

## **PRODUCT MONOGRAPH**

** PROGLYCEM<sup>®</sup>**

Diazoxide capsules, Merck Standard

Hyperglycemic Agent

Merck Canada Inc.  
16750 route Transcanadienne  
Kirkland, Québec H9H 4M7  
Canada  
[www.merck.ca](http://www.merck.ca)  
Control #: 176174

Date of Revision:  
April 30, 2015

**NAME OF DRUG**

PROGLYCEM<sup>®</sup>

Diazoxide capsules, Merck Standard

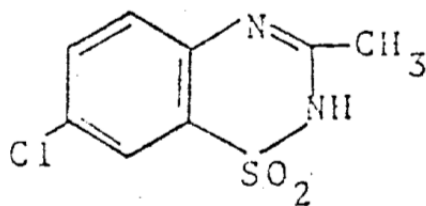
**THERAPEUTIC OR PHARMACOLOGICAL CLASSIFICATION**

Hyperglycemic Agent

**DESCRIPTION**

PROGLYCEM<sup>®</sup> (diazoxide) is a benzothiadiazine derivative. PROGLYCEM<sup>®</sup> Capsules contain 100 mg diazoxide, Ph.Eur..

**STRUCTURAL FORMULA AND CHEMISTRY**



Diazoxide is: 7-chloro-3-methyl-2H-1,2,4-benzothiadiazine 1,1-dioxide

Empirical Formula: C<sub>8</sub>H<sub>7</sub>ClN<sub>2</sub>O<sub>2</sub>S

Molecular Weight: 230.67

Melting Point: 327–329 °C

## **ACTION**

Diazoxide administered orally produces a prompt dose-related increase in blood glucose level, due primarily to an inhibition of insulin release from the pancreas and also to an extrapancreatic effect.<sup>19,28,35</sup>

The hyperglycemic effect begins within an hour and generally lasts no more than eight hours in the presence of normal renal function.

PROGLYCEM<sup>®</sup> decreases the excretion of sodium and water, resulting in fluid retention which may be clinically significant.<sup>1</sup>

Other pharmacologic actions of PROGLYCEM<sup>®</sup> include a possible mild change in blood pressure, increased pulse rate; increased serum uric acid levels due to decreased excretion; increased serum levels of free fatty acids; decreased chloride excretion; decreased para-aminohippuric acid (PAH) clearance with no appreciable effect on glomerular filtration rate.

The concomitant administration of a benzothiazide diuretic may intensify the hyperglycemic and hyperuricemic effects of PROGLYCEM<sup>®</sup>. In the presence of hypokalemia, hyperglycemic effects are also potentiated. PROGLYCEM<sup>®</sup> induced hyperglycemia is reversed by the administration of insulin or tolbutamide.<sup>8,9,15,16,21</sup>

The inhibition of insulin release by PROGLYCEM<sup>®</sup> is antagonized by alpha-adrenergic blocking agents. PROGLYCEM<sup>®</sup> is extensively bound (more than 90%) to serum proteins and is excreted by the kidneys. The plasma half-life following i.v. administration is  $28 \pm 8.3$  hours. Limited data on oral administration revealed a half-life of 24 and 36 hours in two adults. In four children aged four months to six years, the plasma half-life varied from 9.5 to 24 hours on long-term oral administration. The half-life may be prolonged following overdosage and in patients with impaired renal function.<sup>19,35,41,46</sup>

## **INDICATIONS AND CLINICAL USES**

PROGLYCEM<sup>®</sup> (oral diazoxide) is useful in the management of hypoglycemia due to hyperinsulinism associated with the following conditions:<sup>10,17,22,29,31,32,38,39,51,52</sup>

Adults: Inoperable islet cell adenoma or carcinoma or extrapancreatic malignancy.

Infants and Children: Leucine sensitivity,<sup>27,29,33,34</sup> islet cell hyperplasia, nesidioblastosis, extrapancreatic malignancy, islet cell adenoma, or adenomatosis.

PROGLYCEM<sup>®</sup> may be used pro-operatively as a temporary measure and post-operatively if hypoglycemia persists.

