Health Policy & Clinical Effectiveness

Evidence-Based Care Guideline

Anesthesia, Analgesia and Sedation Following Arterial Switch Operation

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Introduction

Anesthetic, analgesic and sedative medications, particularly narcotics and benzodiazepines, are commonly used for three different but related purposes following cardiac surgery in neonates: 1) blunting of the physiologic stress response associated with cardiac surgery, 2) pain control, and 3) sedation.

Cardiac surgery in neonates is associated with a profound physiologic stress response that may place the neonate at an increased risk for adverse hemodynamic events *(Anand 1990 [D])*. Continuous high-dose fentanyl infusion in the post-operative period can blunt this stress response and may therefore impart hemodynamic benefit *(Orsini 1996 [B], Anand 1992 [B])*. The benefits of such an infusion for a prolonged period must be weighed against the consequence of respiratory depression that is associated with high-dose narcotic use *(Orsini 1996 [B])*. Although there is a predictable decrease in cardiac output in the first 6-18 hours following arterial switch operation, many patients are hemodynamically stable enough to be extubated on post-operative day 1 *(Wernovsky 1995 [A])*.

A second important goal guiding the use of these medications is pain control. Narcotics such as morphine and fentanyl are effective controlling pain in this population, and can be administered either by bolus dosing or continuous infusion *(Saarenmaa 1999 [A], Prakanrattana 2002 [C], Farrington 1993 [C])*. When given by continuous infusion, fentanyl and morphine are equally effective in terms of pain relief. Fentanyl is associated with fewer hemodynamic and gastrointestinal side effects, but dosing in neonates may be less predictable *(Saarenmaa 1999 [A], Saarenmaa 2000 [C], Santeiro 1997 [C], Hamon 1996 [C], Katz 1993 [C], Arnold 1991 [C], Murat 1988 [C])*. Furthermore, because of its lipid solubility, undesirable narcotic effects such as respiratory depression may remain for some time, even after the infusion has been discontinued *(CCHMC Formulary 2006 [X])*

Finally, sedation with narcotics and/or benzodiazepines is important for both patient comfort and safety. Following cardiac surgery, the typical neonate has an endotracheal tube, numerous intravascular and intracardiac lines as well as chest drainage tubes and pacemaker wires. These items need to remain secure, and patient discomfort and agitation should be minimized *(Local Expert Consensus [E])*.

In developing this guideline, we recognize the paucity of large-scale studies with direct bearing on this particular focus population. The specific recommendations in this guideline are drawn from directly applicable studies where possible, but are largely extrapolated from smaller studies, and from studies more indirectly related to the present issues.

Target Population

Inclusions: These guidelines are intended primarily for use in neonates (age ≤ 30 days) who have undergone an arterial switch operation (with or without ventricular septal defect closure).

Exclusions: The guidelines do not address all considerations needed to manage those with the following:

- Adverse/allergic reaction to morphine, fentanyl, lorazepam or midazolam.

Guideline Recommendations

References in parentheses ( ) Evidence strengths in brackets [ ] (See last page for definitions)

Clinical Assessments

1. It is recommended that hemodynamic stability be maintained as indicated by mean arterial pressure > 45, left atrial pressure < 15 and urine output > 1cc/Kg/hr. Physical exam should indicate adequate perfusion.

Note 1: Continuous monitoring of ECG and arterial blood pressure via an arterial line is recommended *(Local Expert Consensus [E])*.

Note 2: Continuous monitoring of left atrial pressure with a transthoracic catheter is recommended *(Local Expert Consensus [E])*

2. It is recommended that adequate pain relief is provided as indicated by behavioral assessment and the absence of otherwise unexplained tachycardia or hypertension.

3. It is recommended that patient comfort and sedation be maintained as indicated by behavioral assessment. The patient should not be at risk for inadvertent self-removal of lines and/or tubes.

Treatment Recommendations

4. It is recommended that a fentanyl infusion at 10 mcg/Kg/hr be started on all post-operative arterial switch patients and maintained for at least 6 hours. The infusion should be discontinued if the patient has had no signs or symptoms of low cardiac output (mean arterial pressure < 45, urine output < 1cc/Kg/hr, persistent base deficit > -4 despite correction with $NaHCO_3$ or increase in lactate level > 0.5 mg/dl/hr) and is therefore considered a good candidate for extubation in the next 24 hours.).

