Anesthesia and Glycogen-storage Disease

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Glycogen-storage disease is a rare metabolic disorder of significance to the anesthesiologist. Recently, the opportunity arose to study the effects of anesthesia during a major operation upon an adolescent with this disease. The adverse effect of the combined anesthetic and surgical procedures was reflected in a deterioration of the patient's biochemical parameters. Because of this, we decided to review, from the anesthetic viewpoint, all surgical cases involving this metabolic disorder which were seen in the last decade at Children's Memorial Hospital.

Types of Glycogen-storage Diseases and Their Significance to the Anesthesiologist

The term “glycogen-storage disease” is applied to a group of congenital and familial disorders characterized by deposition of abnormally large or small quantities of glycogen in the tissues. At least seven types of disturbance of glycogen metabolism have been reported. 1, 2

Glycogen is a branched polymer of glucose. Its molecular size is variable, probably reflecting a composite of the action of the enzymes of glycogen synthesis and breakdown at the time of isolation. Figure 1 is a schema of glycogen metabolism, indicating stages at which defects give rise to glycogen-storage disease.

Type I. Glucose-6-phosphatase Deficiency (von Gierke's Disease): This disease of the liver and kidneys usually is diagnosed during the first year of life because of asymptomatic liver enlargement. An absence of glucose-6-phosphatase reduces readily available sources of glucose. Hypoglycemia in turn causes ketosis, convulsions and increased gluconeogenesis. For the first few months the infant appears well, but then anorexia, vomiting and weight loss may develop. Death rarely ensues in the first two years. With modern diagnosis and therapy many patients reach adult life and do moderately well. The incidence of the disease is unknown; the condition appears to be transmitted as a simple autosomal recessive, and consanguinity is usual.

Glucose-6-phosphatase deficiency is treated by frequent feedings to reduce the hypoglycemia. The acidotic tendency is treated with sodium bicarbonate orally. Steroids are of doubtful value.

During the first year of life the child may have to undergo laparotomy and liver biopsy to confirm the diagnosis. He may appear well, but as the disease progresses thrombocytopenia, hypoglycemia, convulsions and some retardation of growth and development are common. Despite low blood sugar levels and failure to respond to injections of epinephrine, these infants do not inevitably show signs of hypoglycemia. The blood pH may be low or normal; blood lactate and pyruvate concentrations are increased, as are plasma lipids and urates. Electroencephalograms recorded in two cases, 3 with high and low blood glucose concentrations, disclosed no abnormalities.

Type II. Acid Maltrase Deficiency (Pompe's Disease): The abnormality is generalized but the clinical manifestations are those of hypotonia and cardiac dysfunction. The patient may have mild to severe cardiac failure with symptoms of dyspnea, cyanosis, hepatic enlargement, ascites, anasarca and pulmonary edema. Muscle biopsy is done to exclude a diagnosis of hypotonic muscular disease.

Type III. Amylo 1,6-Glucosidase Deficiency (Forbes' Disease): The debrancher enzyme is absent and a similar, though milder, form of Type I results. Often treatment is not indicated, and if surgical operation is required the anesthesia should not present a problem.

Type IV. Amylo 1,4-1,6 Transglucosidase Deficiency (Andersen's Disease): There is a diffuse glycogenesis with hepatic cirrhosis.
The clinical manifestations are due to mechanical factors and metabolic failure of the liver, with edema, ascites, esophageal varices and hypoprothrombinemic bleeding tendencies. The hepatic dysfunction increases until death from hepatic failure occurs. Treatment is directed toward the cirrhoses.

**Type V. Muscle Glycogen Phosphorylase Deficiency (McArdle’s Disease):** This muscular disorder is characterized by rapid exhaustion of otherwise mechanically and physiologically normal muscle, with inability to tolerate excessive exercise in a short period of time, although minimal exercise can be tolerated. This entity is so rare that no studies on the effects of muscle relaxants are known.

**Type VI. Liver Glycogen Phosphorylase Deficiency (Hers’ Disease):** A hepatophosphorylase deficiency causes a mild form of Type I disease with a variable hyperglycemic response to epinephrine and glucagon. This type is poorly defined and is only distinguishable biochemically.

**Type VII. Glycogen Synthetase Deficiency:** In contrast to the previous types, this represents deficiency in synthesis of glycogen, characterized by hypoglycemia and starvation in early infancy. Treatment is frequent feeding with glucose.

**Case Report**

A 17-year-old white youth, markedly underweight, was admitted with a diagnosis of von Gierke’s disease complicated by a chondroma in the left femoral head. The patient was one of 13 siblings, three known to have von Gierke’s disease. Liver biopsy had been done in infancy when the diagnosis of glycogen-storage disease was made. A second biopsy was performed at 8 years of age, at which time open drop ether anesthesia was administered without incident; convalescence was uneventful. Apart from marked hepatomegaly and poor development, physical examination disclosed no abnormalities. Height was 129 cm, weight 32 kg, hemoglobin 10.7 g and hematocrit 30 per cent.