PROGLYCEM<sup>®</sup> should be used only after a diagnosis of hypoglycemia due to one of the above conditions has been definitely established. When other specific medical therapy or surgical management either has been unsuccessful or is not feasible, treatment with PROGLYCEM<sup>®</sup> should be considered.<sup>18</sup>

## **CONTRAINDICATIONS**

The use of PROGLYCEM<sup>®</sup> for functional hypoglycemia is contraindicated. The drug should not be used in patients hypersensitive to diazoxide or to other thiazides.

## **WARNINGS**

Usage in Pregnancy:

PROGLYCEM<sup>®</sup> should not be used in women of child-bearing age except in life-threatening situations. Diazoxide may pass into the breast milk of nursing mothers. Reproduction studies using the oral preparation in rats have revealed increased fetal resorptions and delayed

parturition, as well as fetal skeletal anomalies. Evidence of skeletal and cardiac teratogenic effects in rabbits has been noted with the intravenous administration. The drug has also been demonstrated to cross the placental barrier in animals and cause degeneration of the fetal pancreatic beta cells (See TOXICOLOGY).<sup>44,45</sup> Since there are no adequate data on fetal effects of this drug when given to pregnant women, safety in pregnancy has not been established.

When the use of PROGLYCEM<sup>®</sup> in pregnant women is considered, the indications should be limited to those specified above for adults (See INDICATIONS and CLINICAL USES) and the potential benefits to the mother must be weighed against possible harmful effects to the fetus.

The antidiuretic property of diazoxide may lead to significant fluid retention,<sup>1,2,3</sup> which in patients with compromised cardiac reserve may precipitate congestive heart failure. The fluid retention will respond to conventional therapy with diuretics.

It should be noted that concomitantly administered thiazides may potentiate the hyperglycemic and hyperuricemic actions of diazoxide (See DRUG INTERACTIONS and TOXICOLOGY).

Ketoacidosis and non-ketotic hyperosmolar coma have been reported in patients treated with recommended doses of PROGLYCEM<sup>®</sup> usually during intercurrent illness.<sup>50</sup> Prompt recognition and treatment are essential (See OVERDOSAGE) and prolonged surveillance following the acute episode is necessary because of the long drug half-life of approximately 30 hours. The occurrence of these serious events may be reduced by careful education of patients regarding the need for monitoring the urine for sugar and ketones and for prompt reporting of abnormal findings and unusual symptoms to the physician.

In the presence of hypokalemia, the hyperglycemic effects of diazoxide are potentiated.

Transient cataracts occurred in association with hyperosmolar coma in an infant and subsided on correction of the hyperosmolarity. Cataracts have been observed in several animals receiving daily doses of intravenous or oral diazoxide.

## **PRECAUTIONS**

Treatment with PROGLYCEM<sup>®</sup> should be initiated under close clinical supervision, with careful monitoring of blood glucose and clinical response until the patient's condition has stabilized.

This usually requires several days. If not effective in two or three weeks, the drug should be discontinued.

Prolonged treatment requires regular monitoring of the urine for sugar and ketones, especially under stress conditions, with prompt reporting of any abnormalities to the physician.

Additionally, blood sugar levels should be monitored periodically by the physician to determine the need for dose adjustment.

Tachycardia, palpitations, increased levels of serum uric acid, particularly in patients with hyperuricemia or a history of gout, thrombocytopenia with or without purpura, and neutropenia have been observed. Patients at risk should be monitored for these conditions and blood tests for hematological abnormalities should be conducted periodically (See ADVERSE REACTIONS).

Since the plasma half-life of diazoxide is prolonged in patients with impaired renal function, a reduced dosage should be considered. Serum electrolyte levels should also be evaluated for such patients.

The antihypertensive effect of other drugs may be enhanced by PROGLYCEM<sup>®</sup> and this should be kept in mind when administering it concomitantly with antihypertensive agents.

Because of protein binding, administration of PROGLYCEM<sup>®</sup> with coumarin or its derivatives may require reduction in the dosage of the anticoagulant, although there has been no reported evidence of excessive anticoagulant effect (See DRUG INTERACTIONS). In addition, PROGLYCEM<sup>®</sup> may possibly displace bilirubin from albumin; this should be kept in mind particularly when treating newborns with increased bilirubinemia.

