Anaesthesia and pyruvate dehydrogenase deficiency

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A ten-month-old infant with pyruvate dehydrogenase deficiency received anaesthesia on two occasions, once for a laparotomy and once for a tracheostomy. During both anaesthetics (different techniques) she developed an increase in arterial lactate levels and a metabolic acidosis. Pyruvate dehydrogenase deficiency results in the inability to metabolize pyruvate with resultant accumulation of pyruvate and lactate. Inhibition of gluconeogenesis, which may be produced by halothane and thiopentone, will also increase lactate levels. Other causes of increased lactate levels are hypocarbia and high carbohydrate intake. In this patient hypocarbia may have produced increased lactate levels and increased the metabolic acidosis. Recommendations include avoidance of halogenated anaesthetics, avoidance of lactate containing solutions, maintenance of normocarbia, and stress-free anaesthesia.

Key words

GENETIC FACTORS: pyruvate dehydrogenase.

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Inborn errors of metabolism in paediatric patients resulting in chronic lactic acidosis are caused primarily by defects in enzymes of the pyruvate dehydrogenase complex, enzymes of gluconeogenesis, pyruvate carboxylase, or phosphoenolpyruvate carboxykinase. The pyruvate dehydrogenase complex is composed of six enzymes and can be assayed from fibroblast cultures.[1] Deficiencies of the enzymes necessary for gluconeogenesis, most notably glucose-6-phosphatase and fructo-1,6-diphosphatase, have been well described. Defects in the gluconeogenesis pathway produce both lactic acidosis and hypoglycaemia. Cases of pyruvate carboxylase and phosphoenolpyruvate carboxykinase deficiencies are quite rare and not clinically well defined.

Children with primary lactic acidosis are of concern to the anaesthesiologist because of the patient's abnormal metabolism of substrates, the adverse cardiorespiratory effects of acidosis, and the effects of anaesthetics upon enzyme systems. The following case report describes the perioperative management of an infant with pyruvate dehydrogenase deficiency.

Case report

The patient was a 10-month-old female with a known history of chronic lactic acidosis. She had been treated with 18 mEq $NaHCO_3$ per day and a high carbohydrate diet. The day of hospital admission she became comatose and developed an irregular respiratory pattern and respiratory distress. She was admitted to her local hospital with agonal respirations and was unresponsive. Initial arterial blood gases (room air) were PO_2 4.9 kPa (37 torr), PCO_2 9.6 kPa (72 torr), pH 7.16, base excess −10; blood glucose was 5.05 mmol·L^{-1}. Following her initial resuscitation which included mechanical ventilation with 40 per cent oxygen and the intravenous administration of 12 mmoles of $NaHCO_3$ her arterial blood gases were PO_2 15.8 kPa (118 torr),

TABLE Blood gases during laparotomy

Time	*Pre-op*	*1500*	*1600*	*1630*	*1800*	*Post-op*
FIO_2	0.25	0.50	0.50	0.50	0.50	0.50
PO_2 (torr)	95	206	182	168	86	129
PCO_2 (torr)	35	26	26	26	46	25
pH	7.48	7.61	7.59	7.52	7.27	7.55
Base deficit	+2	+7	+5	0	−6	+1

The initial alkalosis is from $NaHCO_3$ infusion immediately before surgery. Note the change in base deficit from +7 to −6 and the period of hypocarbia.