Note 1: A continuous infusion of high-dose fentanyl is maintained to blunt the physiologic stress response that occurs as a consequence of cardiac surgery *(Anand 1992 [B], Anand 1990 [D])*. Because cardiac output decreases for at least the first 6 hours following cardiopulmonary bypass, it is recommended that the infusion be continued for at least this length of time *(Wernovsky 1995 [A])*.

Note 2: Because of the redistribution of fentanyl into lipid tissue, long-term infusion may result in prolongation of side effects such as apnea well beyond termination of the infusion *(CCHMC Formulary 2006 [X])*. Therefore, once pain management, rather than hemodynamic stability becomes the primary reason for narcotic use, it is desirable to use bolus dosing of a less lipophilic agent such as morphine and to discontinue the fentanyl infusion *(Local Expert Consensus [E])*.

Note 3 : Ongoing metabolic acidosis caused by the continued production of lactic acid has been associated with a poor outcome following cardiac surgery in infants and children. *(Charpie 2000 [C], Munoz 2000 [C])*.

5. It is recommended that midazolam (0.1 mg/Kg/dose every 1-2 hours) or lorazepam (0.1 mg/Kg/dose every 6-8 hours)be given concurrently with the fentanyl infusion to ensure adequate sedation in addition to anesthesia/analgesia.

Note: Because of the variability in neonatal response to fentanyl and because of rapid development of tolerance to its sedative effects (in contrast to respiratory depressant effects), additional use of benzodiazepines is often necessary to maintain adequate sedation *(Arnold 1991 [C])*.

6. It is recommended that adequate analgesia and sedation be provided using as needed doses of morphine (0.1 mg/Kg/dose) and midazolam (0.1 mg/Kg/dose) once the fentanyl infusion has been discontinued.

Note: The longer half-life of morphine makes it a better choice for intermittent dosing than fentanyl. The histamine release associated with morphine should be well tolerated hemodynamically by patients who are otherwise stable 6 hours after cardiopulmonary bypass. *(Saarenmaa 1999 [A], Saarenmaa 2000 [C], Santeiro 1997 [C], Hamon 1996 [C], Katz 1993 [C], Arnold 1991 [C], Murat 1988 [C])*.

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Development Process

The process by which this guideline was developed is documented in the Guideline Development Process Manual. The recommendations contained in this guideline were formulated by an interdisciplinary working group which performed systematic and critical literature reviews, using the grading scale that follows, and examined current local clinical practices.

To select evidence for critical appraisal by the group for the update of this guideline, the Medline, EmBase and the Cochrane databases were searched. Evidence from 2000 and before was verified for inclusion in the guidelines. Evidence from 2001 to January, 2006 was reviewed for relevance to the clinical topics/questions to generate an unrefined, "combined evidence" database using a search strategy focused on answering clinical questions relevant to anesthesia, analgesia, or sedation following arterial switch operations and employing a combination of Boolean searching on human-indexed thesaurus terms (MeSH headings using an OVID Medline interface) and "natural language" searching on searching on human-indexed thesaurus terms (MeSH headings using an OVID Medline interface) and "natural language" searching on words in the title, abstract, and indexing terms. The citations were reduced by: eliminating duplicates, review articles, non-English articles, and adult articles. The resulting abstracts were reviewed by a methodologist to eliminate low quality and irrelevant citations. During the course of the guideline development, additional clinical questions were generated and subjected to the search process, and some relevant review articles were identified. April, 2000 was the last date for which literature was reviewed for the previous version of this guideline. The details of that review strategy are not documented. However, all previous citations were reviewed for appropriateness to this revision.

A search using the above criteria was conducted for dates of January, 2006 through July, 2006. No relevant articles were found that would require changes to the January, 2006 version of the recommendations.

Appropriate companion documents have been developed to assist in the effective dissemination and implementation of the guideline. Experience with the implementation of earlier publications of this guideline has provided information which has been incorporated into this revision.

CCHMC Grading Scale			
M	Meta-analysis or Systematic Review	O	Other evidence
A	Randomized controlled trial: large sample	E	Expert opinion or consensus
B	Randomized controlled trial: small sample	F	Basic Laboratory Research
C	Prospective trial or large case series	L	Legal requirement
D	Retrospective analysis	Q	Decision analysis
S	Review article	X	No evidence

Once the guideline has been in place for four years, the development team reconvenes to explore the continued validity of the guideline. This phase can be initiated at any point that evidence indicates a critical change is needed. Time to extubation, hemodynamic stability and length of stay in the Cardiac Intensive Care Unit (CICU) are outcome measures that are monitored and reviewed quarterly.