## **ADVERSE REACTIONS**

### **Frequent and Serious:**

Sodium and fluid retention is most common in young infants and in adults. It may precipitate congestive heart failure in patients with compromised cardiac reserve and it usually responds to diuretic therapy (See DRUG INTERACTIONS).

### **Infrequent but Serious:**

Diabetic ketoacidosis and hyperosmolar non-ketotic coma may develop very rapidly.

Conventional therapy with insulin and restoration of fluid and electrolyte balance are usually effective if instituted promptly. Prolonged surveillance is essential in view of the long half-life of PROGLYCEM<sup>®</sup> (See OVERDOSAGE). Pulmonary hypertension in neonates, infants, and children has also been noted; in most reported cases, pulmonary hypertension improved upon discontinuation of diazoxide.

### **Other Frequent Adverse Reactions:**

Hirsutism of the lanugo-type, mainly on the forehead, back and limbs, occurs most commonly in children and women. It subsides on discontinuation of the drug.

Hyperglycemia or glycosuria may require reduction in dosage in order to avoid progression to ketoacidosis or hyperosmolar coma.

Gastrointestinal intolerance may include anorexia, nausea, vomiting, abdominal pain, ileus, diarrhea, transient loss of taste. Tachycardia, palpitations, increased levels of serum uric acid are common.

Thrombocytopenia with or without purpura may require discontinuation of the drug (See WARNINGS and PRECAUTIONS). Neutropenia is transient, is not associated with increased susceptibility to infection and ordinarily does not require discontinuation of the drug. Skin rash, headache, weakness and malaise may also occur.

Other Adverse Reactions which have been observed:

Cardiovascular and respiratory:

Hypotension occurs occasionally which may be augmented by thiazide diuretics given concurrently. A few cases of transient hypertension, for which no explanation is apparent have been noted. Chest pain has been reported rarely.

Hematologic:

Eosinophilia; decreased hemoglobin/hematocrit; excessive bleeding; decreased IgG.

Hepato-Renal:

Increased SGOT, alkaline phosphatase; azotemia, decreased creatinine clearance, reversible nephrotic syndrome, decreased urinary output, hematuria, albuminuria.

Neurologic:

Anxiety, dizziness, insomnia, polyneuritis, paresthesia, pruritus, extrapyramidal signs.

Ophthalmologic:

Transient cataracts, subconjunctival hemorrhage, ring scotoma, blurred vision, diplopia, lacrimation.

Skeletal, Integumentary:

Monilial dermatitis, herpes, advance in bone age; loss of scalp hair.

Systemic:

Fever, lymphadenopathy.

Other:

Gout, acute pancreatitis/pancreatic necrosis, galactorrhea, enlargement of lump in breast.



## **SYMPTOMS AND TREATMENT OF OVERDOSAGE**

An overdose of PROGLYCEM<sup>®</sup> causes marked hyperglycemia which may be associated with ketoacidosis. It will respond to prompt insulin administration and restoration of fluid and electrolyte balance. Because of the drug's long half-life (approximately 30 hours), the symptoms of overdose require prolonged surveillance for periods up to seven days, until the blood sugar level stabilizes within the normal range. One investigator reported successful lowering of diazoxide blood levels by peritoneal dialysis in one patient and by hemodialysis in another.

## **DRUG INTERACTIONS**

### Diuretics:

The hyperglycemic and hyperuricemic actions of diazoxide may be potentiated by the concomitant administration of thiazides or other commonly used diuretics.

### Coumarin Anticoagulants:

The administration of diazoxide to patients treated with coumarin and its derivatives may result in potentiation of hypoprothrombic action and may necessitate a decrease of anticoagulant dosage.

### Diphenylhydantoin:

The concomitant administration of diazoxide to diphenylhydantoin treated patients can cause loss of seizure control.

### Chlorpromazine:

The hyperglycemic action of diazoxide may be enhanced by concomitant administration of chlorpromazine.

## **DOSAGE AND ADMINISTRATION**

Patients should be under close clinical observation when treatment with PROGLYCEM<sup>®</sup> is initiated. The clinical response and blood glucose level should be carefully monitored until the patient's condition has stabilized satisfactorily; in most instances, this may be accomplished in several days. If administration of PROGLYCEM<sup>®</sup> is not effective after two or three weeks, the drug should be discontinued.

