BRIEF NOTES AND COMMENTS

Prolonged and Recurrent Tolazamide-induced Hypoglycemia

Report of a Case

Juan A. Rull, M.D., and Miguel Lennhoff, M.D., Mexico City

SUMMARY

A case of recurrent hypoglycemic coma precipitated by tolazamide (Tolinase) at therapeutic dosage is here reported. The patient, an elderly woman with diabetes and renal failure, experienced several episodes of profound hypoglycemic coma, the last one forty-eight hours after withdrawal of the sulfonylurea. With this report, cases of prolonged hypoglycemia have been described with all currently available hypoglycemic sulfonylureas. DIABETES *16*: 352-53, May, 1967.

In the last ten years several cases of severe hypoglycemia produced by therapeutic administration or accidental ingestion of sulfonylurea derivatives have been reported.

In 1965, Bergman[1] collected thirty-seven cases of hypoglycemic coma (twenty-four in diabetics) caused by the ingestion of chlorpropamide, tolbutamide, carbutamide or metahexamide, and in 1966, Alexander and Dougherty[2,3] reported three cases of acetohexamide-induced hypoglycemia. No case has been described, however, in relation to tolazamide (N-1-hexahydro-1-acepinyl-N-p-tolyl-sulfonyl urea) ingestion. Accordingly, a case of prolonged and recurrent hypoglycemic coma associated with the use of tolazamide at therapeutic dosage is presented here.

CASE REPORT

This sixty-one-year-old white female developed overt diabetes mellitus in 1947 and received irregular treatment with insulin and diet until 1955. From then until 1962 she was treated with insulin mixtures and occasionally with phenformin (DBI). In 1962, while receiving 105 units of intermediate and long-acting insulins, her requirements started to drop, and treatment was changed to tolbutamide (0.75 to 3.0 gm. daily) and then to tolazamide (0.250 to 0.375 gm. daily).

In 1955, retinopathy and neuropathy were found. During the following years she had several episodes of urinary infection with X-ray findings suggestive of pyelonephritis in 1957. Proteinuria appeared in 1961, edema and hypertension in 1962 and nitrogen retention in 1963. In 1965, she had an episode of congestive heart failure.

She had been on 750 mg. daily of tolazamide for several months when, on April 13, 1966, she suddenly lost consciousness and had profuse sweating (retrospectively, a history of anorexia, vomiting and diarrhea was obtained). Upon admission, she was found to be in coma, with stertorous breathing, palpebral edema and paleness. Blood pressure was 200/100 mm., pulse 94 and temperature 37° C. There were no signs of dehydration or neurologic focalization.

Blood sugar was 34 mg. per 100 ml., urea 264 mg. per cent, and creatinine 11.6 mg. per cent. Treatment was initiated with subcutaneous glucagon and intravenous 5 per cent glucose solution. The patient recovered consciousness fifteen minutes later. Tolazamide was discontinued, and she was discharged nine hours later. The following day, she was admitted again after being in coma for twelve hours. There was pupillary areflexia, and bilateral Babinsky signs, coarse pumonary rales, jugular venous engorgement, and peripheral edema were noted. Blood sugar was 39 mg. per 100 ml. The same treatment was repeated and the patient was conscious after ten minutes. A day later, blood sugars fluctuated between 47 and 129 mg. in spite of parenteral glucose administration but without clinical manifestations of hypoglycemia.

TABLE 1

Hypoglycemic comas due to sulfonylureas in diabetic patients

Sulfonylurea	Number of cases	References	Type of coma*		
			Short	Prolonged	Intermittent
Tolbutamide	15	1,4,5,6,9	5	1	3
Carbutamide	12	1,4,17	1	—	3
Acetohexamide	3	2,3	1	2	—
Chlorpropamide	17	1,8,15,16,18,19	—	3	9
Tolazamide	1	—	0	0	1
Total	48	—	7	6	16

*The type of coma is not described in all cases.

From the Diabetes Clinic, Instituto Nacional de la Nutrición, México, D.F., México.

DISCUSSION

Cases of severe hypoglycemia have been described with almost all the sulfonylurea derivatives: tolbutamide, carbutamide, chlorpropamide, metahexamide, acetohexamide and now tolazamide (table 1).[1-6,15-19]

Although information is lacking regarding some sulfonylurea compound such as tolcyclamide or some other hypoglycemic sulfonamides such as glycodiazine (sulfamepiridine), it is likely that they are all potentially capable of producing similar symptoms.

