligram it is more potent. It is commercially available in liquid, tablet, rectal suppository, and parenteral formulations. The MGH formulary includes 1 and 2 mg tablets; a preparation combined with bupivacaine for epidural administration; and several injectable preparations in varying concentrations and volumes. See the [MGH online formulary](#) for details. For safety reasons (i.e., to better distinguish it from morphine) hydromorphone for continuous infusion or patient-controlled analgesia is provided in a 0.5 mg/ml concentration.

METABOLISM

Hydromorphone is metabolized in the liver and excreted via the kidneys. It has a slightly more rapid onset than morphine and for continuous severe pain should generally be administered at 3 - 4 hour intervals with (breakthrough) rescue doses available every 1-2 hours. Morphine and hydromorphone produce similar metabolites, the absolute and relative concentrations of which have implications for analgesia and side effects. There is wide interpatient variability in their production. Toxic metabolites may accumulate over time even in patients with normal renal function, but the accumulation is more pronounced in those with renal insufficiency. Toxicity is usually manifested by changes in cognition or neuroexcitability progressing to myoclonus and even seizures.

HYDROMORPHONE OR MORPHINE?

There are indications that toxic metabolites may accumulate more rapidly during chronic morphine administration than with hydromorphone administration. This has led some clinicians to conclude that hydromorphone should be used preferentially in patients with compromised renal function and those at risk for compromised renal function such as elders and those with advanced disease. While this is a logical conclusion, studies that support this practice are lacking. If toxicities do appear (with either drug), rotation to another opioid is usually indicated. Because hydromorphone is more potent than morphine, as doses increase smaller volumes of hydromorphone can produce similar analgesia to relatively large volumes of morphine. This can be a critical issue when the subcutaneous route is used, or when intravenous fluid volumes need to be limited. Even by the oral route, some patients prefer the small number of tablets of hydromorphone that can replace large morphine doses. A consideration in the choice of opioid analgesic must also include cost: morphine, for example is much less expensive than hydromorphone.

EQUIANALGESIA

Most clinicians have some familiarity with morphine, but experience with other opioid analgesics may be more limited. For a review of equianalgesic dose conversions, see [Pain Relief Connection Vol 1 #6](#) or the [Pain Topics](#)

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article from that issue and the [equianalgesic chart](#) on the [Pain Relief web site](#). The equianalgesic doses of morphine and hydromorphone are shown below:

ORAL/RECTAL DOSE	ANALGESIC	PARENTERAL DOSE (MG)
30	Morphine	10
7.5	Hydromorphone (Dilaudid)	1.5

Remember: the calculated equianalgesic dose should be reduced by at least 25% to account for incomplete cross-tolerance, then titrate to comfort.

Quotes Worth Remembering

"Many people once believed that if you conducted the right study that the findings would be so compelling that they would lead to immediate change. This is what I sometimes refer to as the Newtonian approach to dissemination: It all rolls downhill from gravity." (Carolyn Clancy, MD, Director of the Agency for Healthcare Research and Quality) In fact, what we have learned is that clinical practice doesn't change simply on the basis of new information. It appears that deeply held beliefs must be actively examined and new behaviors practiced and reinforced. Passive "learning" is an ineffective method of personal or institutional change. Active participation and socialization are probably important keys.

Quotes We'd Like to Forget--But We'd Better Not

"All you really need for anesthesia is paralysis and amnesia." (An anesthesia resident, 1980). Frighteningly, that attitude persists in some quarters. The same sentiment was related in an anecdote two weeks ago, and the February 5 issue of *msJAMA* had an essay on the topic, "[Pain and Forgetting](#)." The rationale behind the statement seems to be that it doesn't matter if the patient has pain (or that *we cause* the patient pain) if the patient has no memory of the pain. The same rationale held sway for many years in the care of neonates and infants. In addition to the ethical and moral questions that are raised, it shows a profound ignorance of the systemic, wholistic nature of pain, with the physical and psychological sequelae that result from severe, unrelieved pain.

Education

May 15-16 (Thur-Fri): **Broadening Your Perceptions of Pain Management**, Sheraton Braintree Hotel. Presented by Brigham & Women's Hospital. For registration form and details call 617-525-3200.

April 1 (Tues): Massachusetts Pain Initiative Annual Meeting, Auburn, MA. For details contact amy.goldstein@cancer.org.

MGH Pain Calendar

March 19: **Pain Pulse**, the annual survey of all MGH patients that provides a "snap shot" of pain at MGH.