The dosage of PROGLYCEM<sup>®</sup> must be individualized based on the severity of the hypoglycemic condition and the blood glucose level and the clinical response of the patient. The dosage should be adjusted until the desired clinical and laboratory effects are produced with the least amount of the drug. Special care should be taken to assure accuracy of dosage in infants and young children.

### **Adults and Children:**

The usual daily dosage is three to eight (3–8) mg/kg, divided into two or three equal doses every eight or 12 hours. In certain instances, patients with refractory hypoglycemia may require higher dosages. Ordinarily, an appropriate starting dosage is 3 mg/kg/day, divided into three equal doses every eight hours. Thus, an average adult would receive a starting dosage of approximately 200 mg daily.

### **Infants and Newborns:**

The usual daily dosage is 8 to 15 mg/kg, divided into 2 or 3 equal doses every 8 or 12 hours. An appropriate starting dosage is 10 mg/kg/day, divided into 3 equal doses every 8 hours.

### **DOSAGE FORM**

PROGLYCEM<sup>®</sup> Capsules, 100 mg, opaque white capsules, blister packs of 100 capsules (5 strips of 20 capsules).

Medicinal ingredient: Diazoxide (100 mg)

Non-medicinal ingredients: Lactose monohydrate, magnesium stearate

Composition of the capsule shell: gelatin, titanium dioxide (E171).

### **STORAGE AND STABILITY**

Store at room temperature (15°C to 30°C).

### **PHARMACOLOGY**

#### Pharmacology in Animals:

Diazoxide administered intravenously, intraperitoneally and orally produces hyperglycemia in animals.<sup>11,13</sup>

Biochemical studies have shown that diazoxide suppresses insulin secretion and inhibits the conversion of cyclic 3', 5' AMP to 5' AMP. The hyperglycemia from diazoxide is also increased in potassium deficiency. Tolbutamide can reverse the insulin blockade of diazoxide. In the dog, diazoxide has been reported to increase the release and turnover of free fatty acids (FFA) and to increase coronary blood flow. Dogs receiving 160 mg/kg diazoxide intraperitoneally showed, in addition to hyperglycemia, statistically significant increases of the serum lactate and pyruvate levels. Alpha and beta adrenergic receptors have been variously involved with the metabolic effects of diazoxide.<sup>8,13,35,36,37</sup>

It has been shown that diazoxide antagonizes noradrenaline, angiotensin and serotonin induced contractions in aortic strips. Experiments suggest diazoxide exerts its vasodilator action by direct

competition for calcium receptor sites. It inhibits spontaneous uterine motility and abolishes ureteral peristalsis. Electrophysiological studies show diazoxide inhibits spontaneous electrical activity in isolated rabbit anterior mesenteric veins, in guinea pig tenia coli and in the stilbestrol treated rabbit uterus.<sup>26,40,47</sup>

Retention of water and electrolytes, particularly sodium has been observed following administration of diazoxide to dogs and other animals. The drug also limits the excretion of excessive quantities of water by water-loaded animals, exerting an antidiuretic action by several mechanisms, primarily direct action on the renal tubules.<sup>2,4</sup>

## TOXICOLOGY

### Acute Toxicity Studies:<sup>6</sup>

In acute toxicity studies, the LD<sub>50</sub> for oral diazoxide suspension is >5000 mg/kg in the rat, >522 mg/kg in the neonatal rat, between 1900 and 2572 in the mouse and 210 mg/kg in the guinea pig. Although the oral LD<sub>50</sub> was not determined in the dog, a dosage of up to 500 mg/kg was well tolerated.

### Subacute and Chronic Toxicity Studies:

In subacute oral toxicity studies, diazoxide at 400 mg/kg in the rat produced growth retardation, edema, increases in liver and kidney weights and adrenal hypertrophy. Daily dosages up to 1080 mg/kg for 3 months produced hyperglycemia, an increase in liver weight and an increase in mortality.