Recommendations have been formulated by a consensus process directed by best evidence, patient and family preference and clinical expertise. During formulation of these recommendations, the team members have remained cognizant of controversies and disagreements over the management of these patients. They have tried to resolve controversial issues by consensus where possible and, when not possible, to offer optional approaches to care in the form of information that includes best supporting evidence of efficacy for alternative choices. The guidelines have been reviewed by clinical experts not involved in the development process, senior management, and other individuals as appropriate to their intended purposes.

The guideline is based, in part, on three independent reviews performed by members of Evidence-Based Care Group of Health Policy & Clinical Effectiveness at Cincinnati Children's Hospital and Medical Center (CCHMC) using AGREE criteria (Appraisal of Guidelines for Research and Evaluation). The guideline was developed without external funding.

Important Information

NOTE: These recommendations result from review of literature and practices current at the time of their formulations. This protocol does not preclude using care modalities proven efficacious in studies published subsequent to the current revision of this document. This document is not intended to impose standards of care preventing selective variances from the guidelines to meet the specific and unique requirements of individual patients. Adherence to this pathway is voluntary. The physician in light of the individual circumstances presented by the patient must make the ultimate judgment regarding the priority of any specific procedure.

For more information about these guidelines and their supporting evidences contact the Heart Center, Division of Cardiothoracic Surgery at 513-636-4770 or thc@cchmc.org .

References

Anand, K. J., D. D. Hansen, et al.: Hormonal-metabolic stress responses in neonates undergoing cardiac surgery. *Anesthesiology*, 73(4): 661-70., 1990, *[D]*.

Hormonal and metabolic responses were measured in 15 neonates who underwent repair of complex congenital heart defects during a standardized anesthetic protocol. Four of the 15 neonates died postoperatively in the intensive care unit. Analysis of arterial plasma samples obtained before, during, and 24 h after surgery showed that plasma epinephrine, norepinephrine, cortisol, glucagon, and beta endorphin increased in all patients (P less than 0.05). Insulin levels increased only at the end of surgery but remained elevated for 24 h postoperatively (P less than 0.02). Intraoperative metabolic changes were characterized by hyperglycemia and lactic acidemia that persisted postoperatively. This pattern of neonatal stress responses is distinct from and more extreme than that seen in adult cardiac surgical patients. The four neonates who died postoperatively tended to have higher stress responses intra- and postoperatively despite having been indistinguishable from survivors by the usual clinical and hemodynamic criteria. These preliminary results suggest that neonatal hormonal and metabolic responses to cardiac surgical operations in neonates are extreme and are associated with a high hospital mortality rate.

Anand, K. J. and P. R. Hickey: Halothane-morphine compared with high-dose sufentanil for anesthesia and postoperative analgesia in neonatal cardiac surgery. *N Engl J Med*, 326(1): 1-9., 1992, *[B]*.

BACKGROUND. Extreme hormonal and metabolic responses to stress are associated with increased morbidity and mortality in sick adults. We hypothesized that administering deep opioid anesthesia to critically ill neonates undergoing cardiac surgery would blunt their responses to stress and might improve clinical outcomes. METHODS. In a randomized trial, 30 neonates were assigned to receive deep intraoperative anesthesia with high doses of sufentanil and postoperative infusions of opiates for 24 hours; 15 neonates were assigned to receive lighter anesthesia with halothane and morphine followed postoperatively by intermittent morphine and diazepam. Hormonal and metabolic responses to surgery were evaluated by assay of arterial blood samples obtained before, during, and after the operations. RESULTS. The neonates who received deep anesthesia (with sufentanil) had significantly reduced responses of beta-endorphin, norepinephrine, epinephrine, glucagon, aldosterone, cortisol, and other steroid hormones; their insulin responses and ratios of insulin to glucagon were greater during the operation. The neonates who received lighter anesthesia (with halothane plus morphine) had more severe hyperglycemia and lactic acidemia during surgery and higher lactate and acetoacetate concentrations postoperatively (P less than 0.025). The group that received deep anesthesia had a decreased incidence of sepsis (P = 0.03), metabolic acidosis (P less than 0.01), and disseminated intravascular coagulation (P = 0.03) and fewer postoperative deaths (none of 30 given sufentanil vs. 4 of 15 given halothane plus morphine, (P less than 0.01). CONCLUSIONS. In neonates undergoing cardiac surgery, the physiologic responses to stress are attenuated by deep anesthesia and postoperative analgesia with high doses of opioids. Deep anesthesia continued postoperatively may reduce the vulnerability of these neonates to complications and may reduce mortality.

