Fentanyl Dosage is Associated with Reduced Blood Glucose in Pediatric Patients after Hypothermic Cardiopulmonary Bypass

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The authors retrospectively reviewed the charts of 36 pediatric patients who had undergone cardiac surgery with hypothermic cardiopulmonary bypass (CPB) (n = 24) or profound hypothermia with circulatory arrest (PHCA) (n = 12), none of whom had received dextrose in the clear CPB pump prime, maintenance iv fluids, or cardioplegia solution. The authors studied whether the doses of fentanyl or methylprednisolone, or rates of dextrose infusion from blood products during CPB or from vasoactive infusions in 5% dextrose in water, were correlated with the blood glucose concentrations at the termination of CPB. Because other investigations have indicated that even moderate hyperglycemia during cerebral hypoxia or ischemia may predispose patients to an increased risk of neurologic deficit, the authors wished to determine whether any of these factors might contribute significantly to the elevation in blood glucose commonly seen in these patients. Multiple regression analysis and ANOVA were performed on these data, and a P value of 0.0125 was considered significant. The dose of methylprednisolone, and rates of infusions of dextrose from blood products in the CPB pump prime or from 5% dextrose in water at the termination of CPB did not correlate significantly with the blood glucose level. The dose of fentanyl administered to patients prior to the end of CPB was significantly correlated with the glucose concentration (r² = 0.416; P = 0.0001). No patient who received ≥50 µg/kg of fentanyl had a blood glucose concentration of >200 mg/dl. This suggests that doses of fentanyl ≥ 50 µg/kg in conjunction with limiting exogenous dextrose infusion can attenuate the hyperglycemic response to hypothermic CPB and PHCA in children undergoing cardiac surgery. (Key words: Analgesics, opioid: fentanyl. Anesthesia: cardiovascular; pediatric. Hyperthermia. Metabolism: hyperglycemia.)

HYPOTHERMIC CARDIOPULMONARY BYPASS (CPB) and profound hypothermia with circulatory arrest (PHCA) are techniques widely used during the repair of congenital cardiac defects. However, despite such measures as cooling to 10–18°C, limiting duration of circulatory arrest, hemodilution, and administration of corticosteroids, approximately 4.5% of pediatric patients develop postoperative neurologic deficits.¹ Neurologic dysfunction may be recognized in the immediate postoperative period,¹实木 decreased cognitive skills can be detected years later by psychometric testing.³

Hyperglycemia may increase the incidence and severity of neurologic deficits that result from cerebral ischemia.²⁴⁻⁹ Hyperglycemia has been noted to occur in pediatric patients undergoing cardiac surgery with deep hypothermia.¹⁰ In an attempt to decrease the incidence of hyperglycemia in pediatric patients undergoing major cardiac surgery, dextrose had been eliminated from the CPB clear pump priming solution and from the intraoperative iv fluid. However, despite these measures, many patients continue to develop moderate hyperglycemia during the procedure. Therefore we studied four other factors that might influence blood glucose concentrations during pediatric cardiac surgery.

We examined whether the doses of fentanyl or methylprednisolone administered correlated with the blood glucose concentrations at the termination of CPB. Also, we evaluated the contribution of exogenous dextrose supplied by citrate-phosphate-dextrose-adenosine (CPDA-1) blood products added to the CPB priming solution, as well as by 5% dextrose in water carrying vasoactive medications at the termination of CPB.

Methods

With appropriate institutional approval, the records of 36 patients were reviewed retrospectively. Included were all patients undergoing cardiac surgery with hypothermic CPB (HYPO) or PHCA during a 6-month period at British Columbia’s Children’s Hospital, who received fentanyl as part of the anesthetic, and who received no dextrose in the CPB clear priming fluids or maintenance iv solutions. Preanesthetic medication, induction techniques, the use of other anesthetic drugs, and the dosage of fentanyl and methylprednisolone, were not controlled but were at the discretion of the individual anesthesiologist. Most anesthetics consisted of nitrous oxide and either low-dose isoflurane or halothane in addition to fentanyl prior to instituting CPB; thereafter, only oxygen and fentanyl were delivered.