In dogs given oral diazoxide at approximately 40 mg/kg/day for one month, no biologically significant gross or microscopic abnormalities were observed. Cataracts, attributed to markedly disturbed carbohydrate metabolism, have been observed in a few dogs given repeated daily doses

of oral or intravenous diazoxide. The lenticular changes resembled those which occur experimentally in animals with increased blood sugar levels.

In chronic toxicity studies, rats given a daily dose of 200 mg/kg diazoxide for 52 weeks had a decrease in weight gain and an increase in heart, liver, adrenal and thyroid weights. Mortality in drug-treated and control groups was not different.

Dogs treated with diazoxide at dosages of 50, 100, 200 mg/kg/day for 82 weeks had higher blood glucose levels than controls. Mild bone marrow stimulation and increased pancreas weights were evident in the drug treated dogs; several developed inguinal hernias, one had a testicular seminoma and another had a mass near the penis. Two females had inguinal mammary swellings. The etiology of these changes was not established. There was no difference in mortality between drug-treated and control groups.

In a second chronic oral toxicity study, dogs given milled diazoxide at 50, 100 and 200 mg/kg/day had anorexia and severe weight loss, causing death in a few. Hematologic, biochemical and histologic examinations did not indicate any cause of death other than inanition. After one year of treatment, there is no evidence of herniation or tissue swelling in any of the dogs.

When diazoxide was administered at high dosages concomitantly with either chlorothiazide to rats or trichlormethiazide to dogs, increased toxicity was observed. In rats, the combination was nephrotoxic; epithelial hyperplasia was observed in the collecting tubules. In dogs, a diabetic syndrome was produced which resulted in ketosis and death. Neither of the drugs given alone produced these effects.

#### Reproduction Studies:

Pregnant rats were treated with oral diazoxide at dose levels of 50, 100, 200 and 300 mg/kg.

Each dose level group was subdivided in two subgroups, one receiving the drug on a specified

day basis, from day 6 to day 10 of pregnancy, the other group being treated daily from day 6 to day 16. There were no significant clinical or autopsy findings. Pre-natal mortality was not different from control group mortality. The body weights of the offspring were unaltered as was the litter size. In a litter of 14 from a dam having received 300 mg/kg at day 7, one offspring was found to have the ulna of the left foreleg missing and only two toes. The ossification centers of the sternum were split and disorganized and it had an extra rib.

In another reproduction study, rats receiving diazoxide orally at 30 mg/kg and 100 mg/kg daily dose levels for 14 days prior to mating and continuing through pregnancy and lactation. No differences between groups (including a control group) could be found in behaviour, appetite or appearance. The litter sizes were not significantly different and although parturition was delayed to the 23rd day in 44% (7/16) of the 100 mg/kg group and 31% (5/16) of the 30 mg/kg group vs. 20% (3/15) of the control group, these differences did not reach a statistically significant level. Conception rate was not significantly different between the 3 groups. At birth, the offspring weights were not different statistically, but at day 4, the 30 mg/kg group weighed significantly more than controls. On day 21, the 100 mg/kg group was found to weigh significantly less than controls while the 30 mg/kg group was no longer different from the control group.

To determine the effect of diazoxide during late pregnancy, the drug was given intravenously to rats daily from day 18 to day 22 (inclusive) to gestation. Dose levels were 10 mg/kg, 30 mg/kg and 100 mg/kg. A saline control group was used. Each group contained 20 animals. No difference was observed between the control and 10 mg/kg group of dams. At 30 mg/kg, one rat died but all survivors had normal behaviour and appearance. All animals in the 100 mg/kg group died after the second or third injection. There was no significant difference in the number of offspring between controls and the 10 mg/kg and 30 mg/kg groups. The four day neonatal survival rates were lower in the 10 mg/kg and 30 mg/kg groups relative to controls but the

difference was attributed to agalactia occurring in two dams of the 30 mg/kg group and one of the 10 mg/kg group. Gross external and visceral examination of the offspring revealed no abnormalities.

A study was made to determine the effect in the rabbit of intravenous diazoxide at dose levels of 7 to 21 mg/kg administered once daily from day 6 to day 18 of gestation. Analysis of variance showed no significant difference in litter size between the 3 treatments (7, 21 mg/kg and control, 13 individuals per group). High dose offspring weighed significantly less than controls. Among the 88 offspring of the 21 mg/kg group, one major abnormality occurred in one of the litters. It consisted of a dead fetus with ectocardia; it also had severe cardiac malformation, no radius in both front legs and only three metacarpals. Its five littermates were normal. Among the other offspring in the 21 mg/kg group, three were found to have an abnormal distribution of sternal ossification nuclei.