April 14-15 (Mon - Tues): 4th Annual **Pain Relief Champions** course, Holiday Inn - Government Center. Presented by MGH Cares About Pain Relief and the Center for Clinical and Professional Development. Contact Judy Patterson (617-724-5554; jlpatrick@Partners.org) or Tom Quinn (617-726-0746; tquinn1@partners.org) for application and details.

Palliative Care Grand Rounds series, Wednesdays at 8:00am in the Ether Dome: March 5, **Me/Not Me? Self, Language, and Pain**; March 12, **Project to Improve Pain Management in Oncology**; March 19, **Bone Pain**; May 7, **Opioid Therapy and Pathological Pain**.

Pain Project Expo: Showcase of pain projects and initiatives throughout MGH. Date TBA. For details: tquinn1@partners.org.

URL notes: **Hold your cursor over the link for a second to see the URL.** If you are reading this in hard copy, this month's links are:

Mayday Fund: <http://www.painandhealth.org/mayday/mayday-home.html>

Center for Clinical & Professional Development course calendar: <http://tinyurl.com/23zk> (shortened from the original URL)

WHO Equianalgesic Ladder: <http://www.mcmahonmed.com/works/CHARTS/3step/default.html>

MGH online formulary: <http://www.crlonline.com/crlsql/servlet/crlonline>

Past issues of *Pain Relief Connection*: http://www.massgeneral.org/painrelief/Newsletter/mghpain_connection.htm

Pain Relief web site: http://www.massgeneral.org/painrelief/mghpain_home.htm

Equianalgesic chart: http://www.massgeneral.org/painrelief/mghpain_equichart.htm

PainTopics equianalgesic conversions article: http://www.massgeneral.org/painrelief/Pain%20Topics/Converting_opioids_Pt1.pdf

Carolyn Clancy, AMNews: http://ama-assn.org/sci-pubs/amnews/pick_03/gvsb0224.htm

Pain and Forgetting: <http://jama.ama-assn.org/cgi/content/full/289/5/617>

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PAIN TOPICS

Meperidine--What's all the Fuss?

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Introduction

The title of this essay was borrowed from Dr. David Weissman's "Fast Fact"¹ of the same name, one of many short reviews of issues in pain and palliative care on the End of Life Physician Education Resource Center ([EPERC](http://www.eperc.org)) web site.

Meperidine (Demerol[®]) was first synthesized in 1939. For both practical and "naïve"² reasons it became the most widely prescribed opioid analgesic in the United States in the 2nd half of the 20th century.³ Meperidine was introduced in a solution conveniently available in single dose ampules or multidose vials at a time when morphine was only available as an injectable hypodermic tablet (it had to be crushed and dissolved).⁴ Furthermore, it was initially thought that meperidine did not have the same toxicities as morphine, including respiratory depression, constipation, and the potential for chemical dependence. Meperidine has been used extensively as a preoperative medication, frequently combined with a phenothiazide such as hydroxyzine (Vistaril); as a postoperative analgesic, historically ordered IM every 4-6 hours PRN; as an IM analgesic for migraine and sickle cell pain; as the drug of choice for biliary colic; and to palliate rigors associated with anesthesia, amphotericin, and blood or biologic products.

However, by the 1990's clinical guidelines^{5,6} were discouraging the use of meperidine as first line therapy for moderate to severe pain. Several major institutions have reported removing it from formularies⁷ or severely restricting its use.⁸ Some anti-meperidine advocates have used relatively inflammatory language to call attention to its problems and overuse or misuse, even referring to it as a "monster"⁹ or declaring "Demerol Free Zones."¹⁰

The reasons for the dramatic rise and fall of the reputation of meperidine are as complex as opiophobia (the irrational fear of addiction) and as common as habit. Pain management is one of the most difficult arenas in which to change clinical behavior. Physicians, nurses, and pharmacists tend to persist in old practices and beliefs in spite of evidence that those practices or beliefs are either erroneous or harmful. An examination of several opioid actions and toxicities finds that meperidine has no advantages over other opioids, but several disadvantageous characteristics.

In early 2002 a team led by Kenneth Latta, a Clinical Pharmacist at Duke University Medical Center, published an extensive review² of meperidine. The team examined every paper previously published on this drug. By today's standards studies of meperidine and other opioids have frequently been of poor design. The preponderance of evidence, however, does not support the wide spread use of this drug.