Arnold, J. H., R. D. Truog, et al.: Changes in the pharmacodynamic response to fentanyl in neonates during continuous infusion. *J Pediatr*, 119(4): 639-43., 1991, *[C]*.

Tolerance to opioid-induced sedation has been reported in neonates sedated with fentanyl by continuous infusion while undergoing extracorporeal membrane oxygenation. We undertook a prospective analysis of eight newborn infants sedated with fentanyl during extracorporeal membrane oxygenation therapy for respiratory failure. We recorded daily mean fentanyl infusion rate, measured serial plasma fentanyl concentrations, and documented the occurrence of spontaneous motor activity or respiratory effort. Mean fentanyl infusion rate increased steadily during the period of infusion from a mean of 9.2 +/- 1.9 (SEM) micrograms/kg per hour on day 1 to a mean of 21.9 +/- 4.5 micrograms/kg per hour by day 6. Mean plasma fentanyl concentrations increased steadily during the period of fentanyl infusion from 3.1 +/- 1.1 (SEM) ng/ml on day 1 to 13.9 +/- 3.2 ng/ml on day 6. All infants exhibited movement in response to gentle tactile stimulation throughout the period of infusion, and seven of eight infants manifested spontaneous movement of the extremities and eye opening. Our results indicate that when fentanyl is used for sedation in neonates, the plasma concentrations required for satisfactory sedation steadily escalate, possibly indicating the rapid development of tolerance to the sedating effects of fentanyl.

CCHMC Formulary (2006). Cincinnati Children's Hospital Medical Center Online Formulary. Hudson, Ohio, Lexicomp, Inc.

Charpie, J. R., M. K. Dekeon, et al.: Serial blood lactate measurements predict early outcome after neonatal repair or palliation for complex congenital heart disease. *J Thorac Cardiovasc Surg*, 120(1): 73-80., 2000, *[C]*.

OBJECTIVES: Neonates with congenital heart disease may appear hemodynamically stable after operation and then suddenly experience catastrophic decompensation. An improved means of predicting which infants will suddenly die in the early postoperative period may lead to lifesaving interventions. Studies indicate that blood lactate level is proportional to tissue oxygen debt, but information linking lactate levels with outcome in infants after operation is limited. We sought to determine whether a change in lactate level over time was predictive of a poor outcome defined as death within the first 72 hours or the need for extracorporeal membrane oxygenation. METHODS: To test this hypothesis, we studied prospectively 46 infants who were less than 1 month old and were undergoing complex

cardiac surgical palliation or repair. Postoperative arterial oxygen saturation, bicarbonate, and lactate levels were recorded on admission to the intensive care unit and every 3 to 12 hours for the first 3 days. RESULTS: Thirty-seven patients had a good outcome, and 9 patients had a poor outcome. Mean initial lactate level was significantly greater in patients with a poor outcome (9.4 +/- 3.8 mmol/L) than in patients with a good outcome (5.6 +/- 2.1 mmol/L; P =.03). However, an elevated initial lactate level of more than 6 mmol/L had a low positive predictive value (38%) for poor outcome. In contrast, a change in lactate level of 0.75 mmol/L per hour or more was associated with a poor outcome (P <.0001) and predicted a poor outcome with an 89% sensitivity value, a 100% specificity value, and a 100% positive predictive value. CONCLUSIONS: Serial blood lactate level measurements may be an accurate predictor of death or the requirement for extracorporeal membrane oxygenator support for patients who undergo complex neonatal cardiac surgery.

Farrington, E. A., G. A. McGuinness, et al.: Continuous intravenous morphine infusion in postoperative newborn infants. *Am J Perinatol*, 10(1): 84-7., 1993, *[C]*.

The efficacy and safety of morphine sulfate was evaluated in 20 neonates requiring surgery. Following surgery, each subject received an intravenous morphine loading dose (50 micrograms/kg) followed by a continuous infusion (15 micrograms/kg/hr) for a minimum of 24 hours. Heart rate, respiratory rate, and blood pressure were frequently monitored during therapy. Blood samples were obtained following surgery and during and after morphine therapy for analysis of serum morphine and beta-endorphin content. A 12-hour urine collection was obtained 12 hours following the start of the constant morphine infusion for analysis of morphine content. The mean (+/- SD) duration of morphine infusion was 34 +/- 15 hours and a steady-rate serum morphine concentration was 39 +/- 23 ng/ml. The respective serum morphine half- life, elimination rate, and volume of distribution were 6.6 +/- 2.9 hr, 0.126 +/- 0.056 hr-1, and 5.0 +/- 6.8 liters/kg. The mean percentage of unchanged morphine recovered in the urine was 39 +/- 19 of the dose administered over 12 hours. A significant reduction in serum beta- endorphin content was observed following the onset of morphine therapy. No adverse reports were noted that could be attributed to morphine therapy. Continuous morphine therapy appears to be effective in controlling neonatal postoperative pain, as suggested by subjective nursing observations and decreased serum beta-endorphin content.