PCO_2 6.5 kPa (49 torr), pH 7.21, base excess −10. After stabilization, the infant was transferred to Riley Children's Hospital where the initial lactate level was 9.2 mEq·L^{-1} (normal 0.5 to 1.6 mEq·L^{-1}). During the first 48 hours of her admission she required mechanical ventilation and the continuous administration of intravenous bicarbonate to maintain normal arterial blood gases. The patient was lethargic and an electroencephalogram showed "diffuse slowing." Computerized tomography of the head was normal. Preoperative fluid therapy consisted of standard maintenance fluid and electrolytes with five per cent dextrose. Seventy-two hours after admission the infant was brought to the operating room for liver biopsy, skin biopsy, gastrostomy, and Nissen fundoplication. Preoperative laboratory values were: arterial blood gases (see Table), hemoglobin 12.4 gms%, hematocrit 37.5, sodium 132 mmol·L^{-1}, potassium 4.5 mmol·L^{-1}, chloride 91 mmol·L^{-1}, glucose 4.9 mmol·L^{-1}, SGOT 84 IU·L^{-1} (normal 25 to 45), SGPT 62 IU·L^{-1} (normal less than 35), lactate 8.4 mEq·L^{-1}. Anaesthesia was induced with thiopental and fentanyl. Relaxation for tracheal intubation was obtained with pancuronium. Maintenance anaesthesia was with nitrous oxide (60 per cent), oxygen (40 per cent), and fentanyl. Intraoperative fluid replacement was with 5 per cent dextrose in normal saline. No blood transfusion was required. Systolic blood pressure was 12 kPa (90 torr) to 16 kPa (120 torr) during the procedure. Nasopharyngeal temperature was 37.2 to 38.0° C. Despite frequent $NaHCO_3$ administration the base deficit and lactate levels increased. The magnitude of these increases can be seen in the Table. Lactate levels returned to baseline values 24 hours after surgery.

Multiple attempts at weaning from mechanical ventilation failed during the ensuing two weeks and the infant underwent tracheostomy. Anaesthesia for tracheostomy consisted of nitrous oxide, oxygen, and isoflurane. No thiopental was used. The blood gas changes and increases in arterial lactate levels were almost identical to the previous anaesthetic. The lactate level increased from 8.4 mEq·L^{-1} preoperatively to 16.2 mEq·L^{-1} immediately after surgery and declined to 8.6 mEq·L^{-1} within 24 hours. A course of progressive deterioration with septicaemia, respiratory distress, and seizures began four days after tracheostomy and the patient died on the 30th day of her hospitalization. The liver biopsy and fibroblast assay demonstrated a marked deficiency of pyruvate dehydrogenase.

Discussion

Of the heritable disorders of metabolism which produce lactic acidosis in children, anaesthetic experience has been reported for the glycogen storage diseases and deficiencies of gluconeogenic enzymes (fructose-1,6-diphosphatase).[2,3] Anaesthetic experience of patients with pyruvate carboxylase, phosphoenolpyruvate carboxykinase, or pyruvate dehydrogenase deficiencies has not been previously reported. Ward reported a case of anaesthesia for Leigh syndrome.[4] Leigh syndrome may represent a deficiency of pyruvate carboxylase or pyruvate dehydrogenase although the exact abnormality has not been defined.[5,6] Ward's report was of an uneventful anaesthetic with thiopental, nitrous oxide, meperidine, and d-tubocurarine. There was no increase in acidosis in his patient. The difference between our case and Ward's may be a different enzyme defect or there may have been a different triggering stimulus in our patient. Analysis of the blood gas changes of our patient (Table) shows an intraoperative change in the base deficit of −13 mEq·L^{-1} (from + 7 to −6). The initial metabolic alkalosis was probably secondary to the preoperative infusion of $NaHCO_3$. The subsequent

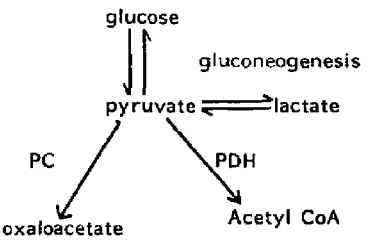

FIGURE Enzymatic reactions involving pyruvate, lactate, pyruvate dehydrogenase (PDH), and pyruvate carboxylase (PC).

increase in lactate levels could well have been produced by the hypocarbia present during the first part of the anaesthetic. Hypocarbia has been shown to increase lactate levels during anaesthesia.[7]

