LONG-TERM USE OF INTRATHECAL DROPERIDOL
AS AN EXCELLENT ANTIEMETIC IN NONMALIGNANT
PAIN-A RETROSPECTIVE STUDY

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Abstract

Over the past five years our pain practice encountered eight patients (5 female, 3 male) with chronic non-malignant pain syndromes, in whom any meaningful pain reduction via opioid analgesics (either by oral or systemic and/or intraspinal route) had resulted in profound nausea and/or vomiting despite generous use of available and/or affordable anti-emetics. After obtaining proper consents, small, incremental doses of intrathecal droperidol were added to these patients having implanted intrathecal narcotic drug delivery system. Significant reduction of nausea and vomiting without any side effects from droperidol was obtained while adequate pain reduction is achieved.

Procedure

All patients had implanted programmable Medtronic Synchromed pumps with intrathecal access catheters. The intrathecal catheter tip placement varied depending on the pain pathology of the patient. Six of eight patients were started and remained on morphine sulfate intrathecally for their opioids. Two patients with contraindications to morphine had fentanyl and hydramorphone as their intrathecal opioid respectively. The intrathecal dose of droperidol was started low (22.7 ± 18.6 micrograms/day). All patients were on simple continuous pump dosing during the study.

Results

All patients achieved statistically significant antiemesis (77 ± 10% P< 0.001) as well as statistically significant pain relief (84 ± 7% P < 0.005) early on (within two pump refills). As the intrathecal dose/day of droperidol was increased to 124.7 ± 114.8 micrograms/day as well as their intrathecal pain medication use, the degree of significance of antiemesis improved to 86 ± 9% (P < .001) which was a statistically significant improvement of P ≤ 0.05 level from the starting dose of droperidol in each patient.

For the six patients on morphine the antiemesis improved to 88 ± 10% (P≤ .003), also statistically significantly different at P ≤ 0.05 level from the starting antiemesis level. During this period the intrathecal morphine dose was doubled from 4.76 ± 2.43 mg/day to 9.5 ± 6.5 mg/day (P ≤ .001).

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Patients had no adverse effects from the use of droperidol at these doses (no sedation, changes in mental status, no signs or symptoms of arachnoiditis, no new sensory or motor disturbance, or any other indications of nerve toxicity detected.). Serial neurological studies involving MRI and CT, with contrast, EMG every 6-12 month showed no intrathecal catheter tip irritation sequelae in our patients either.

**Conclusions**

We find droperidol in microgram doses of 5-300/day intrathecally a safe antiemetic to use along with opioid analgesics. We did not use droperidol intrathecally alone as its use systemically without an opioid companion base is fraught with concern in anesthesia literature (“calm looking on the outside-agitated on the inside”). We would suggest a minimal starting dose of 20-30 micrograms/day of droperidol, adjust most probably upwards by 25-50% on subsequent pump refills until the desired effect is established. The scientific literature is rich with references to the brainstem chemoreceptor trigger zone, the floor of the fourth ventricle, and other nausea center locations (area postrema, the circumventricular organ, etc.). We would like to suggest that droperidol’s direct actions on these centers are involved with antiemesis at these small doses.

**Keywords**

1. Intrathecal Opioids
2. Intrathecal Droperidol
3. Long Term Profound Antiemesis
4. Non-Malignant and Malignant pain

**Introduction**

Since discovery of opioid sensitive receptors in the spinal cord intraspinal opioids have become of great value in both the understanding and management of many acute and chronic pain conditions.

Opioid analgesics are administered by many routes (oral, subcutaneous, transmucosal, transdermal, intramuscular, intravenous, epidural and subarachnoid). Some patients will have refractory nausea to many opioids, regardless of dose, type or duration of therapy, thus preventing adequate opioid dosing for adequate pain relief. In this group of unfortunate people sometimes even the strongest available and affordable antiemetics offered via (oral, subcutaneous, transdermal, transmucosal, intramuscular, and intravenous) routes do not counter the nausea and/or vomiting enough so adequate pain relief can be obtained on a chronic basis.

Control of nausea and vomiting is via two centers in the brain. The involved centers are the emesis center and the chemoreceptor trigger zone (CTZ). Baroreceptors, vagus, peripheral pain receptors (via histamine neural involvement), vestibular area (via acetylcholine involvement), cerebral cortex and CTZ all send provocative signals to the emesis center. Dopamine, emetic drugs, 5HT₃, opioid analgesics, cisplatin, and nitrogen mustard all provoke CTZ. The CTZ/area postrema is located at the floor of the fourth ventricle. The CTZ has at least five different receptor types that may be provoked (dopamine D2, histamine, 5HT₃, muscarinic and substance P).

