Abstracts from the Literature

MIXING RAPID-ACTING INSULIN ANALOGUES WITH INSULIN GLARGINE IN CHILDREN WITH TYPE 1 DIABETES MELLITUS. Fiallo-Scharer R, Horner B, McFann K, et al. J Pediatr 2006;148:481-484.

Background Long-acting insulin combined with rapid-acting insulin is becoming a popular regimen of choice for patients with type 1 diabetes mellitus. However, efficacy data regarding mixing long-acting insulins with others in the same syringe is unknown. A short-term preliminary study found that mixing insulin glargine with a short-acting insulin product for 10 days did not affect glucose concentrations in 13 pediatric patients.[1] Mixing insulin products will allow for a reduction in the number of injections per day and ideally increase compliance.

Objectives To determine if insulin glargine mixed with rapid-acting insulin in the same syringe would affect glycemic control in children.

Methods Patients using insulin glargine and rapid-acting insulin for at least 3 months, diagnosed with type 1 diabetes mellitus for at least 1 year, and consistently attending clinic visits were eligible for the study. Fifty-five children (mean age 13.4 yr ± 3.8 years) were asked to mix their insulin glargine and rapid-acting insulin (insulin aspart or lispro) in the same syringe for 3 months. Patients were asked to draw the rapid-acting insulin into the syringe first and then add the insulin glargine. These children were watched by their physician for this time period. Hemoglobin A1c, timing of doses, occurrence of severe hypoglycemia (seizure or loss of consciousness) or diabetic ketoacidosis (DKA, hyperglycemia with ketones that resulted in hospitalization or an emergency department visit), percent of self-monitored blood glucose levels (below, in, or above range with target 70-180 mg/dL), and occurrence of non-severe hypoglycemic episodes were documented. The authors retrospectively evaluated the same patients' data for the 6 months prior to the mixing of the insulins. A comparable control group was identified and compared for the 12-month period of the study. Data was collected at 6 month prior (3 months prior baseline and 3 months after baseline) and 6 months after the active group began mixing the insulins.

Results At baseline, the control and active group were equivalent regarding hemoglobin A1c and demographic data. At the completion of the study, data for 93 patients were available (active group 44, control group 49); however, data for all patients were available at 3 months. At the 3- and 6-month follow-up, the hemoglobin A1c and percent of blood glucose levels below, in or above range were no different between the two groups. Similarly, no differences were found for severe hypoglycemia or DKA episodes at 3 or 6 months. None of the P values were significant. For the 17 patients who did not complete the study, it was found that they had more severe hypoglycemia events (3 versus 1, $P = .0114$) and fewer non-severe hypoglycemic events (3.4 versus 5.6, $P < .0001$) compared to the patients who finished the study at the 3-month follow-up.

Forty-seven children administered their insulin glargine and rapid-acting insulin at the dinner hour while 4 administered the combination with breakfast and 4 others administered it as a split dose. In the control group, 38 children administered the insulin glargine at dinner or bedtime. Sixteen others in the control group administered it at breakfast, and one administered it as a split dose. Those who mixed the insulins observed cloudiness in the syringe; however, no problems occurred with administration.

Four patients who mixed their insulins returned to using separate injections due to hyperglycemia or hypoglycemia episodes during the first month. These patients were not included in the data analysis. However, their hemoglobin A1c was evaluated at 3 months. Two patients had a 0.5% or less increase, one patient had no change, and the other patient had a 0.6% decrease in hemoglobin A1c. All four were male and administered their mixed syringe at the dinner hour.

Conclusions The mixing of insulin glargine and rapid-acting insulin did not adversely affect blood glucose levels, hemoglobin A1c levels,

DKA episodes, or hypoglycemic episodes in 93 patients who completed the study. Glycemic control was similar to the traditional administration and allowed the reduction of one injection per day for each patient.

Comments This is the second set of published data regarding mixing insulin glargine with rapid-acting insulin in children. Although this preliminary study evaluated a 6-month period and found no adverse affects, further data is warranted. A study of a larger population is still needed in order to gather additional information regarding possible kinetic changes with mixing of the insulin products. This study evaluated timing of the doses but not timing of the glucose readings. This information could be beneficial for identifying trends in hypoglycemic events and changes in administration times to improve control and compliance. Based on the available data, physicians may individually choose patients to attempt this technique, especially if it increases compliance. It may be beneficial for newly diagnosed patients to initiate the mixing technique in the hospital where patients may be observed for a few days prior to discharge. However, close follow-up is necessary to evaluate for hypoglycemic events in all patients mixing insulin glargine and rapid-acting insulin.

