with mediastinal masses who are symptomatic (dyspnea, intolerance of supine position) should include studies to assess cardiac status, that is, an EKG, examination for pulsus paradoxus and echocardiography. If there is evidence of cardiac impairment in a patient who must undergo diagnostic cervical node biopsy, we recommend local anesthesia in the sitting position.[8] If tumor resection is necessary, we advocate preoperative radiation or chemotherapy in an attempt to shrink the tumor mass prior to administering general anesthesia.

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Anesthesiology
55:472–475, 1981

Anesthesia for Patients with Insulinoma Treatment with Oral Diazoxide

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Insulinoma, first described in 1924 by Harris,[1] is a beta islet cell tumor of the pancreas that produces marked hypoglycemia resulting from sudden, episodic, and massive release of endogenous insulin. Avoidance of hypoglycemia is the cornerstone of medical management in patients with this disorder prior to surgical excision of the tumor. Fraser[2] first described hyperinsulinism during anesthesia and the intraoperative and postoperative episodes of hypoglycemia responding to rapid administration of glucose intravenously. The importance of rapid, frequent intraoperative blood glucose determinations has been emphasized by many authors,[2–4] and the prophylactic use of 50 per cent glucose to maintain moderate intraoperative hyperglycemia has been suggested.[4]

Anesthetic techniques previously reported for surgical removal of insulinoma include nitrous oxide–relaxant techniques[3,4] and methoxyflurane.[5] Colella and Vandam[6] recommended diethyl ether as the anesthetic of choice since it has the theoretical advantage of releasing catecholamines which enhance hepatic glycogenolysis and inhibit insulin release. Use of enflurane for maintenance of general anesthesia for insulinoma surgery has not previously been published.

Diazoxide (Proglycem®), a nondiuretic benzothiadiazine derivative with peripheral vascular dilating activity, directly inhibits release of pancreatic insulin and has proven to be a major advance in the medical management of patients with insulinoma.[7] No discussion of anesthetic implications for patients taking oral diazoxide preoperatively exists.

We describe two cases where enflurane was utilized to anesthetize patients for surgical removal of insulinomas, where oral diazoxide was used preoperatively to combat perioperative hypoglycemia. In addition, limiting the intraoperative infusion of 5 per cent dextrose containing solutions to 2 $ml \cdot kg^{-1} \cdot h$ is suggested, and a possible drug interaction between diazoxide and thiopental is proposed.

Report of Two Cases

Patient 1. A 51-year-old, 80-kg female was evaluated for hypoglycemia. A tentative diagnosis of insulinoma was entertained when her

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Received from the Bowman Gray School of Medicine, Winston-Salem, North Carolina. Accepted for publication April 7, 1981.

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Key words: Anesthetics, volatile: enflurane. Hormones: insulin. Metabolism: hyperinsulinism; hyperglycemia; diabetes; insulinoma; diazoxide.

fasting blood glucose fell to 39 mg/dl and immunoreactive insulin levels were four times normal. She became symptomatic during the fast and readily responded to two ampules of 50 per cent dextrose intravenously, fulfilling Whipple's triad of a history of repeated attacks of hypoglycemia, concomitant blood glucose levels under 50 mg/dl, and relief of attacks by glucose administration.[8] Although selective dorsal pancreatic and hepatic angiographic studies were inconclusive, surgery was scheduled.

By history, her trachea was impossible to intubate during a previous general anesthetic because of a narrow maxilla, short, fat neck, and poor temperomandibular joint mobility. Diazoxide, 100 mg, po, tid, was begun seven days prior to surgery, and was continued up to the time of surgery. Premedication consisted of 10 mg diazepam, po, 30 ml Maalox®, po, and 0.3 mg glycopyrrolate, im, 60 min prior to arrival in the operating room. Preoperatively, 5 per cent dextrose in 0.25 per cent saline, with KCl 20 mEq/l, was infused at a rate of 125 ml/h throughout the night and 200 ml/h for the last four hours prior to surgery. These solutions were replaced with 5 per cent dextrose in lactated Ringer's solution on arrival in the operating room.

