Title: A COMPARISON OF METHADONE AND MORPHINE FOR POST-OPERATIVE ANALGESIA IN CHILDREN AND ADOLESCENTS

Authors: C.B. Berde, Ph.D., M.D., R.S. Holzman, M.D., N.F. Sethna, M.B., Ch.B., R.B. Dickerson, M.D., R.M. Brustowicz, M.D.

Affiliation: Department of Anaesthesia, Harvard Medical School, Department of Anesthesia, The Children's Hospital, Boston, Massachusetts 02115

Introduction. Previous studies have shown that: (1) intraoperative administration of methadone (20 mg IV) produced prolonged post-operative analgesia (typically 17-26 hours) in adults [1,2] and (2) the elimination half-life in children and adolescents [3] (mean value 19.2 hours) was similar to that measured previously for young adults. We undertook a randomized prospective double-blind study to determine whether methadone (MD) could produce prolonged analgesia, relative to morphine (MS), in children and adolescents.

Methods. Forty-one patients ages 6-19 were enrolled in two separate protocols (denoted A and B), with informed consent, according to procedures approved by the Institutional Human Studies Committee. Enrollment was restricted to ASA I and II patients having painful surgery lasting at least 90 minutes. In protocol A (orthopedic, urologic, and general surgery) anesthetic induction proceeded with either thiopental or halothane, and was maintained with N_2O/O_2/isoflurane/curare. Immediately following intubation, MD 0.2 mg/kg or MS 0.2 mg/kg was administered IV in double-blind fashion. In the recovery room (RR), patients received the same blinded narcotic (titrated in 0.05 mg/kg increments) until comfortable. On the ward, patients received intramuscular MS (unblinded) via an algorithm based on a visual analogue scale (VAS, 0-10 scale) and countermanded only by signs of somnolence or hypoventilation (MS 0.1 mg/kg IM q3h for VAS between 4 and 7, MS 0.15 mg/kg IM q3h for VAS between 8 and 10). Protocol B was restricted to patients undergoing posterior spinal fusion for scoliosis. Prior to the "wake-up-test", patients received fentanyl (10 mcg/kg initially, and 1-2 mcg/kg/hour thereafter)/curare/N_2O/O_2 isoflurane. Following the "wake-up-test", they received MD or MS 0.1 mg/kg IV in double-blind fashion. For the first 12 hours in the ICU, patients received MS or MD 0.1 mg/kg/dose IV (blinded, according to a similar VAS algorithm). After the first 12 hours, they received injections of MS (unblinded) by criteria similar to those used on the ward in Protocol A.

Results. For both protocols, there was no significant difference in mean ages or weights for the two groups (Table 1). No patient on either protocol had clinically significant hypoventilation postoperatively. In Protocol A, there was no significant difference between MS and MD groups in the number of injections administered for the first 12 hours or for the first 24 hours on the ward. Similarly, no differences were observed in the total MS dose per kg administered during these time periods. In Protocol B, patients in the MD group required significantly fewer supplemental doses of blinded study narcotic during the first 12 hours in the ICU, and required significantly fewer (unblinded) MS injections during the subsequent 12 hours (Table 1).

Discussion. As expected, the analgesic duration of MD in children and adolescents is subject to individual variation and depends in part upon the size of loading doses. Under the conditions of Protocol A, patients receiving a mean "loading dose" (intra-op + RR) of 0.23 mg/kg of MD required no less supplemental MS and no fewer injections than patients receiving a mean "loading dose" of 0.25 mg/kg of MS. Conversely, in Protocol B, a mean total "loading dose" of 0.35 mg/kg of methadone (intra-op + RR + 12 hours in ICU) led to reduced supplemental MS requirements over the next 12 hours and fewer injections compared to patients receiving MS by the same algorithm ("loading dose" 0.8 mg/kg). Because of wide individual variation, the administration of larger intraoperative MD doses to children, e.g. 0.3 mg/kg at the start of surgery, is not recommended since unblinded pilot studies showed a substantial incidence of post-operative hypoventilation at these larger doses. Based on these findings, we suggest: (1) limiting intra-operative MD dosage to 0.2 mg/kg IV at the start of surgery, (2) titration to comfort in the RR with MD in increments of 0.05 mg/kg IV and (3) supplemental MD administered in increments of 0.05-0.07 mg/kg by slow IV infusion (e.g. over 20 minutes) every 4-8 hours as needed.

References.

1. Gourlay GK, Wilson PR, Glynn CJ: Pharmacodynamics and pharmacokinetics of methadone during the perioperative period. Anesthesiology 57:458-467, 1982.

2. Gourlay GK, Willis RJ, Lamberty J: A double-blinded comparison of the efficacy of methadone and morphine in postoperative pain control. Anesthesiology 64:322-327, 1986.

3. Berde CB, Sethna NF, Holzman RS, et al: Pharmacokinetics of methadone in children and adolescents in the perioperative period. Anesthesiology 67(3A):A519, 1987.

Table 1. Analgesic Administration

Protocol A	Morphine Group	Methadone Group
n	14	12
Age	12.2±3.1	12.5±3.8 n.s.
Weight	46.7±12.8	48.6±20.7 n.s.
Total Blinded MS/MD (OR+RR, mg/kg)	0.25±0.07	0.23±0.07 n.s.
Morphine Injections (1st 12 hours)	1.9±0.95	1.6±1.2 n.s.
Morphine Requirement (mg/kg, 1st 12 hours)	0.22±0.12	0.17±0.13 n.s.
Morphine Requirement (mg/kg, 1st 24 hours)	0.46±0.18	0.41±0.19 n.s.

Protocol B	Morphine Group	Methadone Group
n	8	7
Age	13.5±1.4	11.7±2.8 n.s.
Weight	48.2±10.5	37.9±16.8 n.s.
Supplemental MS/MD Doses (1st 12 hours)	6.0±2.1	2.7±1.4*
Total Blinded MS/MD (OR+RR+1st 12 hours in ICU, mg/kg)	0.80±0.21	0.35±0.13**
Morphine Injections (12-24 hours)	3.37±0.92	1.29±0.76**
Morphine Requirement mg/kg,12-24 hours)	0.39±0.14	0.15±0.09*

unpaired t-test: n.s. = not significant * = $p \leq 0.005$, ** = $p \leq 0.0005$