PEDIATRIC PHARMACOTHERAPY

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Use of Hydromorphone in Children and Adolescents
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Hydromorphone, one of the first semi-synthetic derivatives of morphine, was patented in Germany in 1921 and marketed by Knoll Pharmaceuticals as Dilaudid®. It is more lipid soluble than morphine, with a ratio of 580:1, allowing it to more rapidly cross the blood-brain barrier. As a result, hydromorphone has a slightly faster onset of action and is approximately five to seven times as potent as morphine.[1,2] Although hydromorphone is not used as frequently in young children as morphine, it is a valuable alternative for patient-controlled analgesia (PCA) in older children and adolescents.

Mechanism of Action
Hydromorphone is a hydrogenated ketone of morphine. In the central nervous system (CNS), hydromorphone binds to mu- and delta-opioid receptors. It has no effect at kappa, sigma, or epsilon-opioid receptors. Activity at mu-opioid receptors produces analgesia, but also euphoria, miosis, hyperthermia, urinary retention, and constipation. Respiratory depression, nausea, vomiting, pruritus, and the development of physical tolerance result from both mu- and delta-opioid receptor activity. Like other opioids, hydromorphone also depresses the respiratory reflex by a direct effect on brain stem respiratory centers and reduces responsiveness to carbon dioxide tension. It depresses the cough reflex through a direct effect on the cough center in the medulla.[1-4]

As an opioid, hydromorphone also produces miosis, decreases gastric, biliary, and pancreatic secretions, decreases propulsive contractions in the gastrointestinal (GI) tract, and can trigger spasm of the sphincter of Oddi resulting in reflux of biliary and pancreatic secretions. Administration of hydromorphone also causes histamine release, which may result in hypotension, pruritus, and flushing. It has been suggested that the higher lipid solubility of hydromorphone may result in less nausea and a lower incidence of histamine-related adverse effects than morphine. Clinical studies, however, have provided conflicting results on the significance of these differences.[1-5]

Pharmacokinetics
Hydromorphone is available in both parenteral and oral forms. After oral administration, hydromorphone is rapidly absorbed from the GI tract, primarily within the duodenum. It undergoes extensive first-pass metabolism, with a bioavailability of approximately 60%. Peak plasma concentrations of hydromorphone typically occur within 30 minutes to 1 hour after an oral dose. Administration with food lowers peak plasma concentrations by approximately 25% and prolongs the time to peak concentrations by up to an hour, but these differences are generally not considered clinically significant.[3,4]

Hydromorphone is widely distributed into the tissues, including the lungs, liver, kidneys, spleen, and skeletal muscle, with a volume of distribution of 4 L/kg in adults. It is approximately 8 to 20% protein bound. Hydromorphone is extensively metabolized via cytochrome P450 2D6, with 95% converted to hydromorphone-3-glucuronide. The average elimination half-life in adults is 1 to 3 hours, with a clearance of 2 L/min (approximately 29 mL/min/kg).[3,4] Children may eliminate hydromorphone more rapidly than adults. In a study of 20 children receiving hydromorphone for mucositis pain (mean age 14 years), the average clearance rate was 51.7 mL/min/kg, with a range of 28.6 to 98.2 mL/min/kg.[6]

Renal or hepatic dysfunction results in a slower elimination of hydromorphone and its metabolites. Although it produces no significant analgesia, accumulation of hydromorphone-3-glucuronide may result in adverse neuroexcitatory effects, including allodynia, myoclonus, and seizures.[3,4,7]

<u>Use in Children and Adolescents</u>
While it is not used as frequently as morphine or fentanyl, hydromorphone has been studied in pediatric patients for management of both cancer-related and post-operative pain. In 1999, Goodarzi published the results of a double-blind randomized trial comparing epidural morphine, fentanyl, and hydromorphone in 90 children undergoing orthopedic surgery.[8] Patients between 3 and 19 years of age were randomly assigned to one of three treatment groups for postoperative analgesia: morphine (10 mcg/kg/hr), fentanyl (1 mcg/kg/hr), or hydromorphone (1 mcg/kg/hr). All drugs were infused through a lumbar epidural catheter. Patients evaluated their pain with a visual analog scale (VAS). Adverse effects were evaluated by the patients as well as the investigators.