Hypothermia was defined as a rectal temperature between 24°C and 28°C with continuous perfusion; PHCA was instituted after reaching an esophageal temperature of <18°C and a rectal temperature of <20°C. CPB was accomplished using a Sarns® 5000 roller pump with a SciMed® membrane oxygenator appropriate to the size of the child. No dextrose was administered in the maintenance iv fluids, the clear priming fluid for CPB, or in the

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Received from the University of California, San Diego, California; and British Columbia’s Children’s Hospital, Vancouver, British Columbia. Accepted for publication January 2, 1990. Presented at the Annual Meeting of the American Society of Anesthesiologists San Francisco, California, October 1988.
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Reprints will not be available.
FENTANYL AND GLUCOSE AFTER CPB IN CHILDREN

Anesthesiology
V 72, No 5, May 1990

CARDIAC PLUGGLEG SOLUTION. THE DEXTROSE CONTENT IN VASOACTIVE
DRUG INFUSIONS WAS CALCULATED AS DETAILLED BELOW.

A RADIAL ARTERY WAS CANNULATED AFTER INDUCTION OF ANESTHESIA. ARTERIAL BLOOD GLUCOSE CONCENTRATIONS WERE MEASURED AFTER INSERTION OF THE CATHETER (BASELINE), IMMEDIATELY AFTER INITIATION OF CPB (ON CPB), WITHIN 30 MIN OF CESSATION OF CPB (POST-CPB), AND UPON ARRIVAL IN THE INTENSIVE CARE UNIT (ICU). THE DOSES OF FENTANYL AND OF METHYLPRIDENISOLONE ADMINISTERED PRIOR TO TERMINATION OF CPB WERE REPORTED AS µG/KG AND MG/KG, RESPECTIVELY. THE AMOUNT OF DEXTROSE DELIVERED BY BLOOD PRODUCTS IN THE CPB PRIMING SOLUTION WAS AVERAGED OVER THE ENTIRE PERIOD OF CPB OR OF CPB PLUS PHCA, AND REPORTED AS MG·KG⁻¹·MIN⁻¹; FRESH CPDA-1 BLOOD CONTAINS APPROXIMATELY 440 MG OF DEXTROSE/DL.¹¹ THE AMOUNT OF DEXTROSE ADMINISTERED IN VASOACTIVE INFUSIONS PRIOR TO CPB BLOOD SAMPLING WAS CALCULATED AND REPORTED AS MG·KG⁻¹·MIN⁻¹ OVER THE PERIOD INFUSED, AND THE DATA WERE ANALYZED SEPARATELY FROM THOSE OF THE DEXTROSE CONTRIBUTED BY BLOOD PRODUCTS.

THE COMPARISONS OF BLOOD GLUCOSE CONCENTRATIONS TO BASELINE WERE MADE BY TWO-TAILED, PAIRED t TESTS WITH A BONFERRONI CORRECTION OF THE P VALUE TO 0.017. COMPARISONS OF BLOOD GLUCOSE CONCENTRATIONS BETWEEN THE HYPO AND PHCA PATIENTS WERE ANALYZED BY UNPAIRED TWO-TAILED t TESTS WITH A P VALUE OF 0.0125. OTHER DATA FOR HYPO AND PHCA PATIENTS WERE ALSO COMPARED BY TWO-TAILED, UNPAIRED t TESTS, AND THE P VALUES ARE REPORTED IN THE TEXT. THE EFFECTS OF EXOGENOUS SOURCES OF DEXTROSE, AND OF DOSES OF FENTANYL AND METHYLPRIDENISOLONE ON BLOOD GLUCOSE CONCENTRATIONS POST-CPB WERE STUDIED BY MULTIPLE REGRESSION ANALYSIS AND ANOVA, WITH A P VALUE OF 0.0125 CONSIDERED TO BE SIGNIFICANT. ALL DATA ARE REPORTED AS MEAN ± SD.

RESULTS

TWENTY-FOUR CHILDREN UNDERWENT HYPO AND 12 UNDERWENT PHCA. THE AGE OF THE PATIENTS WAS 4.7 ± 5.2 yr (RANGE: 2 DAYS TO 18 YR). THE HYPO GROUP WAS OLDER AND HEAVIER THAN THE PHCA GROUP WITH AN AGE OF 6.43 ± 5.4 yr versus 1.3 ± 1.6 yr (P = 0.003) AND A WEIGHT OF 22.3 ± 14.5 kg versus 6.2 ± 2.2 kg (P = 0.0006). SEVEN PATIENTS HAD REPAIR OF TRANSPOSITION OF THE GREAT ARTERIES, SIX TRIAL VELOCITY, SIX VENTRICULAR SEPTAL DEFECTS, TWO PATRIAL SEPTAL DEFECTS, FOUR OTHER CYANOTIC DISEASES, AND 11 OTHER ACYANOTIC DISEASES. TIME OF CPB WAS 112 ± 40 min FOR HYPO, AND 128 ± 31 min PLUS 52 ± 14 min OF CIRCULATORY ARREST FOR PHCA. ALL DATA ARE REPORTED AS MEAN ± SD.