#### Placental Transfer:

There is scientific evidence from experiments carried out in sheep and goats that diazoxide crosses the placenta. Diazoxide blood levels in the fetuses were approximately half those found in maternal blood while fetal blood glucose levels rose significantly within 30 minutes of administration. Histologic examination of the pancreas of the newborn showed vacuolization degeneration of the islet cells of Langerhans.<sup>44,45</sup>

According to Finnerty, there was no unusual incidence of prematurity, perinatal mortality or abnormality in the children born to 75 eclamptic or pre-eclamptic women treated with diazoxide intravenous for hypertension. In 13 (17.3%) of these cases, the administration of diazoxide was followed by a cessation of labour which responded to oxytocics. Published reports also confirm that the use of diazoxide in the treatment of eclampsia is not incompatible with the delivery of normal infants.<sup>7,20,25,42</sup>

In a Milner<sup>48</sup> study, four infants were born to women treated with oral diazoxide for the last 19 to 69 days of pregnancy. Maternal plasma levels of diazoxide in the five days before delivery were related to the intake of the drug and varied between 11 and 43 µg/mL. At delivery, the umbilical plasma diazoxide level was lower than that in the mother and was 6.5 to 24 µg/mL. At the age of 24 hours, the plasma diazoxide level in the infants had not altered appreciably. Diazoxide was present in the amniotic fluid and was excreted in the urine in the first week of life. Urinary diazoxide excretion was greatest on days two and three and had fallen to low or undetectable levels by 6 and 7. No effect of diazoxide was noted on the blood pressure or blood sugar levels of the infants in the first 24 hours. The glucose tolerance of two of the infants was normal at 24 hours but that of the other two whose mothers had diabetes, was impaired. Each of the infants developed alopecia and one had hypertrichosis lanuginosa. Abnormal hair growth was first noted at the age of one week and persisted when the infants were last seen at the age of five months to one year. The bone age of three was normal at a chronological age of five to seven months but the fourth, when aged one year, had retarded ossification in the wrist. No abnormalities were detected in blood counts, immunoglobulin levels, or ocular development.



**SELECTED BIBLIOGRAPHY**

1. Conway, J., et al.: Hemodynamic Effects of a Sodium-Retaining Thiazide Derivative. Paper Presented at the 34th Ann. Meet. Central Soc. Clin. Res., Chicago, Ill. Nov. 3-4, 1961. Abs. J. Lab. Clin. Med. 58:809-10, Nov. 1961.
2. Taylor, R.M., et al.: Renal Pharmacology of an Anti-Hypertensive Des-Sulfamnyl Benzothiadiazine. Paper presented Amer. Soc. Pharm. Exp. Ther., U. Rochester, Rochester, N.Y., Aug. 29-Sept. 1, 1961. Abs. Pharmacologist 3:58, Fall, 1961.
3. Hutcheon, D.E., et al.: Diazoxide in the Treatment of Hypertension. J. New Drug. 2:292-91, Sept.-Oct. 1962.
4. Milton, R.M., et al.: Further Studies on the Renal Pharmacology of Diazoxide (SRG 95213). Fed. Proc. 21:432, Mar.-Apr. 1962.
5. Okun, R., et al.: Use of Diazoxide with Trichlormethiazide for Hypertension. Arch. Int. Med. 112:882-88, Dec. 1962.
6. Rubin, A.A., et al.: Pharmacology of Diazoxide, An Antihypertensive Non-diuretic Benzothiadiazine. J. Pharmacol. Exp. Ther. 136:344-52, 1962.
7. Finnerty, F.A. Jr.: How to Treat Toxemia of Pregnancy. GP 27:116-21, Jan. 1963.
8. Rowe, G.G.: The Systemic and Coronary Hemodynamic Effects of Diazoxide. Amer. Heart J. 66:636-43, Nov. 1963.
9. Wolff, P.W., et al.: Aetiological Factors in Benzothiadiazine Hyperglycaemia. Letters to Editor. Lancet 2:69, July 13, 1963.
10. Drash, A., et al.: Drug Therapy in Leucine-Sensitive Hypoglycemia. Metabolism. 13:487-92, 1964.
11. Gulbenkian, A., et al.: Diazoxide Hyperglycemia and Free Fatty Acid Mobilization. Abs. Fed. Proc. 23:542 (2643), Part I, Mar.-Apr. 1964.
12. Kvam, D.C., et al.: Studies on Diazoxide Hyperglycaemia. Diabetes 13:639-44, Nov.-Dec. 1964.
13. Tabachnick, I.I.A., et al.: The Effect of a Benzothiadiazine, Diaoxide, on Carbohydrate Metabolism. Diabetes 13:408-18, July-Aug. 1964.
14. Taylor, R.M., et al.: Studies on the Renal Pharmacology of Diazoxide, An Anti-diuretic Benzothiadiazine. J. Pharmacol. Exp. Thor. 144:284-92, May 1964.
15. Wolff, F.: Diazoxide Hyperglycaemia and its Continued Relief by Tolbutamide. Lancet 1:309-10, Feb. 8, 1964.

