

Orinase Diagnostic®

tolbutamide for injection, USP



Pharmacia
&Upjohn

For intravenous use only

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injection, USP

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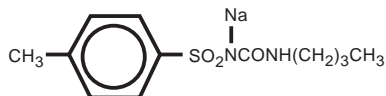
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DESCRIPTION

ORINASE DIAGNOSTIC Sterile Powder contains tolbutamide sodium which is a white to off-white, practically odorless, crystalline powder, having a slightly bitter taste. It is freely soluble in water, soluble in alcohol and in chloroform, very slightly soluble in ether.

Each vial contains the equivalent of 1.0 g of free tolbutamide, present as 1.081 g of the sodium salt of 1-Butyl-3-(*p*-tolylsulfonyl)urea. The 81 mg of sodium present should not interdict the diagnostic use of this preparation in patients maintained on salt-poor regimens.

The structural formula is represented below:



The chemical name for tolbutamide sodium is 1-Butyl-3-(*p*-tolylsulfonyl)urea monosodium salt C₁₂H₁₇N₂NaO₃S.

CLINICAL PHARMACOLOGY

The prompt decrease in blood glucose in normal individuals is associated with a prompt increase in serum insulin levels, as determined by immunoassay, which rise from a fasting mean value of 19 μ U per mL to a peak mean value of approximately 40 μ U per mL (range 27 to 89) 20 minutes after injection. In patients with functioning islet cell adenoma, tolbutamide sodium has a marked and prolonged blood glucose lowering effect associated with an excessive, prompt rise in serum insulin (118 to 1,055 μ U/mL), resulting in a marked and prolonged blood glucose effect (Figure 1).

INDICATIONS AND USAGE

ORINASE DIAGNOSTIC Sterile Powder is indicated for use as an aid in the diagnosis of pancreatic islet cell adenoma.

The difficulties of differential diagnosis of spontaneous hypoglycemia have made clear the need for more definitive diagnostic procedures in order to avoid subtotal pancreatic resection in patients in whom surgery is not indicated. Fully 80% of cases of spontaneous hypoglycemia result from one of three causes: functional hyperinsulinism, organic hyperinsulinism, and hepatogenic hypoglycemia. Functional hyperinsulinism is by far the most common form of the disorder, accounting for 70% of all cases. This form of hyperinsulinism is believed to be basically a psychosomatic disorder associated with an imbalance of autonomic nervous system influences on blood glucose control. The management of such patients is dietary, as is that of patients with hepatogenic hypoglycemia. These must be distinguished from organic hyperinsulinism due to pancreatic islet cell adenoma which requires surgery.

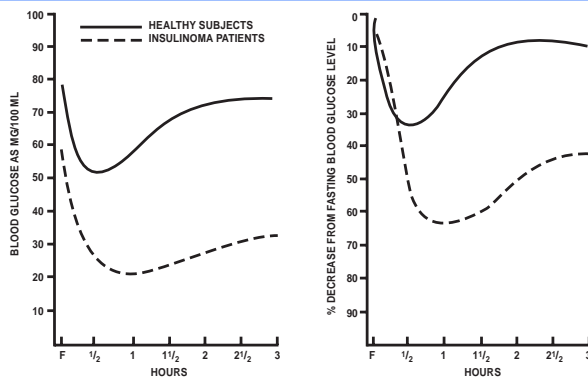


Figure 1

Effect of intravenous injection of ORINASE DIAGNOSTIC on blood glucose in healthy subjects and insulinoma patients.

Patients with functioning insulinomas exhibit hypoglycemic responses to intravenously administered tolbutamide sodium which are sufficiently distinctive to make this drug a valuable adjunct in the diagnosis of functioning insulinomas.

It will be noted from Figure 1 that the administration of 1.0 g of tolbutamide sodium to healthy subjects results in a rapid fall in blood glucose levels for 30 to 45 minutes, followed by a secondary rise of the blood glucose concentration into the normal range in the ensuing 90 to 180 minutes. The initial hypoglycemia results from the rapid release of insulin from the pancreatic beta cells, while the secondary rise is due to activation of counter-regulatory factors. In contrast, patients with insulinomas were found to exhibit tolbutamide induced blood glucose decreases of greater magnitude than healthy persons. Of greater significance than the magnitude of blood glucose fall in these patients is the persistence of the hypoglycemia for three hours after the administration of ORINASE DIAGNOSTIC. It is this phenomenon of persistent tolbutamide induced hypoglycemia for three hours rather than degree of blood glucose decrease which is of importance in the diagnosis of pancreatic islet cell adenomas. False positive responses have been observed in a few patients with liver disease, alcohol hypoglycemia, idiopathic hypoglycemia of infancy, severe under nutrition, azotemia, sarcoma, and other extrapancreatic insulin producing tumors.

CONTRAINDICATIONS

Because of the lack of data to establish ideal dosage and the inability to interpret results, use of ORINASE DIAGNOSTIC Sterile Powder is not recommended in children.