Analgesia

Meperidine is relatively less potent than other opioids, but perhaps more importantly it has a short duration of analgesia, 2 - 3 hours compared to morphine's approximately 4 hours. The more severe the pain, the less effective it is at the published equianalgesic doses. Some equianalgesic references use a 1:7.5 morphine:meperidine ratio,⁶ while others,⁵ and several studies,² suggest that 1:10 is more clinically appropriate. In one study cited by Latta et al, 50 mg of IM meperidine was no more effective than placebo. In another, meperidine 50 mg was no more effective as a preoperative medication than hyoscine, a phenothiazide with no analgesic properties. IM meperidine is variably absorbed and IM injections are painful. Problems inherent in IM administration and differences in duration of action would seem to be overcome if both drugs are administered by IV patient-controlled analgesia (PCA). When meperidine and morphine were compared in this fashion, analgesia was similar when patients were at rest, but morphine was superior during movement, when pain was assumed to increase in severity.²

Oral meperidine is poorly absorbed, having a 1:3 parenteral:oral equivalency. In itself this would not appear to be problematic, but one source reports patient reluctance to take what appears to be large amounts of medication:¹¹ oral meperidine is available in 50 mg tablets, each of which is larger than standard morphine and hydromorphone

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tablets. Oral meperidine 50 mg has been reported to be no more potent than 650 mg of aspirin or acetaminophen.¹² Much more importantly, the toxic metabolite of meperidine, normeperidine, accumulates more rapidly with oral dosing, as will be discussed below.

Meperidine IM has been very commonly used for migraine and for sickle cell pain crisis. There has been no advantage shown compared to other opioid analgesics and its short duration of action would seem an inherent limitation in both indications. Indeed, one study showed that continuous infusion morphine was superior to intermittent scheduled injections (IV or IM) of meperidine, morphine, or codeine for sickle cell vaso-occlusive pain crisis.¹³

Local reactions

Meperidine is too irritating to give subcutaneously. Given intramuscularly, historically the most common route, local irritation is common. Patients describe it as a burning sensation. Repeated IM dosing can cause induration and scarring. The intravenous route appears to be the most appropriate route of administration.

Smooth muscle relaxant

Meperidine was theoretically proposed and then identified early on in animal studies as a smooth muscle relaxant. It was enthusiastically embraced, and in many settings persists, as the preferred opioid for abdominal pain presumed related to spasm of smooth muscle such as biliary colic. Subsequent study has shown that meperidine has local anesthetic properties, and when applied topically to smooth muscle does cause relaxation. This is a rare clinical scenario, however. Meperidine has been shown to be no more effective as an analgesic for biliary colic, and may actually not be as effective as morphine.

Toxicity

The major cause for concern among critics of meperidine is the rapid accumulation of the neuroexcitatory metabolite, normeperidine. While all opioids have the capacity to cause neuroexcitability, most require prolonged use at high doses. With meperidine, subtle changes can be seen in a matter of hours, and significant toxicity within 2 days or less. Initial signs may include fear, anger, and anxiety, whereas morphine tends to be anxiolytic. Mood changes may progress to shaky feelings, tremors and twitches, myoclonus, and even grand mal seizures. Fortunately, few people these days are on MAO inhibitors, since these antidepressants can precipitate neurotoxicity; concurrent use of MAO inhibitors and meperidine is contraindicated. Normeperidine accumulates very rapidly in renal failure, and meperidine should not be used in that setting. Normeperidine accumulates more rapidly when meperidine is taken orally. The analgesic effect of meperidine is reduced when taken orally, but the same amount of normeperidine is produced, milligram for milligram of meperidine, no matter the route. Normeperidine is not an opioid. Therefore, if neurotoxic symptoms develop, opioid antagonists such as naloxone do not reverse the symptoms. Indeed, they are reported to worsen.

Indications for meperidine

Meperidine is not a "monster." It has been widely overused and misused for many years. It has no advantages as an analgesic over any other opioid. However, its rapid onset and short duration of action make it a potentially useful drug for short procedures that do not cause severe pain. Used in conjunction with appropriate sedatives, it can be used for conscious sedation. In the United States, it probably has no equal in palliating the rigors (shivering) associated with anesthesia, amphotericin, and certain biologic agents. For this indication, 25-50 mg by slow IV injection may be used. Outside the United States nefopam and parenteral tramadol appear to be effective for this indication.

References

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