16. Wolff, F.W., et al.: Further Observations Concerning the Hyperglycemic Activity of Benzothiadiazines. *Diabetes* 13:115-21, Mar.-Apr. 1964.
17. Marks, V., et al.: Hyperinsulinism due to Metastasizing Insulinoma Treatment with Diazoxide. *Proc. Roy. Soc. Med.* 58:577-78, Aug. 1965.
18. Drash, A., et al.: Diazoxide-Induced Diabetes Mellitus in a Hypopituitary Dwarf. *Diabetes* 15:319-22, May 1966.
19. Fajans, S.S., et al.: Benzothiadiazine Suppression of Insulin Release from Normal and Abnormal Islet Tissue in Man. *J. Clin. Invest.* 45:481-92, Apr. 1966.
20. Finnerty, F.A. Jr.: Clinical Hemodynamics and Pharmacodynamics of Toxemia. *Ob/Gyn. Dig.* 8:49-51, 54-57, 60, 61, May 1966.
21. Graber, A.L., et al.: Clinical Use of Diazoxide and Mechanism for its Hyperglycemic Effects. *Diabetes* 15:143-8, Mar. 1966.
22. Hunt, P.S.: Adult Hypoglycaemia Associated with Neoplasia. A Report of Three Cases with a Note on the Use of Diazoxide. *Aust. New Zeal. J. Surg.* 35:295-99, May 1966.
23. Javier, Z., et al.: Leucine-Sensitive Hypoglycemia. Treatment with Zinc Glucagon and Corticosteroids. *Amer. J. Med.* 41:638-44, Oct. 1966.
24. Baker, L., et al.: Diazoxide Treatment of Idiopathic Hypoglycemia of Infancy. *J. Pediat.* 71:494-505, Oct. 1967.
25. Finnerty, F.A. Jr.: Drug Treatment of Toxemia of Pregnancy. *Mod. Med.* 35:68-75, Feb. 27, 1967.
26. Boyarsky, S.: The Effect of Diazoxide - An Anti-Diuretic Thiazide on Ureteral Peristalsis. *Cln. Res.* 16:474, Oct. 1968.
27. Ehrlich, R.M., et al.: Diazoxide in the Management of Hypoglycemia in Infancy and Childhood. *Amer. J. Dis. Child.* 117:411-16, Apr. 1969.
28. Fajans, S.S., et al.: Further Studies on Diazoxide Suppression of Insulin Release from Abnormal and Normal Islet Tissue in Man. *Ann. New York Acad. Sci.* 150:Art. 2, 261-80, Apr. 11, 1968.
29. Goodman, H.G.: The Use of Diazoxide in Hyoglycemia in Childhood *Ann. New. York Acad. Sci.* 150:Art. 2, 367-72, April 11, 1968.
30. Goldner, H.: Summary, *Ann. New York Acad. Sci* 150:Art. 2, 464-67, Apr. 11, 1968.