THE DOSE OF FENTANYL FOR ALL PATIENTS WAS 43.4 ± 23.3 µG/KG (RANGE: 7-88 µG/KG); THE HYPO GROUP RECEIVED 47.3 ± 24.1 µG/KG versus 24.7 ± 17 µG/KG (P = 0.0065) FOR THE PHCA GROUP. THE DOSE OF METHYLPRIDENISOLONE FOR ALL PATIENTS WAS 14.2 ± 11.9 mg/kg; THE DOSE FOR THE HYPO PATIENTS WAS 10.2 ± 10 mg/kg AND 22.4 ± 11.7 mg/kg FOR THE PHCA PATIENTS (P = 0.0025). NINE HYPO AND TWO PHCA PATIENTS RECEIVED NO METHYLPRIDENISOLONE. THE CALORIC RATE OF DEXTROSE INFUSION FROM BLOOD PRODUCTS IN THE CPB PRIMING SOLUTION WAS 0.692 ± 0.72 mg·kg⁻¹·min⁻¹ FOR THE HYPO GROUP AND 1.38 ± 0.46 mg·kg⁻¹·min⁻¹ FOR THE PHCA GROUP (P = 0.0052). THE DEXTROSE INFUSION RATE FROM VASOACTIVE MEDICATIONS IN 5% DEXTROSE IN WATER WAS 0.117 ± 0.17 mg·kg⁻¹·min⁻¹ FOR HYPO AND 0.35 ± 0.48 mg·kg⁻¹·min⁻¹ FOR PHCA PATIENTS (P = 0.038).

BLOOD GLUCOSE CONCENTRATIONS FOR HYPO PATIENTS WERE 85.5 ± 20.1 mg/dl (BASELINE), 97.9 ± 14.8 mg/dl (ON CPB), 158.3 ± 34.0 mg/dl (POST-CPB), AND 185.3 ± 53.9 mg/dl (ICU). GLUCOSE CONCENTRATIONS FOR THE PHCA PATIENTS WERE 97.8 ± 23.3 mg/dl (BASELINE), 116.1 ± 26 mg/dl (ON CPB), 178.8 ± 38.9 mg/dl (POST-CPB), AND 210.8 ± 38.5 mg/dl (ICU) (FIG. 1). FOR BOTH GROUPS, THE VALUES POST-CPB AND ICU WERE SIGNIFICANTLY GREATER THAN BASELINE (P < 0.017). THE GLUCOSE CONCENTRATIONS ON CPB DIFFERED SIGNIFICANTLY BETWEEN THE TWO GROUPS (P < 0.0125).

THE TOTAL DOSE OF FENTANYL ADMINISTERED TO ALL PATIENTS PRIOR TO THE TERMINATION OF CPB (TOTAL FENTANYL) APPEARED TO CORRELATE SIGNIFICANTLY WITH POST CPB GLUCOSE LEVELS (T² = 0.416; P = 0.0001). SEPARATELY ANALYZED RESULTS WERE SIMILAR FOR THE HYPO GROUP (T² = 0.409; P = 0.0007) AND SUGGESTED BY THE DATA FOR THE PHCA PATIENTS (T² = 0.268; P = 0.0884) (FIGS. 2 AND 3). NO PATIENT RECEIVING AT LEAST 50 µG/KG OF FENTANYL HAD A GLUCOSE CONCENTRATION ABOVE 200 mg/dl. THE DOSE OF METHYLPRIDENISOLONE WAS NOT CORRELATED WITH POST-CPB GLUCOSE LEVELS. THE RATE OF Fig. 1. Blood glucose concentrations for two groups of patients: those who underwent hypothermic cardiopulmonary bypass (closed circles) and profound hypothermia with circulatory arrest (open circles). Sampling times are after induction of anesthesia (baseline), immediately after initiation of CPB (on CPB), within 30 min of cessation of CPB (post-CPB), and upon arrival in the Intensive Care Unit (ICU). Data shown are mean ± SE. *P < 0.017 indicates a significant difference from baseline for that group. **P < 0.0125 indicates a significant difference between the two groups.
infusion of dextrose from either blood products in the pump prime or from vasoactive infusions did not correlate with post-CPB glucose concentrations.