At yearly examinations blood glucose levels ranged from 50–60 mg/100 ml; lactate 45–60 mg/100 ml; ketones 14–16.3 mg/100 ml; uric acid 13–17 mg/100 ml; cholesterol 300–450 mg/100 ml; phospholipids 400–600 mg/100 ml; triglycerides 900–1500 mg/100 ml; free fatty acids 1,500–1,800 Eg/l. ECG pattern was normal.

Two hours prior to operation for excision of the chondroma blood samples were taken for biochemical studies. Meperidine (Demerol), 50 mg, atropine, 0.6 mg, was injected intramuscularly a half hour before operation. Anesthesia was induced with thiopental, 200 mg, intravenously, followed by succinylcholine, 40 mg. The trachea was intubated with a no. 34 cuffed tube. Five per cent dextrose in 0.2 per cent saline solution was infused intravenously. A radial artery was cannulated for blood sampling and a central venous pressure catheter was inserted via the basilic vein. Electrocardiogram and rectal temperature were monitored. Anesthesia was maintained with halothane (Fluothane), nitrous oxide, and oxygen.
Soon after induction the patient was turned on the right side and the endotracheal tube connected to an Engström respirator. The figures for ventilation, calculated from the nomogram, were 7 liters per minute V\textsubscript{E}\text{,} with a rate of 20 per minute. Blood gas studies (Astrup technique) indicated normal arterial P\textsubscript{aCO}\textsubscript{2}.

In the 30- to 45-minute period following induction, extrasystoles three to four minutes in duration were observed twice. Blood pressure was normal. The premature ventricular contractions were thought to be due to light anesthesia and the concentration of halothane was increased, with good results. Four hundred ml of blood were given. Total anesthesia time was three hours, 15 minutes.

The first arterial blood sample revealed metabolic acidosis, which gradually increased with subsequent samples (table 1). Sodium bicarbonate, 44.8 mEq, was injected intravenously about an hour before the end of the surgical procedure. This alleviated the acidic state only slightly. An additional 44.8 mEq of sodium bicarbonate was injected intravenously in the recovery room without significant result. The patient received 500 ml of 5 per cent dextrose and 0.2 per cent saline throughout the surgical procedure.

Follow up three weeks after operation showed delayed wound healing and acute onset of gouty arthritis of the left knee. The electrocardiogram was within normal limits and results of blood gas studies were identical with those recorded on the day after operation.

**DISCUSSION**

A review of anesthetic experiences in the children treated for glycogen storage diseases is summarized in table 2. The majority of the cases were of Type I (von Gierke's disease), and most operations were brief. The anesthetics used were ether, cyclopropane and halothane, and the techniques varied. Operations performed were generally minor, and although laparotomy for liver biopsy is a major procedure, it was of short duration, usually free of blood loss and shock. In patient 6 an open-heart operation was performed at age 7. Biochemical studies were not done, and except for laryngospasm on induction, anesthesia was without incident. This patient had mild Type III disease. In patient 9 an episode of hypoxia and bradycardia was caused by strong abdominal retraction.

In patient 5, the only death in this series, the course of the events leading to cardiac arrest is not clear. There were no ventilatory or circulatory complications. Whether an acidic state contributed to death is unknown.
### CLINICAL WORKSHOP