There were no statistically significant differences in VAS scores among the three groups or in assessments made by the patients' nurses. At the end of the 30-hour observation period, 25% of the patients in the morphine group had experienced some degree of respiratory depression (defined as an oxygen saturation less than 90%), compared to none of the patients in the fentanyl or hydromorphone groups. There were no reports of significant apnea or severe respiratory insufficiency. Pruritus was more common in the morphine group (35%) than in the other two groups (15% with fentanyl and 8% with hydromorphone; p<0.02). The incidence of urinary retention was also higher in the morphine group (55% versus 20% with hydromorphone and 15% with fentanyl; p<0.05). There were no other statistically significant differences between the groups, although the authors noted prolonged somnolence in the morphine patients and more severe pruritus.[8]

In 2001, Lowry and colleagues published a prospective study of epidural hydromorphone in 10 adolescents between 12 and 17 years of age who had undergone anterior spinal fusion for scoliosis.[9] The epidural catheters were placed during surgery. Initial doses of 1 mcg/kg fentanyl and 5 mcg/kg hydromorphone were given at the time of surgery. After surgery, hydromorphone was infused at 2 mcg/kg/hr, along with 0.1% ropivacaine, until the epidural catheter was removed 5 days later. Daily pain scores were assessed with a 0-10 point VAS and adverse effects were documented. The median pain score after surgery was 2.1. The mean maximum score was 4.1 Three patients required an additional bolus and a 20% increase in their infusion rate. In one patient, the epidural hydromorphone was decreased by 20% due to excessive sedation. Three patients developed

mild pruritus. No other adverse effects were noted. The authors concluded that epidural hydromorphone may be a useful means of providing analgesia after spinal surgery.

In 2005, Sucato and colleagues at Texas Scottish Rite Hospital conducted a retrospective study comparing epidural hydromorphone infusion with standard PCA regimens following scoliosis repair.[10] The authors reviewed the records of 613 adolescents treated between 1990 and 2001. During this period, patients received either epidural hydromorphone 20 mcg/mL with bupivacaine 0.1% infused at 0.1 to 0.2 mL/kg/hr (providing 2 to 4 mcg/kg/hr hydromorphone) or a PCA with a bolus morphine dose of 0.02 to 0.03 mg/kg or a meperidine dose of 0.2 to 0.3 mg/kg. The PCA lock-out period was 7 to 12 minutes. Patients could also receive a basal rate of either morphine 0.015 mg/kg/hr or meperidine 0.15 mg/kg/hr. For all patients, the doses were titrated to maintain adequate pain relief.

The average of the pain scores taken within the first 48 hours of treatment were significantly lower in the epidural infusion group (1.3 versus 1.9; p<0.001). The range of pain scores (2.3 versus 2.7) and the average maximum score (2.6 versus 3.2) were both significantly lower in the epidural group than in the PCA group (p<0.05). However, the need to temporarily stop because of adverse effects or problems with catheter function was greater in the epidural group (12.3 versus 7.0%; p=0.04), as well as the rate of treatment discontinuation (13.1% versus 0; p<0.001). Based on the overall study results, the authors concluded that both epidural infusion and PCA provided effective pain control for adolescents following spinal fusion, but epidural infusion produced better overall pain scores.[10]

In addition to its use after surgery, hydromorphone has been shown to be an effective means of pain control in children with cancer. Collins and colleagues conducted a double-blind, randomized cross-over study of hydromorphone and morphine PCA in 10 children with mucositis pain after bone marrow transplantation.[5] The intermittent doses were 0.028 mg/kg morphine or 0.004 mg/kg hydromorphone, with a 5 minute lock-out period. A basal infusion of either morphine at 0.1 mg/kg/hr or hydromorphone at 1.4 mcg/kg/hr was used in all patients initially, and discontinued when patients used fewer than 6 intermittent doses per day. After receiving their initial regimen for 3 days, the patients were switched to the alternate agent for another three days. They switched back to the initial agent for a final three day period. On day 10, all patients

received a continuous infusion of the opioid administered during the previous day.