Hamon, I., J. M. Hascoet, et al.: Effects of fentanyl administration on general and cerebral haemodynamics in sick newborn infants. *Acta Paediatr*, 85(3): 361-5., 1996, *[C]*.

Despite the wide use of fentanyl for analgesia in newborns, concerns have been raised about potential haemodynamic side-effects. Since sick newborns may lose their cerebral blood flow autoregulation, a drug- induced haemodynamic instability could lead to brain injury. We assessed the effects of a 15-min infusion of fentanyl (3 micrograms/kg) on the general and cerebral haemodynamics in 15 newborns (median gestational age 29 weeks, 25th-75th percentile, range 28-31 weeks; birthweight 1170 g, range 955-1790 g). The heart rate and mean arterial blood pressure were continuously recorded. Mean cerebral blood flow velocity and pulsatility index were measured using pulsed Doppler ultrasound before, during and up to 60 min after the onset fentanyl administration. No significant modification of general or cerebral haemodynamics was observed. In conclusion, the infusion of 3 micrograms/kg of fentanyl did not lead to any deleterious effect on the general or cerebral haemodynamics in sick normovolaemic newborns.

Katz, R. and H. W. Kelly: Pharmacokinetics of continuous infusions of fentanyl in critically ill children. *Crit Care Med*, 21(7): 995-1000., 1993, *[C]*.

OBJECTIVE: To determine the pharmacokinetics of fentanyl when used as a long-term continuous infusion for sedation/analgesia in mechanically ventilated critically ill infants and children. DESIGN: Prospective, case series. SETTING: A university hospital pediatric intensive care unit (ICU). PATIENTS: Nineteen mechanically ventilated infants and children (0.05 to 14 yrs of age) who received continuous infusions of fentanyl for > 24 hrs. INTERVENTIONS: None. MEASUREMENTS: Plasma concentrations of fentanyl were measured 1 hr after a loading dose and at various intervals during and after the infusions were discontinued. Noncompartmental pharmacokinetic variables, total body clearance, volume of distribution at steady state, and terminal elimination half- life were calculated. Clinical sedation scores, ventilatory settings, pupillary size and reactivity, and patient demographics were recorded. RESULTS: After the use of fentanyl by long-term infusion, the volume of distribution at steady state was increased 15.2 L/kg (range 5.1 to 30.5) and the terminal elimination half-life was prolonged 21.1 hrs (range 11.2 to 36.0) compared with previous studies. Clearance was rapid and consistent with other studies. There was a large interpatient variability in clearance that was age dependent. Clearance did not appear to increase over time. CONCLUSIONS: Total body clearance of fentanyl is highly variable and it should be dosed to effect. Patients seen in a pediatric ICU may require a ten-fold variability in fentanyl infusion rates to achieve similar levels of sedation.

Local Expert Consensus: During guideline development timeframe. *[E]*.

Munoz, R., P. C. Laussen, et al.: Changes in whole blood lactate levels during cardiopulmonary bypass for surgery for congenital cardiac disease: an early indicator of morbidity and mortality. *J Thorac Cardiovasc Surg*, 119(1): 155-62., 2000, *[C]*.

OBJECTIVE: Our objective was to evaluate the change in lactate level during cardiopulmonary bypass and the possible predictive value in identifying patients at high risk of morbidity and mortality after surgery for

congenital cardiac disease. METHODS: We prospectively studied lactate levels in 174 nonconsecutive patients undergoing cardiopulmonary bypass during operations for congenital cardiac disease. Arterial blood samples were taken before cardiopulmonary bypass, during cardiopulmonary bypass (cooling and rewarming), after cardiopulmonary bypass, and during admission to the cardiac intensive care unit. Complicated outcomes were defined as open sternum as a response to cardiopulmonary instability, renal failure, cardiac arrest and resuscitation, extracorporeal membrane oxygenation, and death. RESULTS: The largest increment in lactate level occurred during cardiopulmonary bypass. Lactate levels decreased between the postbypass period and on admission to the intensive care unit. Patients who had circulatory arrest exhibited higher lactate levels at all time points. Nonsurvivors had higher lactate levels at all time points. A change in lactate level of more than 3 mmol/L during cardiopulmonary bypass had the optimal sensitivity (82%) and specificity (80%) for mortality, although the positive predictive value was low. CONCLUSIONS: Hyperlactatemia occurs during cardiopulmonary bypass in patients undergoing operations for congenital cardiac disease and may be an early indicator for postoperative morbidity and mortality.