**Table 2. Children with Glycogen-storage Disease—Review of Anesthetic Experience**

<table>
<thead>
<tr>
<th>Patient</th>
<th>D.O.B.</th>
<th>Type of G.S.D.</th>
<th>Operation</th>
<th>Anesthesia</th>
<th>Duration</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. T. G.</td>
<td>9/3/50</td>
<td>I</td>
<td>Open liver biopsy 1/51&lt;br&gt;Reduction fractured forearm 6/60</td>
<td>Open drop ether&lt;br&gt;C₃H₆ to-and-fro</td>
<td>1 hr&lt;br&gt;½ hr</td>
<td>Uneventful&lt;br&gt;Uneventful</td>
</tr>
<tr>
<td>2. D. R.</td>
<td>4/31/48</td>
<td>I</td>
<td>Open liver biopsy 6/54&lt;br&gt;Curettage &amp; biopsy of chondroma (L) femoral neck-bone grafting 2/67</td>
<td>Open drop ether&lt;br&gt;Endotracheal halothane</td>
<td>⅓ hr&lt;br&gt;3 hr</td>
<td>Uneventful&lt;br&gt;See text</td>
</tr>
<tr>
<td>3. E. W.</td>
<td>3/30/55</td>
<td>I</td>
<td>Open liver biopsy 3/56</td>
<td>Open drop ether</td>
<td>1½ hr</td>
<td>Uneventful</td>
</tr>
<tr>
<td>4. J. G.</td>
<td>12/14/51</td>
<td>I</td>
<td>T and A 3/58</td>
<td>Open drop ether</td>
<td>1 hr</td>
<td>Uneventful</td>
</tr>
<tr>
<td>5. T. M.</td>
<td>1/31/55</td>
<td>I</td>
<td>T and A and removal of chalazion 5/58</td>
<td>Open drop ether</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. J. B.</td>
<td>11/29/55</td>
<td>III</td>
<td>Open liver biopsy 12/58&lt;br&gt;Correction of aortic subvalvular stenosis with use of extracorporeal circulation 5/62</td>
<td>Open drop ether&lt;br&gt;Halothane endotracheal</td>
<td>1 hr&lt;br&gt;4 hr</td>
<td>Uneventful&lt;br&gt;Unsuccessful, CHD aortic stenosis. Some laryngospasm on induction, otherwise uneventful; no acid-base balance studies available</td>
</tr>
<tr>
<td>7. B. M.</td>
<td>10/12/59</td>
<td>I</td>
<td>Open liver biopsy 12/60</td>
<td>C₃H₆ to and fro</td>
<td>1 hr</td>
<td>Uneventful</td>
</tr>
<tr>
<td>8. J. M.</td>
<td>2/5/61</td>
<td>I</td>
<td>Open liver biopsy 8/62</td>
<td>C₃H₆ to and fro</td>
<td>1 hr</td>
<td>Uneventful</td>
</tr>
<tr>
<td>9. K. C.</td>
<td>6/18/62</td>
<td>I</td>
<td>Open liver biopsy 10/62</td>
<td>Halothane endotracheal nonbreathing</td>
<td>1 hr</td>
<td>Anoxia and bradycardia caused by excessive retraction by instruments; uneventful after situation was corrected</td>
</tr>
<tr>
<td>10. W. Mc.</td>
<td>8/19/63</td>
<td>I</td>
<td>Open liver biopsy 1/65&lt;br&gt;Open liver biopsy 11/65</td>
<td>Halothane endotracheal nonbreathing&lt;br&gt;Halothane endotracheal nonbreathing</td>
<td>2 hr&lt;br&gt;2 hr</td>
<td>Uneventful&lt;br&gt;Second operation to determine spread of fibrotic element. Gross pulmonary secretions; incipient URI, suctioned endotracheally. Operation well tolerated</td>
</tr>
<tr>
<td>12. C. D.</td>
<td>10/21/64</td>
<td>I</td>
<td>Open liver biopsy 1/66</td>
<td>Halothane endotracheal nonbreathing</td>
<td>1 hr</td>
<td>Uneventful</td>
</tr>
</tbody>
</table>
In the case reported here, the child was in severe metabolic acidosis shortly after induction of anesthesia. Acidosis increased, and was only slightly alleviated by administration of two ampules of sodium bicarbonate. Not until approximately three hours postoperatively, was the acid-base state satisfactory. Blood glucose levels rose during operation as a result of the infusion of dextrose. There was a preoperative lactic acidosis of 58.4 mg/100 ml (normal 5–20 mg/100 ml), rising to 98.6 mg toward the end of the operation with reversion almost to the preoperative level by the next day. The levels of the triglycerides and free fatty acids fell during operation and remained low the following day. This may have reflected metabolism of the infused glucose in preference to the metabolic pathways leading to fatty acid formation. Infusion of glucose equates with the frequent small feedings used in day-to-day treatment of this disease. Ether and methoxyflurane cause a rise in blood sugar unrelated to sympathetic stimulation by hypercarbia. It is generally accepted that the rising blood sugar during ether anesthesia is due to the epinephrine released by its action on brain centers governing autonomic activity. The results of investigation by Hunter indicate that blood sugar changes during halothane anesthesia are negligible in comparison.

The main adverse effect on patients with Type I glycogen-storage disease is augmentation of an already-present acidotic tendency. Howland, Schweizer and Boylan have shown that the acid load attributable to anesthesia is not large, 1 to 2 mEq/l depression of standard bicarbonate representing a shift toward metabolic acidosis. Thus, in short uncomplicated procedures, the effect upon patients is probably not significant; however, the additive effects of lengthy anesthesia, shock, blood replacement and hypothermia can produce significant metabolic acidosis. The tendency toward lactic acidosis in the case reported may have been offset by the administration of glucose but the magnitude of the operation and the blood loss (400 ml lost, or approximately 18 per cent of the estimated blood volume), were probably factors.

The experience of this case suggests that when a patient with Type I glycogen-storage disease (von Gierke’s) undergoes a major operation it is desirable to have an arterial catheter inserted at the outset to do serial blood gas and acid–base studies preoperatively and postoperatively. Intravenous solutions of 5 per cent dextrose in water or 5 per cent dextrose in 0.2 per cent normal saline solution should be used in preference to lactated Ringer’s solution. There is no advantage to using the latter because of the relationship of lactate to lactic acid.

\[
\text{Lactate} + \text{H}^+ \rightarrow \text{lactic acid} \rightarrow \text{glycogen}
\]

\[
3 \text{O}_2 \rightarrow 3 \text{CO}_2 + 3 \text{H}_2\text{O}
\]

Where liver function is compromised, and in lactic acidosis, lactate may not be metabolized completely and may be excreted in the urine without the beneficial effect of removal of \(\text{H}^+\) ions. Moderate-to-severe metabolic acidosis should be treated with sodium bicarbonate according to the measured base excess; blood used in transfusion should be prebuffered with THAM or sodium bicarbonate. Finally, the care of the patient must extend well into the postoperative period until there is a satisfactory acid–base status and the other biochemical parameters have returned to preoperative levels.

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REFERENCES