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. If tumor resection is necessary, we advocate preoperative radiation or chemotherapy in an attempt to shrink the tumor mass prior to administering general anesthesia.

REFERENCES


Anesthesia for Patients with Insulinoma Treatment with Oral Diazoxide

PATRICK G. BURCH, M.D.,* AND CHARLES H. McLESKEY, M.D.†

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. Fraser2 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,2,3 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 techniques3,4 and methoxyflurane.5 Colella and Vandam6 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·kg⁻¹·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

---

* Resident, Department of Anesthesia, Bowman Gray School of Medicine of Wake Forest University, Winston-Salem, North Carolina 27103.

† Assistant Professor, Department of Anesthesia, Bowman Gray School of Medicine of Wake Forest University, Winston-Salem, North Carolina 27103.

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

Address reprint requests to Dr. McLeskey: Assistant Professor, Department of Anesthesia, Bowman Gray School of Medicine of Wake Forest University, 300 S. Hawthorne Road, Winston-Salem, North Carolina 27103.

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. 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 temporomandibular 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 Etacaine® 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 H₂O (fig. 1A). 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 pH was 7.36, PaO₂ 133 torr, PaCO₂ 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 anesthesiain 1 per cent enfurane 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 Dextrositol® and by a DuPont Automatic Clinical Analyzer, were shown in figure 2.

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 anesthetic evaluation revealed no contraindications to general anesthesia. Premedication consisted of 30 ml Maalox®, po, and 5 per cent dextrose in water, 100 ml per hour, was given iv for eight hours intraoperatively. 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. 1B). 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 enfurane 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 one unit 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

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 Dextrositol® 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.

---

† 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 dextrose 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 90 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. Bourke⁶ 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 30–50 ml·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 Schwartz¹² 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 upsing in peripheral blood glucose levels as an indicator for complete tumor resection is not warranted.

Competition for binding sites by drugs which are
strongly bound to plasma proteins can result in serious
interactions. Both thiopental and diazoxide are strongly
protein bound. Five independent binding sites for
thiopental have been found on bovine serum albumin.
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. Competitive
dislocation of thiopental and other barbiturates from
binding sites on plasma proteins has been described for
many drugs. In a similar fashion, binding site inter-
actions with diazoxide have been described for many
highly protein bound drugs.
Decreased plasma protein binding has been demonstrated for both drugs in patients with uremia.

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 dia-
zoxide. First, a bolus of thiopental could conceivably
displace diazoxide from its protein binding sites, thereby
releasing pharmacologically active (unbound) drug to
attack 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. In support of this theory, accelerated distribution and
increased thiopental concentrations in the brain and
heart have been demonstrated during periods of de-
creased plasma protein binding caused by pretreatment
with sulfadimethoxine, a highly plasma protein-bound
drug.
Third, a combination of the first two mechanisms
would tend to have at least an additive effect on depres-
sion 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 intra-
operative hypoglycemia. Reducing the intraoperative in-
fusion of 5 per cent dextrose containing solutions to 2
ml·kg⁻¹·h⁻¹ appears to limit hyperglycemia, and finally,
undertow drug interaction between diazoxide and
thiopental is proposed.

REFERENCES

1. Harris S: Hyperinsulinism and dysinsulinism. JAMA 83:729-
733, 1924

2. Fraser RA: Hyperinsulinism under anesthesia in a case of islet
cell tumor of the pancreas. Anesthesia 18:3-8, 1963

3. Hargaden JJ, Ormston TOG: Anesthesia for excision of islet-

4. Bourke AM: Anaesthesia for the surgical treatment of hyperin-

5. Char P, Pandit SK, Kataria RN, et al: Anaesthetic management of
insulinoma. Anaesthesia 32:261-264, 1977

6. Colella JJ, Vandam LD: Diesel oil anaesthesia for a patient
with hyperinsulinism. ANESTHESIOLOGY 37:354-356, 1972

7. Fajans SS, Floyd JC: Diagnosis and medical management of

Surgery 16:289-305, 1944

9. Sellers EM, Koch-Weser J: Protein binding and vascular activity

10. Woodruff RE, Lewis SB, McLeskey CH, et al: Avoidance of sur-
gical hyperglycemia in diabetic patients. JAMA 244:160-168,
1980

normal and obese surgical patients. ANESTHESIOLOGY 51:250, 1979

toring and control of plasma glucose during operation for re-

cell during anesthesia for surgical removal of insulinoma. Anesth
Analg (Cleveland) 59:950-952, 1980

agement of functioning islet cell tumors of the pancreas. Ann
Surg 178:485-495, 1973

15. Davie IT: Specific drug interactions in anaesthesia. Anaesthesia
32:1000-1008, 1977

16. Sellers EM, Koch-Weser J: Binding of diazoxide and other ben-
zohiadiazines to human albumin. Biochem Pharmacol 23:553-
556, 1974

17. Becker KE: Gas chromatographic assay for free and total plasma
evels of thiopental. ANESTHESIOLOGY 45:656-660, 1976

18. Yoshikawa K, Loehning RW: Thiopental binding to serum al-
bumin. EXPERIENIA 21:376-377, 1965

19. Cosgro SI, Kerek SF: Enhancement of thiopentone anaesthesia by

20. Lasser EC, Elizondo-Marchel G, Cranke RC: Potentiation of pen-
tobarbital anaesthesia by competitive protein binding. ANES-
THESIOLOGY 24:665-671, 1963

albumin by diazoxide and ethacrynic, mafenamic, and nalidixic

22. Petro DJ, Vannucchi RC, Kulin HE: Diazoxide-diphenylhydantoin

23. Aynsley-Green, A: Enhancement by chlorpromazine of hypergly-

binding of diazoxide in uremia. Clin Pharmacol Ther 18:53-
57, 1975

25. Ghoneim MM, Pandya H: Plasma protein binding of thiopental
in patients with impaired renal or hepatic function. ANESTHE-
SIOLoy 42:545-549, 1975

26. Becker KE, Tonnnesen AS: Cardiovascular effects of plasma levels
of thiopental necessary for anesthesia. ANESTHESIOLOGY 49:197-
200, 1978

to plasma proteins. ANESTHESIOLOGY 45:635-639, 1976