Murat, I., J. C. Levron, et al.: Effects of fentanyl on baroreceptor reflex control of heart rate in newborn infants. *Anesthesiology,* 68(5): 717-22., 1988, *[C]*.

Baroreceptor reflex control of heart rate was studied in ten neonates and young infants before and after intravenous fentanyl (10 micrograms/kg). All infants were in stable condition while being mechanically ventilated. Mean (+/- SD) corrected gestational age was 40.1 +/- 3.7 weeks, mean weight 3120 +/- 700 g. The pressor response was tested using phenylephrine and the depressor response using nitroglycerin. Changes in heart rate (R-R interval) were plotted against changes in systolic arterial pressure, and the slope of the linear portion of this relationship expresses the baroreflex sensitivity. No significant changes in systolic arterial pressure, heart rate, and blood gas values were observed after fentanyl injection when compared to control values. Mean (+/- SEM) control phenylephrine slope was 8.44 +/- 2.05 msec/mmHg, and mean nitroglycerin slope was 2.54 +/- 0.37 msec/mmHg. Both slopes decreased significantly by 48% and 42%, respectively, after fentanyl injection (P less than 0.02). Mean plasma fentanyl concentrations measured at the end of each test were not statistically different (5.11 +/- 0.65 ng/ml and 4.28 +/- 0.58 ng/ml, respectively). This suggests that the baroreflex control of heart rate is present in term neonates and markedly depressed during fentanyl anesthesia. Changes in blood pressure occurring during fentanyl anesthesia have to be carefully considered, because cardiac output is principally rate-dependent in newborns.

Orsini, A. J., K. H. Leef, et al.: Routine use of fentanyl infusions for pain and stress reduction in infants with respiratory distress syndrome. *J Pediatr,* 129(1): 140-5., 1996, *[B]*.

OBJECTIVE: To determine whether fentanyl infusions given to premature infants with respiratory distress syndrome reduce stress and improve long- and short-term outcome. METHODS: Twenty premature infants undergoing mechanical ventilation for respiratory distress syndrome were randomly assigned, in a double-blind fashion, to receive fentanyl by continuous infusion or a volume-matched placebo infusion. A behavioral state score was used to assess the infants' behavior. Cortisol and 11-deoxycortisol levels were measured as physiologic markers of stress. Urinary 3-methyl histidine/creatinine molar ratio was determined and the fractional excretion of urea was measured to assess catabolic state. Ventilatory indexes were recorded for each infant. RESULTS: Infants receiving fentanyl showed significantly lower behavioral state scores ($p < 0.04$) and lower heart rates ($p < 0.001$) than those receiving placebo. 11-Deoxycortisol levels were lower in the fentanyl group on days 3, 4, and 5 of the study ($p < 0.003$). 3-Methyl histidine/creatinine ratios and fractional excretion of urea were not significantly different between the two groups. On the third day of the study, infants receiving fentanyl required a higher ventilator rate ($p < 0.01$), higher peak inspiratory pressures ($p < 0.001$), and higher positive end-expiratory pressure ($p < 0.0001$) than those receiving placebo. There was no difference in long-term outcome with respect to the incidence of bronchopulmonary dysplasia, intraventricular hemorrhage, or sepsis or with respect to the duration of ventilator use. CONCLUSIONS: Although there was a reduction in stress markers in the infants receiving fentanyl, we were unable to demonstrate an improvement in catabolic state or long-term outcome. In addition, the infants receiving fentanyl required higher ventilatory support in the early phase of respiratory distress syndrome than did those receiving placebo.

Prakanrattana, U., S. Suksompong, et al.: Anesthesia for arterial switch operation in simple transposition of the great arteries: experience at Siriraj Hospital. *J Med Assoc Thai,* 85 Suppl 3: S815-23, 2002, *[C]*.

