Diethyl Ether Anesthesia for a Patient with Hyperinsulinism

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Hyperinsulinism and the resultant hypoglycemia are hallmarks of functioning beta islet-cell tumors of the pancreas. Reviews by Whipple 1 in 1935 and by Hartsuck and Brooks 2 in 1969 established the importance of the following findings in this syndrome: 1) blood glucose level less than 50 mg after prolonged fasting, with symptomatic relief following intravenous administration of glucose; 2) early, persistent hypoglycemic response to the intravenous tolbutamide (Orinase) tolerance test; 3) increased fasting serum insulin levels associated with delayed, peak serum insulin levels following tolbutamide, iv.

A review of anesthesia writings revealed only a few case reports on this subject. The premise of each author was noteworthy, namely, to avoid or recognize and treat hypoglycemia so as to prevent irreversible brain damage. All used nitrous oxide, opioids and neuromuscular blockers for anesthesia. In 1963, Fraser 3 described a patient who had bouts of hypoglycemia during anesthesia, as evidenced by hypotension, cyanosis and sweating, corrected by intermittent intravenous injections of glucose (blood glucose levels not given). Hargaden and Ormston 4 performed rapid intraoperative blood glucose determinations utilizing an Autoanalyzer; however, they found blood glucose levels of less than 50 mg, supporting clinical evidence of hypoglycemic attacks during anesthesia, which necessitated treatment with 50 per cent glucose. Bourke 5 recognized the shortcomings of intermittent analysis and therefore maintained two patients in moderate hyperglycemia by frequent doses of 50 per cent glucose, including 30 grams administered during manipulation of the tumor.

It occurred to us that diethyl ether could be a safe alternative to the nitrous oxide sequence, because diethyl ether not only enhances hepatic glycogenolysis, but also may induce insulin resistance. 6 A report of such a case, in which diethyl ether was used as the primary anesthetic, follows.

REPORT OF A CASE

A 17-year-old girl (Hosp. no. 14-39-74) had been well until the age of 10 years, when she had begun to experience episodic lightheadedness, dizziness, and weakness, accompanied by sweating, tremor, paresthesias, diplopia, tinnitus, and emotional lability. Two years prior to admission, she had been found unconscious in bed, and a demonstrated hypoglycemia had responded well to glucose, administered iv at a local hospital. Similar episodes had occurred twice more, blood glucose values obtained during the spells ranging from 36 to 40 mg/100 ml. Glucose tolerance tests showed both fasting and 4-hour samples in the 50-mg range, while a tolbutamide tolerance test resulted in a marked decrease in blood glucose to 11 mg after prolonged fasting (64 hours).

When the frequency and severity of the attacks increased, the patient was referred to the Peter Bent Brigham Hospital. Examination disclosed that she was overweight for her height, with acne vulgaris of the face. The remainder of the physical examination was unremarkable. Positive laboratory findings were: calcium 11.9–12.5 mg/100 ml, phosphorus 2.7–3.1 mg/100 ml, alkaline phosphatase 115 International units, glucose tolerance test abnormal as before, and an immunoreactive insulin level of 67 μU/ml (normal 7–39 μU/ml). Following a 14-hour fast, blood glucose was 35 mg/100 ml, with the patient lethargic. A celiac arteriogram showed an 8-mm lesion with a dense vascular blush near the right pedicle of the T12 vertebra, probably in the superior border of the pancreas, as well as numerous smaller nodules in the tail, supporting the diagnosis of pancreatic insulinoma. Roentgenograms of the chest and skull, bone series, and liver scan disclosed no abnormalities.

Operative Course: An infusion of 10 per cent dextrose in water was started two hours preoperatively; premedication was pentobarbital, 150 mg, and atropine, 0.5 mg, im, 1½ hours before induction; preoperative blood pressure was 105 mm Hg.

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systolic, 70 mm Hg diastolic, pulse 80/min, and respirations 20/min, with the patient awake and cooperative. A central venous line, continuous ECG, bladder catheter, and Dextrostix for rapid blood glucose tests comprised additional monitoring devices. Denitrogenation was accomplished with 100 per cent oxygen, followed by induction with nitrous oxide and gradually increasing concentrations of ether in oxygen. Tracheal intubation was accomplished without a neuromuscular blocker, and anesthesia was maintained with 10–20 per cent inspired diethyl ether in oxygen plus assisted ventilation for 7 hours. Glucose and insulin in blood drawn from the central venous line were measured at intervals (table 1). At no time was there laboratory or clinical evidence of hypoglycemia. Infusion of dextrose in water was maintained at 6 g/hr; other fluids included dextrose in saline solution at 3 g/hr and Ringer’s lactate totaling 900 ml, plus 1,500 ml of whole blood. Postoperatively the patient experienced none of the complications of partial pancreatectomy except mild hyperglycemic rebound, which was treated with only one dose of insulin.