31. Graber, A.L., et al.: Clinical Use of Diazoxide and Studies on the Mechanism of its Hyperglycemic Effects in Man. Ann. New York Acad. Sci. 150:Art.2, 303-08, Apr. 11, 1968.
32. Green, O.C., et al.: The Clinical Use of Diazoxide in Leucine-Sensitive Hypoglycemia. Ann. New York Acad. Sci. 150:Art. 2, 356-66, Apr. 11, 1968.
33. Koblenzer, P.J., et al.: Hypertrichosis Lanuginosa Associated with Diazoxide Therapy in Pre-pubertal Children - A Clinico-pathologic Study. Ann. New York Acad. Sci. 150:Art. 2, 373-82, Apr. 11, 1968.
34. Rennert, O.M.: Diazoxide in von Gierke's Disease. Arch. Dis. Child. 43:358-61, 1968.
35. Seltzer, H.S., et al.: Insulin Secretory Blockade by Benzothiadiazines and Catecholamines - Reversal by Sulfonylureas. Ann. New York Acad. Sci. 150:Art. 2, 309-21, Apr. 11, 1968.
36. Senft, G.: Biochemical Aspects of the Hyperglycemic Action of Diazoxide. Ann. New York Acad. Sci. 150:Art. 2, 242-55, Apr. 11, 1968.
37. Tabachnick, I.I.A., et al.: Mechanism of Diazoxide Hyperglycemia in Animals. Ann. New York Acad. Sci. 150:Art. 2, 204-18, Apr. 11, 1968.
38. Tucker, W.R., et al.: Studies in a Patient with Retroperitoneal Sarcoma Associated with Severe Hypoglycemia. Ann. New York Acad. Sci. 150:Art. 2, 395-405, Apr. 11, 1968.
39. Wegienka, L.C.: Clinical Experience with Diazoxide. Ann. New York Acad. Sci. 150:Art. 2, 373-82, Apr. 11, 1968.
40. Wohl, A.J.: The Role of Calcium in the Mechanism of the Anti-hypertensive Action of Diazoxide. Life Sci. 7:381-87, Apr. 1, 1968.
41. Sellers, E.N., et al.: Protein Binding and Vascular Activity of Diazoxide. New Eng. J. Med. 281:1141-45, Nov. 20, 1969.
42. Finnerty, F.A. Jr.: Treatment of Acute Hypertension in Pregnancy. Ob./Gyn. Dig. 12:30-37, Apr. 1970.
43. Spitzer, J.J., et al.: Effects of Diazoxide on Myocardial Free Fatty Acid Metabolism and Hemodynamics in the Dog. Arch. Int. Pharmacodyn. 184:405-14, Apr. 1970.
44. Boulos, B.M.: Studies Show Diazoxide Crosses Placenta. J.A.M.A. 212:720, May 4, 1970.
45. Boulos, B.M., et al.: Placental Transfer of Diazoxide and its Hazardous Effect on the Newborn. J. Clin. Pharmacol. 11:206-10, May-June 1971.

46. Pruitt, A.W., et al.: A Comparison of the Binding of Drugs to Adult and Cord Plasma. *Eur. J. Clin. Pharmacol.* 4:59-62, Dec. 1971.
47. Rhodes, H.J.: The Action of Diazoxide on Isolated Vascular Smooth Muscle Electrophysiology and Contraction. *Canad. J. Physiol. Pharmacol.* 49:276-87, Apr. 1971.
48. Milner, R.D.G., et al.: Effects of Fetal Exposure to Diazoxide in Man. *Arch. Dis. Child.* 47:537-543, 1972.
49. Frerichs, H. et al.: Pharmacotherapy of Hormone-Secreting Tumours. *Clin. Gastroenterol.* 3:721-32, Sept. 1974 (Review).
50. Savage, J.M. et al.: Hyperosmolar Non-Ketotic Hyperglycaemia during Oral Diazoxide Therapy of Prolonged Hyperglycaemia in Infancy. *Ulster Med. J.* 46:123-26, 1977.
51. Paulissian, R.; Diazoxide, In. *Anesthesiol. Clin.* 16:201-37, 1978 (comprehensive review).
52. Medical Letter: Oral Diazoxide for Hypoglycemia. No. 20:110-11, Dec. 15, 1978.