Anesthetic management of cardiac patients with complete transposition of the great arteries (TGA) undergoing arterial switch operation (ASO) is challenging. The anesthetic course and perioperative problems were studied. A prospective data collection study of 87 patients was performed between January 1991 and February 2002. The patients were divided into 3 groups: Group 1; 27 neonates with TGA with an intact ventricular septum (IVS), Group 2; 21 with TGA, with IVS who underwent two-stage ASO, and Group 3; 39 with TGA, with a large VSD. The anesthesia consisted of low-dose fentanyl, thiopental, atracurium and isoflurane. Monitoring included ECG, radial or femoral arterial pressure, CVP, LAP, core temperature, SpO2, P(E)CO2, urine output, ABG's, Hct, ACT, serum glucose and potassium. Fortunately the courses of anesthesia were uneventful. Usual vasoactive medication administered following CPB included nitroglycerin, dobutamine and dopamine. Groups I, 2 and 3 contained 18.5 per cent,

14.3 per cent and 33.3 per cent of patients who required adrenaline respectively. And only 7.7 per cent of patients in Group 3 had milrinone as an inotrope. Early tracheal extubation, 2 hours after admission to ICU was performed in 3 patients. Perioperative complications included bleeding, low cardiac output, diaphragmatic paresis, digitalis intoxication, metabolic alkalosis, convulsion, pulmonary hypertensive crisis and death. Two patients who developed a pulmonary hypertensive crisis were successfully managed with inhaled nitric oxide. The overall hospital mortality rate was 19.54 per cent. In conclusion, the anesthetic management for ASO in 87 simple dTGA patients was uneventful at Siriraj Hospital. The major perioperative morbidity and hospital mortality were not directly anesthetic contribution.

Saarenmaa, E., P. Huttunen, et al.: Advantages of fentanyl over morphine in analgesia for ventilated newborn infants after birth: A randomized trial. *J Pediatr*, 134(2): 144-50., 1999, *[A]*.

OBJECTIVE: To compare the efficacy and adverse effects of fentanyl or morphine analgesia during the first 2 days of life in newborn infants who underwent mechanical ventilation. STUDY DESIGN: In a randomized double-blind trial, 163 infants were allocated to receive a continuous infusion of fentanyl (10.5 microg/kg over a 1-hour period followed by 1.5 microg/kg/hr) or morphine (140 microg/kg over a 1-hour period followed by 20 microg/kg/hr) for at least 24 hours. The severity of pain was assessed with physiological parameters, a behavioral pain scale, and stress hormone concentrations before and 2 and 24 hours after the start of treatment. RESULTS: The analgesic effect was similar in both groups, as judged by the pain scale. Plasma adrenaline and noradrenaline concentrations decreased significantly from 0 to 24 hours in both groups. Median adrenaline decrease was 0.5 nmol/L (interquartile range [IQR] 1.1;0.0) in the fentanyl and 0.7 nmol/L (IQR 1.3;0.1) in the morphine group, noradrenaline 2.1 nmol/L (IQR 9.0;0.2), and 3.0 nmol/L (IQR 7. 5;0.3), respectively. beta-endorphin decreased significantly only in the fentanyl group (14 pmol/L (IQR 28; 7), P <.05). Decreased gastrointestinal motility was less frequent in the fentanyl group (23% vs 47%, P <.01). CONCLUSIONS: With at least as effective analgesia as with morphine, fentanyl had fewer side effects. Fentanyl may be superior to morphine for short-term postnatal analgesia in newborn infants.

Saarenmaa, E., P. J. Neuvonen, et al.: Gestational age and birth weight effects on plasma clearance of fentanyl in newborn infants. *J Pediatr*, 136(6): 767-70., 2000, *[C]*.

OBJECTIVE: To provide a rational basis for the dosage of fentanyl in newborn infants by determining clearance in the first days of life. STUDY DESIGN: A continuous infusion of fentanyl for 2 to 3 days (10. 5 microg/kg over a 1-hour period followed by 1.5 microg/kg/h) was administered to 38 newborn infants who had undergone ventilation (gestational ages 26 to 42 weeks and birth weights 835 to 3550 g). Fentanyl concentrations were measured in arterial blood samples collected at 2, 12, 24, 48, and 60 hours after the start of fentanyl infusion. Fentanyl levels were correlated with a pain score. RESULTS: The mean (+/-SD) steady-state fentanyl concentration of 2.5 (+/-1) ng/mL achieved between 24 and 48 hours of infusion correlated significantly with the concomitant pain score (r = -0.57, P <.01). The clearance, 11.5 (+/-4.0) mL/min/kg, correlated significantly with the gestational age (r = 0.46, P <.01) and birth weight (r = 0. 48, P <.01). CONCLUSIONS: Because plasma fentanyl clearance increases with maturity, gestational age should be taken into account when fentanyl is administered to newborn infants.