**Discussion**

Infants and children undergoing HYPO or PHCA for cardiac surgery frequently develop an increase in blood glucose concentrations despite withholding dextrose from the maintenance iv fluids and CPB pump priming and cardioplegia solutions. Significant hyperglycemia (>250 mg/dl) has been reported in infants undergoing cooling prior to PHCA, and after CPB with deep hypothermia even when the rate of glucose infusion was below suggested guidelines for maintenance glucose needs in pediatric patients.

Concern regarding hyperglycemia during CPB and hypothermia has been triggered by reports in animals, and children that suggest that even modest elevation of the blood glucose level prior to cerebral ischemia is associated with an increased incidence of neurologic deficit.

Studies in adults have suggested that high-dose fentanyl anesthesia attenuates the hyperglycemic response to CPB without uniformly suppressing the adrenergic response. Fewer investigations have been performed in children. Baum et al. noted that infants undergoing PHCA with surface cooling for cardiac surgery demonstrated marked hyperglycemia only if they received dextrose infusions. They attributed this to a decreased insulin response during hypothermia. Anand et al. have reported that sufentanil 35–40 µg/kg decreased both glucose and β endorphin concentrations in pediatric patients undergoing PHCA. Because the potency of sufentanil is seven to ten times that of fentanyl, Anand et al.’s dose of sufentanil was very high compared with the dose of fentanyl that our patients received. Our data indicates that a much smaller equivalent dose of fentanyl, 50 mg/kg, may be sufficient to attenuate the hyperglycemic response to hypothermic CPB and to PHCA when dextrose administration is restricted.

Glucocorticosteroids are alleged to have a protective effect on the myocardium during ischemic cardiac arrest and are sometimes administered prior to cardiopulmonary bypass in infants and children who require repair of complex lesions. Their administration is also associated with elevations in blood glucose. We were unable to demonstrate any effect of methylprednisolone treatment on the blood glucose level post-CPB.

**Limitations of the Study**

This study was not designed to address the association between hyperglycemia and neurologic outcome after cerebral ischemia, although this is an important related question. None of the surviving patients studied exhibited gross neurologic deficit; two of the HYPO patients and three of the PHCA patients died postoperatively.

This was a retrospective data collection obtained from anesthesia and perfusionist records, which relied on the accuracy of information recorded during the time of surgery. It cannot be assumed that all patients received comparable anesthetic and surgical management.

Because there was no control group, our results cannot be interpreted as proving that fentanyl doses of ≥50 µg/kg in conjunction with limiting exogenous glucose administration block the hyperglycemic response to hypothermic CPB and PHCA; the data indicate that there may be an association between the fentanyl dosage and blood post-CPB glucose levels.

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**Fig. 2.** Fentanyl dose versus blood glucose concentration post-CPB for HYPO patients (closed circles) with calculated regression line. Blood for glucose concentrations was sampled within 30 min of cessation of CPB. Total fentanyl is the dose administered intraoperatively prior to the termination of CPB.

**Fig. 3.** Fentanyl dose versus blood glucose concentration post-CPB for PHCA patients (open circles) with calculated regression line. Blood for glucose concentrations was sampled within 30 min of cessation of CPB. Total fentanyl is the dose administered intraoperatively prior to the second termination of CPB.
glucose concentration. This association should be further investigated by a controlled prospective study.

To determine the temporal relationship between hyperglycemia and possible cerebral ischemia, blood glucose concentrations should be determined throughout CPB. Catecholamine, cortisol, and insulin concentrations should be measured to determine whether the attenuation of hyperglycemia is secondary to a modified neuroendocrine response. Finally, fentanyl plasma or tissue concentrations should be measured as a more precise estimate of the opioid effect than total dose administered.

Because of the possible increased risk of neurologic deficit associated with preschismic hyperglycemia, avoidance of hyperglycemia is warranted during surgery which has significant potential for cerebral hypoxia or ischemia (e.g., cardiac surgery with CPB or PHCA). Our results suggest that the administration of fentanyl in a dosage range of 50 μg/kg or greater, in conjunction with limiting exogenous glucose infusion, attenuates the hyperglycemic response to hypothermic CPB and PHCA in children undergoing cardiac surgery. A carefully controlled prospective study that includes serial determinations of catecholamine, cortisol, insulin, glucose, and fentanyl concentrations should be conducted to confirm this observation and to attempt to elucidate the mechanism of this response.

The authors wish to thank Drs. Mark Zornow and Jerry Fleischer for their assistance with the graphics.

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