REFERENCES

1. Kaplan W, Rodriguez LM, Smith OE, et al. Effects of mixing glargine and short-acting insulin analogs on glucose control. Diabetes Care 2004;27:2739-2740.

Lea S. Eiland, PharmD, BCPS
Auburn University Harrison School of Pharmacy
Huntsville, Alabama

INITIAL EXPERIENCE WITH FENOLDOPAM AFTER CARDIAC SURGERY IN NEONATES WITH AN INSUFFICIENT RESPONSE TO CONVENTIONAL DIURETICS. Costello JM, Thiagarajan RR, Dionne RE, Allan CK, Booth KL, Burmester M, Wessel DL, Laussen PC. Pediatr Crit Care Med 2006;7:28-33.

Background Neonates undergoing complex cardiac procedures with cardiopulmonary bypass may experience significant complications post-operatively, which may delay chest closure and prolong the duration of mechanical ventilation and length of stay in the intensive care unit and in the hospital. Diuresis in these patients is instituted to help establish negative fluid balance and is traditionally achieved by using a combination of intermittent or continuous furosemide with intermittent chlorothiazide. It is hypothesized that fenoldopam, a selective postsynaptic dopamine (D_1) agonist, may aid in diuresis in this post-operative population by acting at the kidneys to cause increased renal blood flow and vasodilation.

Objective The objective of this study was to determine if the addition of fenoldopam to traditional diuretics following cardiopulmonary bypass in neonates would improve increased urine output and allowed for negative fluid balance post-operatively.

Design, setting, and participants This was a time-series-designed, retrospective cohort study. All patients receiving fenoldopam in the pediatric cardiac intensive care unit at Children's Hospital Boston from February 2002 to December 2004 who met inclusion criteria were eligible for this study. Neonates were included if they underwent surgery requiring cardiopulmonary bypass (CPB), were < 28 days old at time of study, were treated with at least 1 diuretic for > 12 hours prior to initiating fenoldopam, and received fenoldopam for at least 24 hours post-operatively. Neonates were excluded if they were receiving extracorporeal membrane oxygenation (ECMO), if they were on fenoldopam for an indication other than diuresis, or if fenoldopam was initiated prior to conventional diuresis. A total of 46 neonates received fenoldopam during the study period; 25 neonates met inclusion criteria. Patients ranged between 0 and 23 days old and were

between 1.9 and 4.5 kg. Seventy-two percent of patients were male, and 12% of patients were premature. Cardiopulmonary bypass time ranged between 20 and 302 min (mean 143 min), with aortic cross clamp time of 38 to 273 min (mean 74 min), and circulatory arrest time between 3 and 72 min (48 min). The majority of patients underwent a Norwood procedure (14 of 25). Traditional diuretic use in the study population included furosemide continuous infusion (median dose 0.3 mg/kg/hr) and intermittent IV chlorothiazide (median dose 20 mg/kg/day).

Methods Medical records of neonates who met inclusion criteria for study were analyzed for study outcomes in the 24-hour period before initiating fenoldopam and then for 24 hours after initiating fenoldopam. The primary study outcome was urine output. Other data collection included concomitant diuretic use, inotrope score, vital signs, and serum electrolytes. Inotrope score was defined by investigators as (dopamine + dobutamine + [milrinone X 10] + [epinephrine X 100]) with all doses in micrograms/kg/min.