Santeiro, M. L., J. Christie, et al.: Pharmacokinetics of continuous infusion fentanyl in newborns. *J Perinatol*, 17(2): 135-9., 1997, *[C]*.

Although fentanyl administration by continuous infusion in newborns during ventilatory support has increased, pharmacokinetic data are lacking. Our objective was to determine the pharmacokinetics of fentanyl continuous infusions for sedation/analgesia in newborns who had undergone mechanical ventilation. Fentanyl was administered per routine care in seven newborns who had undergone mechanical ventilation and had normal hepatic, renal, and cardiac function. Five blood samples were collected from each newborn's umbilical artery catheter. Sample 1 was obtained at > or = 36 hours after constant fentanyl was infused, and sample 2 was collected 12 hours later. Fentanyl was then discontinued and meperidine given. Additional samples were obtained 6, 12, and 24 hours after fentanyl was discontinued. Decanted plasma was stored at -20 degrees C until gas chromatography analysis was performed. Total body clearance (TBC), elimination half-life, and volume of distribution at steady state were determined. Patient weights were 1.88 +/- 1.12 kg (mean +/- SD) with postnatal age 16 +/- 9 days; the mean gestational age was 32 +/- 4 weeks. Mean final fentanyl dosage was 1.28 +/- 0.58 microgram/kg/hr (range 0.53 to 1.9 micrograms/kg/hr). Mean elimination half-life was 9.5 +/- 2.6 hours (range 5.7 to 12.7 hours), and volume of distribution at steady state was 17 +/- 9 L/kg (range 10.1 to 30.3 L/kg). Mean TBC was 1154 +/- 494 ml/kg/hr (range 565 to 2000 ml/kg/hr). Significant correlation between postnatal age and TBC occurred (r = 0.80; p = 0.03). Newborns were hemodynamically stable during the sampling period. We found an increased volume of distribution at steady state and prolonged elimination half-life compared with single-dose administration in newborns. TBC was similar to reported values for infants and young children but was higher than for older patients.

Wernovsky, G., D. Wypij, et al.: Postoperative course and hemodynamic profile after the arterial switch operation in neonates and infants. A comparison of low-flow cardiopulmonary bypass and circulatory arrest. *Circulation*, 92(8): 2226-35., 1995, *[A]*.

BACKGROUND: The neurological morbidity associated with prolonged periods of circulatory arrest has led some cardiac surgical teams to promote continuous low-flow cardiopulmonary bypass as an alternative strategy. The nonneurological postoperative

effects of both techniques have been previously studied only in a limited fashion. METHODS AND RESULTS: We compared the hemodynamic profile (cardiac index and systemic and pulmonary vascular resistances), intraoperative and postoperative fluid balance, and perioperative course after deep hypothermia and support consisting predominantly of total circulatory arrest or low-flow cardiopulmonary bypass in a randomized, single- center trial. Eligibility criteria included a diagnosis of transposition of the great arteries and a planned arterial switch operation before the age of 3 months. Of the 171 patients, 129 (66 assigned to circulatory arrest and 63 to low-flow bypass) had an intact ventricular septum and 42 (21 assigned to circulatory arrest and 21 to low-flow bypass) had an associated ventricular septal defect. There were 3 (1.8%) hospital deaths. Patients assigned to low-flow bypass had significantly greater weight gain and positive fluid balance compared with patients assigned to circulatory arrest. Despite the increased weight gain in the infants assigned to low-flow bypass, the duration of mechanical ventilation, stay in the intensive care unit, and hospital stay were similar in both groups. Hemodynamic measurements were made in 122 patients. During the first postoperative night, the cardiac index decreased (32.1 +/- 15.4%, mean +/- SD), while pulmonary and systemic vascular resistance increased. The measured cardiac index was < 2.0 L.min-1.m-2 in 23.8% of the patients, with the lowest measurement typically occurring 9 to 12 hours after surgery. Perfusion strategy assignment was not associated with postoperative hemodynamics or other nonneurological postoperative events. CONCLUSIONS: After heart surgery in neonates and infants, both low-flow bypass and circulatory arrest perfusion strategies have comparable effects on the nonneurological postoperative course and hemodynamic profile.