The test should not be performed on persons who have previously shown allergy to tolbutamide or related sulfonylureas.

WARNINGS

Severe and prolonged hypoglycemia following oral administration of tolbutamide has been reported in patients suffering from severe liver disease and severe renal disease.

Severe hypoglycemic symptoms may develop during the test, particularly in patients with fasting blood glucose levels in the hypoglycemic range. If they occur, the test should be terminated immediately by intravenously injecting 12.5 to 25 g of glucose in a 25 to 50% solution.

PRECAUTIONS

General: Although the hypoglycemic symptoms produced by this test dose are usually not severe, certain nondiabetics may develop moderate to severe symptoms. To avoid this occurrence, the diagnostic test should be terminated by the oral administration of carbohydrate immediately after the 30-minute blood sample has been withdrawn.

It is essential that only a true glucose procedure (Somogyi-Nelson, Modified Folin-Wu, AutoAnalyzer*, or glucose oxidase) be used to determine blood glucose in order to eliminate highly variable amounts of nonglucose reducing substances as a major source of error.

As with all intravenous injections, epinephrine and other resuscitative drugs should be at hand to administer in the event of anaphylaxis.

Because hypoglycemia of considerable magnitude can occur in certain nondiabetics, it would be wise to routinely terminate each test immediately upon withdrawal of the 30-minute blood sample by the oral administration of carbohydrate, especially in the testing of persons with atherosclerosis.

Drug interactions: Certain drugs may potentiate the hypoglycemic action of tolbutamide. These include dicumarol, phenylramidol, salicylates, sulfonamides, oxyphenbutazone, phenylbutazone, probenecid, monoamine oxidase inhibitors, beta-adrenergic blocking agents, and chloramphenicol. There is a danger of both increased and/or prolonged hypoglycemia if these drugs are used together.

Concomitant ingestion of salicylates, sulfonamides, oxyphenbutazone, phenylbutazone, probenecid, and monoamine oxidase inhibitors may interfere with results of a tolbutamide tolerance test.

Response to tolbutamide is diminished in patients on therapy with beta-adrenergic blocking agents.

Drug-Laboratory test interactions: On very rare occasions, urine containing the tolbutamide metabolite may give a false positive reaction for albumin by the usual test (acidification after boiling) since this procedure causes the metabolite to precipitate as flocculent particles. This problem may be circumvented by the use of bromphenol reagent strips.

Carcinogenesis, mutagenesis, impairment of fertility: Bioassay for carcinogenicity was performed in both sexes of rats and mice following tolbutamide ingestion for 78 weeks. No evidence of carcinogenicity was found.

Tolbutamide has also been demonstrated to be nonmutagenic in the Ames salmonella/mammalian microsome mutagenicity test.

Pregnancy: Teratogenic Effects. Pregnancy Category C. Tolbutamide sodium has been shown to be teratogenic in rats given doses 25 to 100 times the human dose. In some studies, pregnant rats given high doses of tolbutamide have shown increased mortality in offspring and ocular and bony abnormalities. Repeat studies in other species (rabbits) have not demonstrated a teratogenic effect. There are no adequate and well controlled studies in pregnant women. ORINASE DIAGNOSTIC Sterile Powder is not recommended for the treatment of pregnant diabetic patients. Serious consideration should also be given to the possible hazards of the use of ORINASE DIAGNOSTIC in women of childbearing age and potential who might become pregnant while using the drug.

Nonteratogenic Effects: Prolonged severe hypoglycemia (four to ten days) has been reported in neonates born to mothers who were receiving a sulfonylurea drug at the time of delivery. This has been reported more frequently with the use of agents with prolonged half lives. Use of the drug in pregnant patients is not recommended.

Nursing mothers: Tolbutamide is excreted in small amounts in the breast milk of nursing mothers. Because of the potential for serious adverse reac-

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tions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric use: See CONTRAINDICATIONS.

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Rarely a patient may experience a mild pain in the shoulder or slight burning sensation along the course of an arm vein during the intravenous injection.

(continued below)

tion. Such pain which lasts no more than 2 to 3 minutes, is attributed to venospasm and may be obviated by administering the test solution over a period of no less than two, preferably, three minutes. Thrombophlebitis with thrombosis of the injected vein has been found to occur in a small percentage of patients (0.8 to 2.4%). This is usually painless, detectable only by careful palpation and may not appear for one or two weeks after injection. No sequelae have been noted. The vein gradually shrinks or recanalizes.

OVERDOSAGE

Overdosage of sulfonylureas, including ORINASE DIAGNOSTIC Sterile Powder, will produce symptoms of hypoglycemia. The symptoms produced may be mild, consisting only of sweating, trembling, weakness, fatigue, nervousness, hunger, or nausea. They may be more severe, including lethargy, confusion, stupor, loss of consciousness, or coma. Seizures may occur with marked hypoglycemia. In these cases, laboratory evaluation will reveal a low blood glucose level.