Results Twenty-four of twenty-five patients received at least 2 diuretics prior to initiation of fenoldopam. Diuretic use included intermittent metolazone (3/25 patients), continuous infusion furosemide (23/25 patients), intermittent furosemide (2/25 patients), and intermittent chlorothiazide (23/25 patients). All patients received equal doses of diuretics during the control and fenoldopam period except for 5 patients who received less chlorothiazide in the fenoldopam period. The median net fluid balance prior to initiation of fenoldopam was +191 mL (range, -549 to +2032 mL), with fenoldopam being initiated 2 to 19 days post-operatively (median 6 days). The initial dose of fenoldopam ranged between 0.05 and 0.3 microgram/kg/min (median 0.1 microgram/kg/min), with a maximum dose of 0.1 to 1 microgram/kg/min (median 0.3 microgram/kg/min) for a total of 1 to 15 days (median 3 days). Patients receiving fenoldopam experienced a significant increase in urine output compared to the control period, with an increase from a median of 3.6 mL/kg/hr (range, 0.2-7.2 mL/kg/hr) to 5.8 mL/kg/hr (range, 1.6-11.7 mL/kg/hr), P = .001. There was a small decrease in inotrope score between the control and fenoldopam period (10.5 vs. 8.5-10) as well as no difference in heart rate. There was a small but significant increase in blood pressure during the fenoldopam period. There was no change in serum sodium, potassium, or creatinine between the two time periods; however, median blood urea nitrogen increased during the fenoldopam period (25 mg/dL [11-71 mg/dL] vs. 30 mg/dL [8-88 mg/dL], P = .002). One significant adverse event was reported; a neonate clotted his modified Blalock-Taussig shunt and required ECMO as part of his resuscitation. This may have been associated with the patient's diuresis.

Conclusions The investigators concluded that the addition of fenoldopam to traditional diuretics in neonates following cardiopulmonary bypass increased urine output and allowed for negative fluid balance post-operatively.

Comments Although fenoldopam has been studied as an agent to preserve renal function after CPB in adults,[1,2] this is the first published study to assess the use of fenoldopam for diuresis following CPB in pediatric patients. Infants are especially at risk for developing significant edema and fluid retention following CPB due to neurohormonal and inflammatory responses. Fenoldopam selectively binds to dopamine receptors in the renal arteries and increases cyclic adenosine monophosphate activity, promoting vascular smooth muscle relaxation. Renal blood flow is also increased through blunted aldosterone production. Fenoldopam is 6 times more potent than dopamine in producing renal vasodilation and is rapidly titratable, with a half life of < 10 minutes, making it ideal for use in increasing urinary output.[3] In addition, larger studies in adults have shown that fenoldopam is safe and effective for treating hypertensive emergencies and may preserve renal function after CPB. Although this was not a prospective, randomized controlled trial, this study shows that fenoldopam has potential as an adjunctive agent for diuresis following CPB. Since fenoldopam is used for hypertensive emergencies to lower blood pressure, a potential adverse effect of using fenoldopam for diuresis would be decreased blood pressure. There is some evidence to suggest that this effect may not occur in patients that are not hypertensive. Fenoldopam decreased blood pressure in hypertensive adults but had no effect on normotensive adults in a random-

ized, double-blind trial.[4] In the present study, blood pressure actually increased slightly. However, 4 patients were excluded from the study because of evolving septic shock requiring high-dose catecholamines or hemodynamic instability during fenoldopam infusion. The retrospective nature of this study prevented any conclusions about safety; monitoring for hypotension is warranted. Fenoldopam has been used in our institution for diuresis following CPB procedures; however, further trials are needed to determine safety and efficacy in this population.

REFERENCES

1. Ranucci M, Soro G, Barzaghi N, et al. Fenoldopam prophylaxis of postoperative acute renal failure in high-risk cardiac surgery patients. Ann Thorac Surg. 2004;78:1332-1337.
2. Caimmi PP, Pagani L, Micalizzi E, et al. Fenoldopam for renal protection in patients undergoing cardiopulmonary bypass. J Cardiothorac Vasc Anesth. 2003;17:491-494.
3. Fenoldopam. In: Lacy CF, Armstrong LL, Goldman MP, Lance LL, eds. Lexi-Comp's Drug Information Handbook. 13th ed. Hudson: Lexi-Comp;2005:612-613.
4. O'Connell DP, Ragsdale NV, Boyd DG, et al. Differential human renal tubular responses to dopamine type 1 receptor stimulation are determined by blood pressure status. Hypertension. 1997;29:115-122.

Elisabeth Mouw, PharmD
Pharmacy Practice Resident, Emphasis in Pediatrics
Medical University of South Carolina
Charleston, South Carolina

A. Jill Thompson, PharmD, BCPS
Clinical Pharmacy Specialist, Pediatric Intensive Care/Pediatrics
Dept of Pharmacy Services
Medical University of South Carolina
Charleston, South Carolina