Examination of pathology specimens revealed insulinomas of the uncinate process and superior border of the pancreas, and 25 tumors in the tail (mostly insulinomas, a few non-beta-cell tumors). The insulin level of resected tissue was 93 U/g (normal 1–3 U/g).

The patient had slightly elevated blood glucose for 4 months postoperatively, after which time the level returned to normal. A parathormone level, obtained because of the elevated calcium, was 0.75 mg/100 ml. Accordingly, subtotal parathyroidectomy was performed without incident during a later admission, using halothane anesthesia.

**Discussion**

There are theoretical grounds for advocating diethyl ether for anesthesia with hyperinsulinism, although close monitoring and continuous glucose infusion are additional considerations to be weighed. There is a significant increase in blood glucose in man during diethyl ether anesthesia, probably owing to hepatic glycogenolysis secondary to increased sympathetic discharge. This effect is most evident in the first half hour of anesthesia. Other effects observed include increases in circulating norepinephrine, twofold increases in 17-hydroxycorticosteroids, and probable release of antidiuretic hormone. Henneman and Vandam found that blood glucose levels were not lowered as much by insulin administered during diethyl ether anesthesia as in the awake state. In their cases, blood glucose increased an average of 90 per cent during the first hour of diethyl ether anesthesia. They postulated an insulin resistance, suggesting that diethyl ether interferes with the cellular transfer of glucose.

Brunner has since demonstrated that diethyl ether causes a significant decrease in glucose uptake in isolated skeletal muscle, while insulin seems to stimulate glucose uptake under this circumstance. Although the insulin effect, per se, was not blocked by diethyl ether, the latter altered net glycogen formation, with glycogenolysis as well as lactate production. The combined effect of diethyl ether and insulin, then, demonstrates that the former depresses uptake of glucose by muscle, but does not block insulin-induced increases in uptake of glucose by tissue.

These data suggest that diethyl ether may be protective in the patient with insulinoma. Whereas Hargadon has recommended that inhalation anesthetics other than nitrous oxide not be used because a hyperglycemic effect could “complicate the picture,” we reject this reasoning in favor of the protective effect of diethyl ether. While persistently low blood glucose can indicate the presence of functioning tumor, as would an acute episode of hypoglycemia during tumor manipulation, the dangers of hypoglycemia with attendant hypoxia under these conditions are well known. The EEG slows as the cerebral A-V oxygen difference decreases, indicating diminution in cerebral metabolism; injection of glucose increases the A-V oxygen difference. Fructose, an al-

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**Table 1. Blood Glucose and Insulin Levels of the Patient during Hospitalization**

<table>
<thead>
<tr>
<th>Time</th>
<th>Glucose (mg/100 ml)</th>
<th>Insulin (μU/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admission, fasting</td>
<td>53</td>
<td>67</td>
</tr>
<tr>
<td>Baseline, operation, 8:25 AM*</td>
<td>208</td>
<td>33</td>
</tr>
<tr>
<td>Manipulation, 9:05 AM</td>
<td>134</td>
<td>198</td>
</tr>
<tr>
<td>After excision of the tumor, 10:55 AM</td>
<td>282</td>
<td>7</td>
</tr>
<tr>
<td>After resection of the tail of the pancreas, 11:55 AM</td>
<td>323</td>
<td>2</td>
</tr>
<tr>
<td>Ten days postoperatively, fasting</td>
<td>85</td>
<td>16</td>
</tr>
</tbody>
</table>

* 15 minutes after incision.
ternative sugar for infusion in hypoglycemic and diabetic patients, converts to blood glucose at a relatively high rate, the remainder of its biodegradation being unaffected by insulin. Its value in hyperinsulinism is controversial at best, and it was not used in this instance.

In the case reported here, the absence of hypoglycemia was not a hindrance to successful operation, although the importance of monitoring blood glucose for tumor localization has been cited by Hartsuck, and more recently by Schnelle et al. Selective angiography as an aid in diagnosis, described by Epstein et al., is still controversial because of the high incidence of failure in visualizing tumor patterns, as well as false-positive results. Nevertheless, this is a valuable adjunct in localization, and in some cases may add assurance to interpretation of intraoperative blood glucose levels.

In our patient, stable anesthesia was provided with a single agent for many hours without risk of central nervous system hypoglycemia. Nevertheless, manipulation of the tumors produced a 36 per cent decrease in blood glucose, while excision was accompanied by a gradual increase in blood glucose, strengthening the clinical impression of successful resection.

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Incorrect Performance of Allen’s Test—Ulnar-artery Flow Erroneously Presumed Inadequate

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The increasing use of radial arterial cannulae for continuous monitoring of arterial pressure and blood gases has renewed interest in the
determination of the condition of the hand. In our department, we perform about a thousand percutaneous radial artery cannulations annually. Prior to insertion of the cannula, an Allen’s test, modified as described by Richards, is done, unless the urgency of the case necessitates immediate cannulation. In this test, both radial and ulnar arteries are occluded by the examiner, and the

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