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 ($77 \pm 10\%$ $P < 0.001$) as well as statistically significant pain relief ($84 \pm 7\%$ $P < 0.005$) 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 $86 \pm 9\%$ ($P < .001$) which was a statistically significant improvement of $P \leq 0.05$ level from the starting dose of droperidol in each patient.

For the six patients on morphine the antiemesis improved to $88 \pm 10\%$ ($P \leq .003$), also statistically significantly different at $P \leq 0.05$ 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 ($P \leq .001$).

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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[1-7]. 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, $5HT_3$, 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, $5HT_3$, 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.

- For six of the above patients we used morphine sulfate as the intrathecal opioid. For one patient we used hydromorphone and another patient had fentanyl. The tip of the intrathecal catheter placement was in the lumbar spine for one patient, lower thoracic spine for two patients, midthoracic spine for one, and very high thoracic spine for three CRPS patients. The pertinent data of patients are tabulated in Table 1.

Intrathecal narcotics and droperidol were all preservative-free, made specifically under strict aseptic conditions in "clean rooms". They were placed in 20 cc luerlock capped, marked syringes and airmailed via Federal Express overnight to our clinic. The drugs in the syringes were then used within two weeks of their arrival. For all the patients in this study the interval between subsequent pump refills was less than ninety days. We have not done any in-vitro or in-vivo (the removed portion of pump solution before fresh drug is injected during pump refill) of the stability of the opioid/droperidol combination. There was no incidence of precipitation out of solution (removed portion of pump solution) during any pump refill. There was no clinical evidence of loss of antiemesis during the study.

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 1

Patient #	Year of birth	Disease state for which pump was implemented	Site of intrathecal catheter tip	Year of implantation	Currently (2006) using the system	Intrathecal narcotic used
I	1955	CRPS-left upper extremity* CRPS-right lower extremity	T1-T2	2002	Yes	Fentanyl
II	1957	CRPS-right upper extremity* CRPS-right lower extremity	T1-T2	2002	Yes	Morphine sulfate
III	1949	CRPS-right upper extremity CRPS-right lower extremity*	T5-T6	2002	No-removed in 2004 due to insurance problems	Morphine sulfate
IV	1949	CRPS-right upper extremity * CRPS-right lower extremity	T1-T2	2003	Yes	Morphine sulfate
V	1928	Short bowel syndrome, abdominal pain with chronic nausea	T10-T11	2002	No-deceased in 2004 secondary to pneumonia	Morphine sulfate
VI	1942	Severe multilevel degenerative lumbar disc disease	T12-L1	2003	Yes	Morphine sulfate
VII	1958	Failed back surgery syndrome	T12-L1	1998 ⊗ 2003 ¾	Yes	Morphine sulfate
VIII	1957	Failed back surgery syndrome	L3-L4	2001	Yes	Dilaudid

*- site of worst symptoms

⊗ - implanted by another pain physician

¾ - year droperidol was added

eighteen months after implantation secondary to insurance problems. An elderly patient with short bowel syndrome/abdominal pain who, prior to our pump placement, was living only on hyperalimentation for two-and-one-half years was able to take some oral food after the pump placement (morphine/droperidol). The patient was able to enjoy eating and partially absorb food. The patient died two years afterwards secondary to COPD complications.

Conclusion

We find droperidol a rather safe drug at the above doses intrathecally. Droperidol was given a "black box warning" by the Food and Drug Administration in 2001. If it is given as an intravenous bolus, at a dose of 0.1 mg/kg, there is an increased chance of ventricular arrhythmia of Torsades de Pointes type, and even at a much lower dose (from 0.675 to 1.25 mg) droperidol intravenously will prolong QT. The Medwatch Report that spurred the FDA was by Habib and Gan[13]. The represented cases in that study were not so *clear cut*. There have been a number of other editorials from respected sources agreeing to safety and efficiency of droperidol in intravenous doses from 0.625 to 1.25 mg to prevent nausea and vomiting[14,15,16].

Recent studies comparing droperidol and ondansetron[17,18,19,20] 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.

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[18]. 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.

There has been a reported rat study involving intrathecal droperidol administration, with or without morphine to evaluate antinociception[19]. In this study droperidol had no effect on antinociception intrathecally. Droperidol exerted no histopathological effects on the rat spinal cord.

Epidural drug delivery is a potent weapon in the anesthesiologist and pain specialist' armamentarium. It is well known that most drugs injected epidurally must cross the dura to achieve proximity to the site(s) of action. We did not use epidural droperidol, but a quick look through the literature shows its use as conceivable and appropriate in both an acute and chronic setting.

Epidural droperidol has been reported as a potent

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, induced 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

1. VANDER KOOY D, KODA LY: Organization of the Projections of a Circumventricular Organ: The Area Postrema in the Rat. *The Journal of Comparative Neurology;* 2004, 219(3):328-338.

2. PEDIGO NW JR, BRIZZEA KR: Muscarinic Cholinergic Receptors in Area Postrema and Brainstem Areas Regulating Emesis. *Brain Research Bulletin;* 1985, 14:169-177.

3. HARDING RK, HUGANINOLTZ, HEARNEY M, KUCHARCZKY J: Discrete Lesions of the Area Postrema Abolish Radiation-induced Emesis in the Dog. *Neurosci Lett;* 1985, 1:95-100.