We took advantage of the presence of opioid receptors in the spinal cord and brain for pain reduction, as well as the presence of dopaminergic D2 receptors in CTZ and used a dopamine D2 antagonist (droperidol) in small quantities intrathecally to see if effective antiemesis as well as pain relief could be simultaneously achieved on a chronic basis.

**Materials And Methods**

- Over the past five years we took eight patients who fit the above category: four patients with Complex Regional Pain Syndrome (CRPS), three patients with lower back syndrome (two failed back syndrome, one multilevel degenerative joint disease), one patient with short bowel syndrome/abdominal pain.

- We obtained proper and appropriate informed consents regarding use of droperidol in the pain clinic institution. We followed all the guidelines dictated in Declaration of Helsinki (http://www.wma.net/e/policy/pdf/17c.pdf) for the use of preservative-free compounded antiemetic droperidol in the intrathecal space. Then we obtained consent as a new and not yet FDA-approved drug for this purpose from each patient.
Results

The intrathecal dose of droperidol was always started low (22.7 ± 18.6 micrograms/day).

Depending on the patient’s antiemetic response to this dose, and the pain relief response to increasing doses of the opioid used intrathecally, we increased our daily dose of droperidol by 15-50 micrograms/day on subsequent pump refills, if it was needed.

The use of non-intrathecal antiemetics significantly decreased (86 ± 9% P< 0.01) in all patients. One patient with CRPS, prior to visiting our pain clinic, had a pump and intrathecal catheter placed with trial of morphine and fentanyl, and then the pump and catheter removed. She had been unable to take any type of opioids (severe emesis) despite trial of high doses of all available antiemetics and/or passage of time to get used to the opioids. After the addition of intrathecal droperidol this patient was able to gradually tolerate intrathecal fentanyl as well as oral oxycontin up to 40 mg p.o. QID within three months of the start of intrathecal droperidol.

One of our CRPS patients’ pump was removed

<table>
<thead>
<tr>
<th>Patient #</th>
<th>Year of birth</th>
<th>Disease state for which pump was implemented</th>
<th>Site of intrathecal catheter tip</th>
<th>Year of implantation</th>
<th>Currently (2006) using the system</th>
<th>Intrathecal narcotic used</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>1955</td>
<td>CRPS-left upper extremity’ CRPS-right lower extremity</td>
<td>T1-T2</td>
<td>2002</td>
<td>Yes</td>
<td>Fentanyl</td>
</tr>
<tr>
<td>II</td>
<td>1957</td>
<td>CRPS-right upper extremity’ CRPS-right lower extremity</td>
<td>T1-T2</td>
<td>2002</td>
<td>Yes</td>
<td>Morphine sulfate</td>
</tr>
<tr>
<td>III</td>
<td>1949</td>
<td>CRPS-right upper extremity’ CRPS-right lower extremity’</td>
<td>T5-T6</td>
<td>2002</td>
<td>No-removed in 2004 due to insurance problems</td>
<td>Morphine sulfate</td>
</tr>
<tr>
<td>IV</td>
<td>1949</td>
<td>CRPS-right upper extremity’ CRPS-right lower extremity</td>
<td>T1-T2</td>
<td>2003</td>
<td>Yes</td>
<td>Morphine sulfate</td>
</tr>
<tr>
<td>V</td>
<td>1928</td>
<td>Short bowel syndrome, abdominal pain with chronic nausea</td>
<td>T10-T11</td>
<td>2002</td>
<td>No-deceased in 2004 secondary to pneumonia</td>
<td>Morphine sulfate</td>
</tr>
<tr>
<td>VI</td>
<td>1942</td>
<td>Severe multilevel degenerative lumbar disc disease</td>
<td>T12-L1</td>
<td>2003</td>
<td>Yes</td>
<td>Morphine sulfate</td>
</tr>
<tr>
<td>VIII</td>
<td>1957</td>
<td>Failed back surgery syndrome</td>
<td>L3-L4</td>
<td>2001</td>
<td>Yes</td>
<td>Dilaudid</td>
</tr>
</tbody>
</table>

⊗ - implanted by another pain physician
¾ - year droperidol was added

* - site of worst symptoms
Discussion

The proximity of most of the brainstem nausea/vomiting centers to the walls of the fourth ventricle, and the ease by which a partly lipophilic drug like droperidol gets to the active site of action of nausea centers is a promising new avenue for treatment of intractable nausea/vomiting. To optimize antiemesis we hoped for the lowest effective dose, with the least number of negative side effects, no toxicity and as close to the nausea centers as possible.