All patients required a rapid escalation in dose at the start of the study, followed by a plateau phase and then a decline in dose as their mucositis resolved. There were no statistically significant differences in pain scores, sedation, nausea, vomiting, or pruritus between the drugs. The hydromorphone doses required in the study were higher than those anticipated based on standard equipotency dosing charts, causing the authors to conclude that hydromorphone may be less potent in children than in adults. They also noted the lack of significant differences in adverse effects with the drugs, calling into question the belief that hydromorphone may be better tolerated.[5]

Precautions
Hydromorphone produces dose-dependent respiratory depression. Patients with underlying pulmonary conditions or depressed respiratory function should receive hydromorphone only under close observation in areas with appropriately trained personnel and equipment to support respiratory function.[1-4]

Hydromorphone should be used with caution in patients with biliary tract disease, because of its effects on the sphincter of Oddi. It should also be used with caution in patients with increased intracranial pressure, thyroid disease, adrenocortical insufficiency, CNS depression (including alcoholism or substance abuse), psychoses, urinary diseases, or following GI surgery. Some hydromorphone products contain metabisulfite as a preservative and should be avoided in patients with sulfite sensitivity.[3,4]

Like other opioids, hydromorphone is a Schedule II controlled substance. It has a high potential for misuse, abuse, and diversion. Prolonged administration will result in the development of tolerance and physical dependence. Withdrawal symptoms may occur after abrupt discontinuation of hydromorphone in patients who have developed tolerance.[3,4]

Adverse Effects
The most frequent adverse effects reported after hydromorphone use include constipation, dizziness and sedation (each estimated to occur in 20 to 23% of patients), nausea and vomiting (in approximately 9% of patients), diaphoresis, alterations in mood, dry mouth, flushing, and pruritus (in 5% of patients). Less frequent adverse effects include headache, agitation, tremor, arthralgias, parathesias, blurred vision, hallucinations, increased intracranial pressure, respiratory depression, apnea, bronchospasm or laryngospasm, alterations in heart rate and blood pressure, anorexia, diarrhea, urinary retention or hesitancy, and skin rashes. Seizures and myoclonus have been reported to occur with hydromorphone, but appear to be rare.

Hydromorphone inhibits the release of gonadotropin-releasing hormone and corticotropin-releasing hormone. As a result, patients receiving long-term hydromorphone may have decreased levels of adrenocorticotropic hormone, lutenizing hormone, and follicle-stimulating hormone. It increases prolactin and growth hormone secretion and may decrease cortisol and testosterone levels.[3,4]

Drug Interactions
Administration of hydromorphone with other CNS depressants (including general anesthetics, other opioids, phenothiazines, sedative/hypnotics, antipsychotics, or antidepressants) may produce additive sedation and respiratory depression. If combination therapy is used, doses of hydromorphone and the adjunctive agent should be reduced. Use of mixed agonist/antagonist opioid analgesics (buprenorphine, butorphanol, nalbuphine, and pentazocine) may result in rapid precipitation of opioid withdrawal. Hydromorphone, as with other opioids, may potentiate the effects of neuromuscular blocking agents.[3,4]