In addition to the usual monitors, central venous pressure (CVP) was measured via a catheter in the right internal jugular vein. Arterial blood pressure was continuously monitored via a catheter in the left radial artery. Using 3 ml Innovar®, iv, and topical Cetacaine® spray, an awake oral endotracheal intubation was performed without difficulty. Thiopental, 250 mg, and 6 mg pancuronium, were then administered intravenously. Thirty seconds later, arterial systolic blood pressure dropped to 40 torr, and the CVP dropped from 15 to 0 cm H_2O (fig. 1*A*). Intravenous fluids (5 per cent dextrose in lactated Ringer's solution) were infused rapidly and ephedrine, 20 mg, was administered intravenously in divided doses before the systolic blood pressure reached 90 torr. The blood *p*H was 7.36, Pa_{O_2} 133 torr, Pa_{CO_2} 40 torr, and the blood glucose was greater than 250 mg/dl. Following surgical incision, the systolic blood pressure increased to 160 torr, and inhalation anesthesia with 1 per cent enflurane and 50 per cent nitrous oxide in oxygen was begun.

Surgery proceeded with splenectomy, partial pancreatectomy, and incidental cholecystectomy with an estimated blood loss of 1500 ml. No further anesthetic difficulty was encountered. Intravascular fluid administration intraoperatively included one unit of whole blood, one unit of packed erythrocytes, 5 per cent dextrose and lactated Ringer's solution, 3200 ml, lactated Ringer's solution, 1000 ml, and normal saline, 500 ml. Urine output totaled 1650 ml. Perioperative blood glucose measurements, determined by Dextrostix®‡ and by a Dupont Automatic Clinical Analyzer,§ are shown in figure 2.

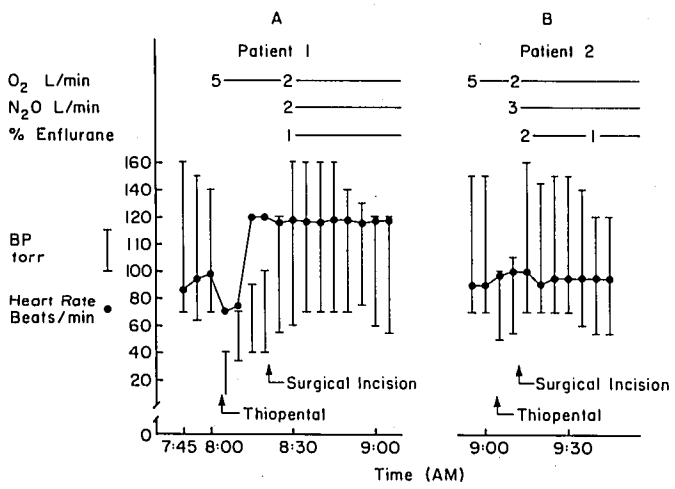

FIG. 1. Initial anesthetic records of two patients with hyperinsulinism treated with oral diazoxide. Rapid drop in blood pressure is temporally related to thiopental administration. *A*. The initial portion of the anesthetic record for patient 1; and *B* the initial portion of the anesthetic record for patient 2.

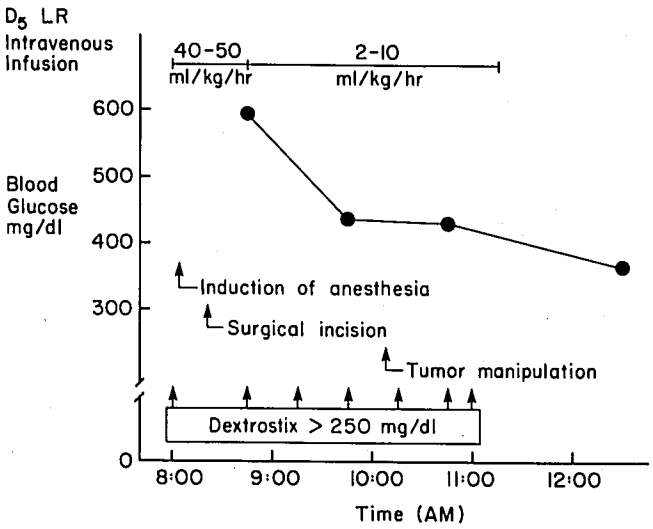

FIG. 2. Perioperative blood glucose levels in patient 1 determined by two methods. Determinations with Dextrostix® are indicated by vertical arrows (|) and determinations by a Dupont Automatic Clinical Analyzer are indicated by closed circles (●). Hyperglycemia is presumed to have resulted from 5 per cent dextrose in lactated Ringer's solution infused rapidly in an attempt to combat sudden unexpected hypotension following administration of thiopental.

Following completion of the 3-hour surgical procedure, neuromuscular blockade was reversed, and the trachea was extubated with the patient fully awake. In the recovery room, the blood pressure was 130/90 torr, heart rate 80 beats/min, and respiratory rate 24/min.