The chemoreceptor trigger zone (CTZ) has been known, so far, to have at least five kinds of receptors that may activate nausea. It would be very interesting to see what the antagonist of each receptor system, if placed appropriately intrathecally, either singular or in combination would do in management of intractable nausea/vomiting.

Intrathecal droperidol, an effective antiemetic, was recently reported by Dr. Stearns in the literature. Their patient population had malignant disease. In the retrospective portion of their study, in 41 patients, intractable nausea was caused by opioid intolerance in 46%, abdominal tumors in 49%, and chemotherapy or radiation in 5%. Intrathecal droperidol either reduced or resolved nausea in over 95% of their patients. The droperidol dose in their study ranged from 25 to 455 micrograms per day. Both the percentage of the patients in that study who had significant nausea reduction and the dose range of intrathecal droperidol that allowed antiemesis is in general agreement with our study.

Recent studies comparing droperidol and ondansetron revealed that QT does increase by a small but significant percentage within 2-3 minutes after giving from 0.625 to 1.25 mg droperidol in men and women, and to about the same extent in the same 2-3 minutes after giving 4 mg of intravenous ondansetron both of the “mild” prolongation of QT moved towards normal within ninety minutes.

In our study the dose of droperidol given over 24 hours is below a single dose given IV as above.

All of our patients on the combination of intrathecal droperidol/opioid reduced use of almost all forms of (oral/rectal) antiemetics (86% ± 9% P < 0.001 reduction in use). If the ratio of droperidol to opioid in the pump was to be drastically adjusted (to manage increasing pain level in a patient) we offered short term oral Antiemetics until the new steady state was established. Over time we increased the dose of droperidol along with the opioid in those situations, as to be more proactive to the patient’s needs.
antinausea, antiemetic and excellent anti-pruritic when
given along with epidural fentanyl. Single bolus of
epidural droperidol (2.5 mg) significantly reduced
epidural fentanyl’s induced pruritus. Continuous
infusion of epidural droperidol (2.5 mg/day for 2 days)
also significantly reduced fentanyl’s pruritus as well
as postoperative nausea and vomiting\(^ {22}\). Epidural
droperidol bolus of 2.5 mg also decreased the incidence
of nausea, emesis and pruritus associated with epidural
sufentanil\(^ {23}\). Continuous epidural droperidol (2.5 mg/
day) inhibited nausea, vomiting and pruritus during
epidural morphine analgesia\(^ {24}\). Epidural droperidol, in a
group of women undergoing cesarean section delivery,
duced a dose-related reduction in the incidence of
pruritus (2.0 mg of morphine + 1.25 mg or 2.5 mg or
5.0 mg of droperidol as a single epidural bolus)\(^ {21}\). The
mechanism(s) by which pruritus inhibition occurs is
not yet clear.

Epidural droperidol, as 50 mcg/kg body weight,
given as a bolus and repeated every six hours x three,
has been reported for short term use to suppress
cisplatin-induced emesis with good success\(^ {20}\).

The above representative epidural droperidol
studies in battling postoperative nausea and vomiting
suggest a useful role for central neuroaxis use of
droperidol in the perioperative setting. The reduction
of cisplatin-induced emesis by epidural droperidol, as
well as the reduction in intractable nausea in a significant
number of patients undergoing chemotherapy and/
or radiation\(^ {18}\) also suggests a useful role for central
neuroaxis use of droperidol in oncology.

We recently took our own advice: in August 2006 a
45-year-old male with metastatic rectal adenocarcinoma
to the pelvis, large bowel and retroperitoneal area was
referred for pain management. He was on 2000-2500
mg/day MS Contin and 1500 mg/day MS-IR. He had
significant pain in his abdomen, pelvis and lower back,
pain upon micturition, and neuropathic lower pelvis
pain. He also had severe nausea, anorexia and mild
confusion from the oral.

Opioids and had failed transdermal opioids.
An implanted intrathecal access catheter (tip at T9
level) and totally implanted programmable pump was
installed. We started him on simple continuous dose
of 30 mg/day of morphine sulfate and 300 mcg/day of
droperidol. Within two weeks he had no more nausea/
anorexia or pain. He remains that way three months
later and has gained ten pounds.
References