Dosing Recommendations
In opioid-naïve adolescents and adults, the recommended starting dose for hydromorphone is 1 to 2 mg given orally or 0.2 to 1 mg given subcutaneously, intramuscularly, or IV every 4 to 6 hours as needed. Subsequent doses should be adjusted based on patient response. Intravenous doses should be given slowly over at least 2 to 3 minutes, as rapid injection may increase the risk for respiratory depression and orthostatic hypotension. Hydromorphone may be administered by continuous IV or epidural infusion at doses of 0.1 to 0.3 mg/hr. For hydromorphone PCA, the recommended intermittent (bolus) dose is 0.1 to 0.2 mg with an 8 to 15 minute lock-out period. The intermittent dose may be used alone or with a basal infusion rate of 0.1 to 0.3 mg/hr. Hydromorphone may also be administered rectally at a dose of 3 mg (1 suppository) every 6 to 8 hours in adults.[3,4]

In children, the recommended oral dose is 0.03 to 0.08 mg/kg/dose (up to the adult dose) given every 3 to 4 hours as needed. The recommended parenteral dose for intermittent administration is 0.01 to 0.02 mg/kg/dose, also given every 3 to 4 hours. Continuous IV or epidural infusions should be initiated at 1 mcg/kg/hr (0.001

mg/kg/hr). For hydromorphone PCA in children, an intermittent dose of 2 to 4 mcg/kg (0.002 to 0.004 mg/kg) may be given with a lock-out period of 8 to 15 minutes. A basal infusion rate of 1 to 5 mcg/kg/hr (0.001 to 0.005 mg/kg/hr), up to the recommended rate for adults, may be added if needed.[1-6, 8-11]

Availability and Cost
Hydromorphone is marketed as Dilaudid® (Abbott Laboratories) and as generic products from several manufacturers. It is available in 1, 2, and 4 mg/mL ampules and multi-dose vials for injection, a concentrated 10 mg/mL injection (referred to as high-potency hydromorphone injection) and premixed IV bags for infusion. The injection or solution should be clear, but may have a slight yellow discoloration which does not adversely affect potency. Hydromorphone is also available as 2, 4, and 8 mg tablets, a 1 mg/mL oral liquid, 3 mg rectal suppositories, and a bulk powder for use by compounding pharmacies.[3,4]

The cost of hydromorphone varies based on the strength and volume of the product. The average wholesale price (AWP) for hydromorphone injection is approximately $1.50 to $2.00 for a single 2 mg/mL 1 mL ampule. High-potency hydromorphone injection (10 mg/mL) is approximately $2.50 to $4.50 per 1 mL ampule. The cost of a bottle of 100 hydromorphone 2 mg tablets ranges from $37.00 to $64.00. The AWP for hydromorphone oral liquid is $140.00 per 480 mL bottle.[12]

Summary
Hydromorphone is a useful alternative to morphine for PCA, epidural therapy after surgery, or for intermittent or continuous therapy for the management of severe pain in children. It may be particularly useful in children who develop significant nausea, vomiting, or pruritus with morphine, although further research is needed to determine the comparative frequency of these adverse effects in children. The role of hydromorphone in older children and adults is still being defined.

References
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Pharmacology Literature Review
Zolpidem pharmacokinetics in children
The pharmacokinetic profile of zolpidem was assessed in an open-label, dose-escalation study of 21 children. The patients were divided into groups by age (2-6 years, >6-12 yrs, and >12 years) and received single doses of 0.125 mg/kg, 0.25 mg/kg, or 0.5 mg/kg. The maximum dose used was 20 mg. There was a linear relationship between dose and maximum concentration, as well as between dose and area under the plasma concentration-time curve (AUC). As age increased, there was an increase in AUC and half-life and a decrease in total body clearance. True sleep time was increased by approximately 20 minutes and sleep latency was slightly increased. Based on their results, the authors recommend a pediatric zolpidem dose of 0.25 mg/kg for future studies. Blumer JL, Reed MD, Steinberg F, et al. Potential pharmacokinetic basis for zolpidem dosing in children with sleep difficulties. **Clin Pharmacol Ther 2008;83:551-8.**

Formulary Update
The Pharmacy and Therapeutics Committee did not meet during June.