Our patient represents a proven case of pyruvate dehydrogenase deficiency. The lack of pyruvate dehydrogenase produces the inability to convert pyruvate into acetyl CoA with the subsequent accumulation of lactate and pyruvate (Figure).[8] Three enzyme defects of the pyruvate dehydrogenase complex have been identified. Deficiency of the first enzyme of the complex (pyruvate decaboxylase or E1) is clinically characterized by a progressive and severe neurologic dysfunction. The E1 defect is unaffected by diet control. Steroids may however alleviate some symptoms. Deficiency of the second enzyme of the complex (dihydrolipoyl transacetylase or E2) features neurologic dysfunction and lactic acidosis. The lactic acidosis may be precipitated by high carbohydrate intake. A high fat–low carbohydrate diet may have beneficial effect in these patients. Deficiency of the third enzyme of the complex (dihydrolipoyl dehydrogenase or E3) is characterized by lactic acidosis, lethargy, optic atrophy, laryngeal stridor, irregular respiration, and irritability.[9] Our patient fit the clinical pattern of the E3 deficiency. She had optic atrophy, irregular respiration, and lactic acidosis. Her acidosis was unaffected by a high carbohydrate diet. It must be remembered that these enzyme deficiencies are rare. Further clinical and laboratory work is necessary before all of these patients can be adequately classified.

Although two different anaesthetic regimens were used for our patient the metabolic responses (increased lactate levels and acidosis) were identical. Other causes of acidosis such as sepsis, hypothermia, low cardiac output, hypovolaemia, and hypoxaemia were not present during anaesthesia. In addition to an increase in lactate levels produced by hypocarbia, other causes must be considered. Halothane is known to inhibit gluconeogenesis.[10] Although the effects of isoflurane are not known, they are probably similar to halothane. There is also evidence that thiopental could have similar metabolic effects as halothane although the evidence is not as conclusive.[11] The actual effects of anaesthetic drugs on enzyme activity is complex and unclear. In vitro experiments indicate that most enzymes are resistant to anaesthetics.[12] Anaesthetics may however produce their known alterations in metabolism by affecting substrate availability or by interfering with hormonal activation of enzymes.[13] The effect of an inhibition of gluconeogenesis would be to increase lactate levels and thereby increasing the lactic acidosis. The increased lactate levels in this patient could also reflect increased lactate production as a metabolic response to surgery. Non-surgical stress has been reported to exacerbate neurologic symptoms in patients with pyruvate dehydrogenase deficiency.[14] This stress effect would most likely occur with inadequate levels of anaesthesia. Although our report represents experience with only one such case, we feel that the following recommendations are indicated for management of future cases. The patient should be thoroughly evaluated preoperatively for signs of any abnormality which might produce metabolic acidosis such as sepsis, hypothermia, hypoxaemia, or low cardiac output. The patient's metabolic profile should be reviewed with specific reference to the finding that a carbohydrate load may produce lactic acidosis in some patients. Lactate containing intravenous solutions should not be administered as the lactate load would only be increased. For anaesthesia, halogenated agents should be avoided. The choice of an induction agent is not clear, since induction agents such as althesin and diazepam may have similar metabolic effects as thiopental. The patient should be normothermic and normocarbic during anaesthesia. An adequate level of anaesthesia should be produced and is best accomplished with narcotics. Because children with primary lactic acidosis are prone to central respiratory depression, careful observation for postoperative hypoventilation is required. Certainly more anaes-

thetic experience is necessary with patients with pyruvate dehydrogenase deficiency before firm recommendations can be made.

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Résumé

Un enfant de dix mois déficient en déshydrogénase pyruvique a été anesthésié à deux occasions; pour laparotomie et pour trachéotomie. Deux techniques différentes ont été utilisées. Lors de deux opérations, il a développé une acidose métabolique et une élévation des concentrations artérielles d'acide lactique. La déficience enzymatique en déshydrogénase pyruvique produit une altération du métabolisme de l'acide pyruvique avec comme résultat accumulation d'acide pyruvique et d'acide lactique.

L'inhibition de la glyconéogénèse que l'on peut rencontrer avec l'halothane et le thiopental, provoquera aussi chez ces malades une augmentation des concentrations d'acide lactique. D'autres causes d'acidose lactique comprennent l'hypocarbie et l'apport important de glucides. Chez ce patient, l'hypocarbie peut avoir augmenté l'acidose métabolique et les concentrations d'acide lactique.

Nous recommandons d'éviter les halogénés ainsi que les solutions contenant de l'acide lactique, de maintenir une normocarbie et d'administrer une anesthésie suffisamment profonde pour protéger du stress chirurgical.