4. BAKER PC, BERNAT JL: The Neuro Anatomy of Vomiting in Man: Association of Projectile Vomiting with Solitary Metastasis in the Lateral Tegmentum of the Pons and the Middle Cerebellar Peduncle. *J Neurol Neurosurg Psychiatry;* 1985, (48):1165-1168.

5. ISNETSOV VV: The Central Neurophysiological and Neurochemical Mechanisms of Vomiting (a Review of the Literature). {Article in Russian}. *Aviakosm Ekolog* Med; 1992, 26:10-18.

6. CARPENTER DO: Neural Mechanisms of Emesis. *Can. J. Physiolo Pharmacol;* 1990, (68):230-236.

7. MILLER AD, NONAKA S, JAKUS J: Brain Areas Essential or Nonessential for Emesis. *Brain Res;* 1994, (647):255-264.

8. HYDE TM, GIBBS M, PEROUTKA SJ: Distribution of Muscarinic Cholinergic Receptors in the Dorsal Vagal Complex and Other Selected Nuclei in the Human Medulla. *Brain Res;* 1988, (447):287-292.

9. BODIS S, ALEXANDER E III, KOOY H, LOEFTER JS: The Prevention of Radiosurgery Induced Nausea and Vomiting by Ondansetron: Evidence of a Direct Effect on the Central Nervous System Chemoreceptor Trigger Zone. *Surg Neurol;* 1994, (42):249-252.

10. FABLING JM, GRAN TJ, EL-MOALEM HE, WARNER DS, BOREL CO: A Randomized, Double-Blinded Comparison of Ondansetron, Droperidol and Placebo for Prevention of Post-Operative Nausea and Vomiting After Supratentorial Craniotomy. *Anesth Analg;* 2000, (91):358-361.

11. HYDE TM, KNABLE MB, MURRAY AM: Distribution of Dopamine D1-D4 Receptor Subtype in Human Dorsal Vagal Complex. *Synapse,* 1996, (24):224-232.

12. STAHL SM: The Ups and Downs of Novel Antiemetic Drugs, Part 1: Substance P, 5-HT, and the Neuropharmacology of Vomiting. *J. Clin Psychiatry;* 2003, 64:498-499.

13. HABIB AND GAN TJ: Food and Drug Administration Black Box Warning on the Preoperative Use of Droperidol: A Review of Cases. *Anesth Analg;* 2003, 965:1377-1379.

14. MILLER DP: Arrhythmogenic Potential of Antiemetics: Perspective on Risk-Benefit. *Can J Anaesh;* 2003, 50:215-220.

15. DERSHWITZ M, DROPERIDOL: Should the Black Box be Light Gray? *J Clin Anesth;* 2002, 14:298-603.

16. WHITE PF, DROPERIDOL: A Cost-Effective Antiemetic for Over Thirty Years, *Anesth Analg;* 2002, 95:789-790.

17. SAMUEL HASSENBUSCH, MD, PHD, KIM BURCHIEL MD, FACS, ROBERT J. COFFEX, MD, MICHAEL J. COUSINS, MBBS, TIM DEER, MD, MARC B. HAHN, DO, STURARD DU PEN, MD, KENNETH FOLLETT, MD, PHD, ELLIOT KRAMES, MD, JAMES N. ROGERS, MD, OREN SAGHER, MD, PETER S. STAATS, MD, MARK WALLACE, MD, AND KENNETH DEAN WILLIS, MD: Management of Intrathecal Catheter-Tip Inflammatory Masses: A Consensus Statement, *Pain Medicine;* 2002, 3:313-323.

18. STEARNS LJ: Intrathecal Droperidol Found to Relieve Intractable Nausea. *Clinical Anesth;* 2006, (32).

19. GRIP G, SVENSSON BA, GORDTH JR T, POST C, HARTVIG P: Histopathology and Evaluation of Potentiation of Morphine-induced Antinociception by Intrathecal Droperidol in the Rat. *Acta Anaesthesia Scand;* 1992, (36):145-152.

20. IWAMA H, ARAI M: Epidural Administration of Droperidol Suppresses Cisplatin-induced Emesis: Preliminary Findings. *Surgery Today, publisher Springer Japan;* 1998, (28):231-234.

21. HORTA ML, RAMOS L, GONCALVEZ R: The Inhibition of Epidural Morphine-induced Pruritus by Epidural Droperidol. *Anesthesia and Analgesia;* 2000, (90):638-641.

22. LEE IH, LEE IO: Antipruritic and Antiemetic Effect of Epidural Droperidol: Comparative Study between Single and Continuous Epidural Injection. *Eur. J. Anesthesiol;* 2006, (23):213-218.

23. WILDER-SMITH CH, WILDER-SMITH OH, FARSCHTSCHIAN F, NAJI P: Epidural Droperidol Reduces the Side Effects and Duration of Analgesia of Epidural Sufentanyl. *Anesthesia and Analgesia;* 1994, (79):98-104.

24. NAKATA K, MAMMOTO T, KITA T, TANIGUCHI H, KANBARA N, AKAMATSU T, SAKAI T, KISHI Y: Continuous Epidural, Not Intravenous Droperidol Inhibits Pruritus, Nausea and Vomiting During Epidural Morphine Analgesia. *Journal of Clinical Anesthesia;* 2002, 121-125.