Mild symptoms of hypoglycemia without loss of consciousness should be treated aggressively with oral glucose and appropriate adjustment in drug dosage and meal patterns. Monitoring should continue until such time as the patient is out of danger. Severe hypoglycemic reactions with coma, seizure, or other neurological impairment are rare, but constitute medical emergencies and require immediate hospitalization. If hypoglycemic coma is suspected or diagnosed, the patient should be given a rapid intravenous injection of concentrated (50%) dextrose solution. This can be repeated as needed. This should be followed by a continuous infusion of a more dilute (10%) dextrose solution at a rate which will maintain the blood glucose level above 100 mg/dL. Patients should be closely monitored in the hospital for a minimum of 24 to 48 hours, since hypoglycemia may recur after apparent clinical recovery.

Overdosage with sulfonylurea drugs has not been reported to be responsive to either peritoneal dialysis or hemodialysis. The experience, however, is quite limited.

The oral LD₅₀ of tolbutamide in the rat was greater than 2344 mg/kg.

The dose of medication which may cause hypoglycemia in humans is variable. In some individuals, usual therapeutic doses have been known to cause symptomatic hypoglycemia.

DOSAGE AND ADMINISTRATION

(Fajans Test)

1. The patient should receive a high carbohydrate diet of from 150 to 300 g daily for at least three days prior to the test.
2. On morning of test, after an overnight fast, withdraw a fasting blood specimen.
3. Inject entire volume (20 mL) of tolbutamide sodium solution intravenously at a constant rate over a two to three minute period.
4. Withdraw blood specimens at the following intervals (in minutes) after the midpoint of the injection: 20, 30, 45, 60, 90, 120, 150, and 180. Of greater significance than the magnitude of blood glucose fall in these patients is the persistence of the hypoglycemia for three hours after the administration of tolbutamide sodium. The determination of serum insulin levels before, and at 10, 20, and 30 minutes after the intravenous administration of the drug as described below, provides a specific and safer test for insulinoma. It also permits the performance of the test in the presence of moderate fasting hypoglycemia, since interpretation is not based on the decline of the blood glucose.
5. Blood glucose determinations are made by the true glucose procedures. The procedure is terminated with a feeding of readily assimilable carbohydrate or breakfast.

Interpretation of results—Healthy subjects: A decrease to a blood glucose of 38 to 79% of the fasting level may be expected. At 90 to 120 minutes a level of from 78 to 100% of initial level may be seen. Similar responses are to be found in patients with functional hyperinsulinism.

Insulinoma patients: Minimum blood glucose levels of 17 to 50% of fasting values are seen. In the 90 to 180 minute interval, levels are in the range of 40 to 64%. Some patients with liver disease may show the same type of blood glucose response as do patients with insulinomas. Therefore, appropriate laboratory and clinical tests must be employed to distinguish between these two conditions.

Use with serum insulin determination in insulinoma patients: If a method of assay for serum insulin is available, the test for insulinoma may be made shorter and more specific. Using an immunoassay, serum insulin levels rose to peak values of 160 to 300 μ U per mL in five subjects with proven insulinoma (normal range 27 to 89). In four of the subjects the peak was attained in 20 to 30 minutes, the first determination being performed at 60 minutes in the fifth subject. Excessive increases in plasma insulin of five patients with insulinomas (range 118 to 1,055, mean 486 μ U/mL) were also found by immunoassay.

The serum insulin response returned to normal after the removal of the insulinoma in two other patients.

Accordingly, the determination of serum insulin levels before, and at 10, 20, and 30 minutes after the intravenous administration of the drug described above, provides a specific and safer test for insulinoma, and permits the performance of the test in the presence of moderate fasting hypoglycemia, since interpretation is not based on the decline of the blood glucose. The test may be terminated after the 30-minute specimen by the feeding of carbohydrate as described above.

Preparation of tolbutamide sodium solution

1. Remove the protective metal cap from the vial and sterilize the top of the rubber stopper with a suitable germicide.
2. Using a 20 mL syringe, inject 20 mL of Sterile Water for Injection into the vial containing ORINASE DIAGNOSTIC Sterile Powder.
3. Shake thoroughly until solution is complete.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

STORAGE CONDITIONS

Store unconstituted product at controlled room temperature 20° to 25°C (68° to 77°F) [see USP].

Use immediately after reconstitution (within one hour) but only if solution is complete and clear.

HOW SUPPLIED

ORINASE DIAGNOSTIC Sterile Powder is available in vials containing 1 g tolbutamide, present as 1.081 g tolbutamide sodium—NDC 0009-0741-02. When necessary, pH is adjusted with sodium hydroxide.

Rx only

*TECHNICON CORPORATION, TARRYTOWN, NEW YORK

Pharmacia & Upjohn Company • Kalamazoo, Michigan 49001, USA

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