Patient 2. A 69-year-old 60-kg female with a one-year history of "crazy spells" was found to be hypoglycemic, and a clinical diagnosis of insulinoma was established. Diazoxide, 100 mg, po, bid, was begun three days prior to surgery, and continued up to the time of surgery. Preoperative anesthesia evaluation revealed no contraindications to general anesthesia. Premedication consisted of 30ml Maalox®, po, and 5 per cent dextrose in water, 100ml per hour, was given iv for eight hours immediately preoperatively. The same monitoring and intravenous cannulations as described in Case 1 were used. Anesthesia was induced with 150 mg thiopental, and 6 mg pancuronium, iv. Immediately following induction of anesthesia, arterial blood pressure fell from 150/70 torr to 100/50 torr (fig. 1*B*). Rapid intravenous infusion of lactated Ringer's solution, 1000 ml, combined with endotracheal intubation and subsequent surgical stimulation restored arterial blood pressure to preinduction levels. Anesthesia was maintained with inspired concentrations of 1–2 per cent enflurane and 60 per cent nitrous oxide. Splenectomy, partial pancreatectomy, and incidental cholecystectomy were completed with an estimated blood loss of 1450 ml. Intraoperative fluid administration included three units of packed erythrocytes, lactated Ringer's solution, 3000 ml, 5 per cent dextrose in lactated Ringer's solution, 3000 ml, and normal saline, 750 ml. Urine

‡ Reagent strips, Ames Division, Miles Laboratories, Inc., Elkhart, Indiana 46515.

§ Dupont Company, Wilmington, Delaware 19898.

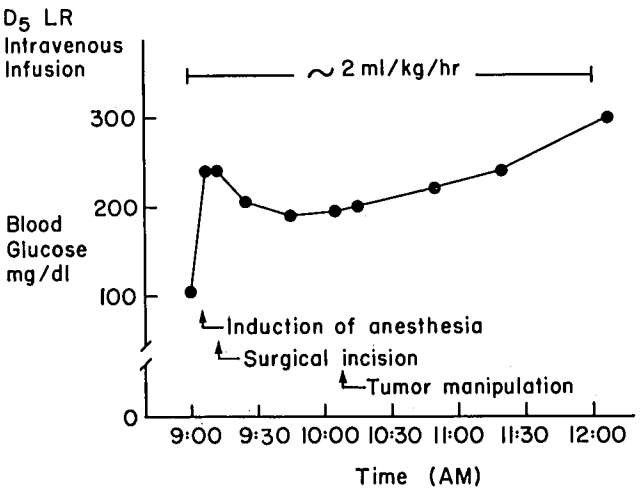

FIG. 3. Perioperative blood glucose levels in patient 2 determined with an Ames Eyetone® reflectance colorimeter in conjunction with Dextrostix®. Glucose administration limited to 2 ml·kg^{-1}·h of 5 per cent dextose in lactated Ringer's prevented hypoglycemia and resulted in blood glucose levels less than 300 mg/dl.

output totaled 500 ml. Perioperative blood glucose levels determined with an Ames Eyetone®¶ reflectance colorimeter in conjunction with Dextrostix®¶ reagent strips are illustrated in figure 3.

Following completion of the 3.5-hour surgical procedure, neuromuscular blockade was reversed, and the trachea was extubated with the patient fully awake. In the recovery room, the blood pressure was 120/80 torr, heart rate 96 beats/min, and respiratory rate 28/min.

DISCUSSION

In these two obese patients, use of a high inspired concentration of oxygen technique with a potent inhalation agent was considered advantageous. Bourke[4] has suggested that halothane be avoided in the anesthetic management of patients with insulinoma, since it may cause an increased sensitivity to insulin. Methoxyflurane was not selected due to its disadvantages including fluoride toxicity, especially in obese patients, and slow emergence characteristics because of a high blood/gas solubility coefficient. Therefore, by a process of elimination and not for any demonstrated advantages in patients with insulinoma, we chose enflurane for the maintenance of general anesthesia.

Avoidance of preoperative and intraoperative hypoglycemia in patients with insulinoma may be accomplished by the oral administration of diazoxide, a peripheral vasodilator which is known to inhibit insulin release. In fact, medical management of patients with insulinoma has been successfully accomplished for as long as twelve years using oral diazoxide in combination with trichlormethiazide.[7] The plasma half-life of diazoxide is twenty-six hours,[9] resulting in sustained inhibition of insulin release and prolonged maintenance of blood glucose levels. Thus, unwanted hypoglycemia may be prevented throughout the perioperative period by oral administration of diazoxide preoperatively.

Although avoidance of intraoperative hypoglycemia in patients with insulinoma is certainly beneficial, the degree of hyperglycemia which we observed in patient 1 (fig. 2) is unnecessary and may be harmful.[10] We presume that the increase in blood glucose in this case resulted from the intraoperative administration of 5 per cent dextrose in lactated Ringer's solution which was infused more rapidly than anticipated in order to combat the sudden unexpected hypotension resulting from induction of anesthesia. Infusion of 5 per cent dextrose in lactated Ringer's solution at a rate of 10 ml·kg^{-1}·h^{-1} has been noted to produce blood glucose levels in obese patients greater than 300 mg/dl.[11] Therefore, the rapid intraoperative infusion of 5 per cent dextrose in lactated Ringer's solution in patient 1 (at an initial rapid rate of 30–50nl·kg^{-1}·h) would be expected to result in blood glucose levels similar to those observed (fig. 2). Five per cent dextrose containing solutions were never infused more rapidly than 2 ml·kg^{-1}·h in patient 2, and as a result, blood glucose levels never exceeded 300 mg/dl (fig. 3). However, hypoglycemia was avoided with this moderate infusion rate of 5 per cent dextrose in lactated Ringer's solution, while blood volume expansion was more appropriately accomplished with plain lactated Ringer's solution.

Continuous monitoring and control of plasma glucose levels utilizing an artificial pancreas during surgical removal of insulinoma has recently been described.[12,13] Use of these devices has the theoretical advantage of permitting rapid and essentially continuous measurement of blood glucose levels during tumor manipulation and resection. However, caution is needed in the interpretation of fluctuating intraoperative glucose levels, because although complete tumor removal may be followed by a rise in blood glucose levels in patients with insulinoma, the lack of reliability in using this technique solely to confirm total removal of hyperfunctioning beta islet cell lesions has been demonstrated.[12,14] Schwartz[12] has shown that of four patients undergoing surgery for suspected insulinoma, only one demonstrated the expected rise in blood glucose after tumor excision. In one of the other three patients, plasma glucose started to rise with the onset of operation, in another, blood glucose levels rose prior to complete tumor removal, and in the third, there was a 90-min delay before glucose levels increased. Thus, utilizing an artificial pancreas for continuous measurement of blood glucose levels is helpful, while relying on a rapid upswing in peripheral blood glucose levels as an indicator for complete tumor resection is not warranted.

Competition for binding sites by drugs which are

¶ Ames Division, Miles Laboratories, Inc., Elkhart, Indiana 46515.

strongly bound to plasma proteins can result in serious interactions.[15] Both thiopental and diazoxide are strongly protein bound.[16,17] Five independent binding sites for thiopental have been found on bovine serum albumin.[18] In contrast, diazoxide has been shown to have only one major binding site with at least four other binding sites of lesser affinity for the albumin molecule.[9] Competitive dislocation of thiopental and other barbiturates from binding sites on plasma proteins has been described for many drugs.[19,20] In a similar fashion, binding site interactions with diazoxide have been described for many highly protein bound drugs.[21-23] Decreased plasma protein binding has been demonstrated for both drugs in patients with uremia.[24,25]

Therefore, at least three mechanisms can be postulated to explain the sudden fall in blood pressure which we observed following administration of a relatively small dose of thiopental to patients pretreated with oral diazoxide. First, a bolus of thiopental could conceivably displace diazoxide from its protein binding sites, thereby releasing pharmacologically active (unbound) drug to attach to arterial smooth muscle receptor sites producing rapid vasodilation and resultant hypotension. Second, if diazoxide occupied thiopental binding sites or interfered with the binding of thiopental to serum proteins or tissue, exaggerated central nervous system and cardiovascular depression by a "small" dose of thiopental might be expected, since cardiovascular depression by thiopental has been related to the serum concentration of unbound drug.[26] In support of this theory, accelerated distribution and increased thiopental concentrations in the brain and heart have been demonstrated during periods of decreased plasma protein binding caused by pretreatment with sulfadimethoxine, a highly plasma protein-bound drug.[27] Third, a combination of the first two mechanisms would tend to have at least an additive effect on depression of blood pressure.

In summary, this paper reports the use of enflurane to anesthetize two patients with hyperinsulinism, utilizing preoperative oral diazoxide to protect against intraoperative hypoglycemia. Reducing the intraoperative infusion of 5 per cent dextrose containing solutions to 2 $ml \cdot kg^{-1} \cdot h$ appears to limit hyperglycemia, and finally, an untoward drug interaction between diazoxide and thiopental is proposed.

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