Up to now it has not been possible to relate the abnormal hypoglycemic action of the various sulfonylureas to any of the structural variations which differentiate these compounds.[1-6]

Likewise, no constant relation has been found between hypoglycemia production and the compound half life, its inactivation site or the hypoglycemic potency of its metabolites. Thus, cases have been observed with compounds of long and short half lives, with substances which are almost completely inactivated in the liver, such as tolbutamide, eliminated almost unchanged as chlorpropamide or degraded to metabolites with hypoglycemic action such as is the case with acetohexamide.[7,8]

Although in some cases—especially in accidental or surrepetitious ingestion—hypoglycemia has been associated with excessive amounts of the drug, for the most part this complication has resulted from the usual therapeutic doses.[1,3] There are only a few reports in which hypoglycemia seems to be related to a specific characteristic of the drug. They concern cases with an apparent inability to metabolize normally a certain compound or with potentiation of the sulfonylurea by another drug (sulfisoxasole).[9-11]

Actually, sulfonylurea-induced hypoglycemia has a more constant relation with some findings in the patient such as renal failure, malnutrition, advanced age, severe intercurrent diseases, alcoholism, liver disease, endocrine disorders and ingestion of other drugs. Of these, the most frequent are malnutrition, hepatic lesions and renal failure.[1,2,8,12]

Tolazamide is a sulfonylurea with a moderately short half life (five to seven hours) but with a more potent hypoglycemic action than tolbutamide. Some of its metabolites (p-carboxi-tolinase, etc.) have hypoglycemic properties but they are excreted almost completely in twenty-four hours by the kidney.[13,14]

The present patient had some of the aforementioned complications: she was a diabetic with advanced renal failure and in the last days before the hypoglycemic episode she had had vomiting and anorexia with an insufficient food intake. Under these conditions, the marked and prolonged hypoglycemic effect can be attributed to the retention of hypoglycemic metabolites, due to renal failure, and to the decreased alimentary intake.

The case is an example of the potential capacity of all the oral hypoglycemic drugs to produce severe hypoglycemia when administered to a certain type of patient.

REFERENCES

[1] Bergman, H.: Hypoglycemic coma during sulfonylurea therapy. Acta Med. Scand. *177*:287, 1965.

[2] Alexander, R. W.: Prolonged hypoglycemia following acetohexamide administration. Report of two cases with impaired renal function. Diabetes *15*:362, 1966.

[3] Dougherty, J.: Hypoglycemic stupor caused by acetohexamide. New Eng. J. Med. *274*:1256, 1966.

[4] Heikinheimo, R.: Severe prolonged hypoglycemia following tolbutamide and carbutamide treatment. Diabetes *14*:606, 1965.

[5] Soeldner, J. S., and Steinke, J.: Hypoglycemia in tolbutamide treated diabetics, report of two cases with measurement of insulin. JAMA *193*:398, 1965.

[6] Spurny, O. M., Wolf, J. W., and Devinis, G. S.: Protracted tolbutamide induced hypoglycemia. Arch. Intern. Med. *115*:53, 1965.

[7] Ueda, H., Sakurai, T., Ota, M., Nakajima, A., Kamii, K., and Maezawa, H.: Disappearance rate of tolbutamide in normal subjects and in diabetes mellitus, liver cirrhosis and renal disease. Diabetes *12*:414, 1963.

[8] Rothfeld, E. L., Crews, A. H., Ribot, S., and Bernstein, A.: Severe hypoglycemia. Result of renal retention of chlorpropamide. Arch. Intern. Med. *115*:468, 1965.

[9] Bird, E. D., and Schwalbe, F. C.: Prolonged hypoglycemia secondary to tolbutamide. Ann. Intern. Med. *62*:110, 1965.

[10] Barett, A. M.: Modification of the hypoglycemic response to tolbutamide and insulin by mebanazine—an inhibitor of monoamino oxidase. J. Pharm. Pharmacol. *17*:19, 1965.

[11] Christensen, K. L., Hansen, J. M., and Kristensen, M.: Sulphaphenazole-induced hypoglycemic attacks in tolbutamide-treated diabetics. Lancet *2*:1,298, 1963.

[12] Cohn, H. J., Perlmutter, M., Silverstein, J. N., and Numeroff, M.: Prolonged hypoglycemia in response to intravenous tolbutamide in a patient with Laennec's cirrhosis and severe malnutrition. J. Clin. Endocr. *24*:28, 1964.

[13] Abelove, W., Echenique, A., Gorman, A., and Hills, R.: Clinical evaluation of a new hypoglycemic sulfonylurea, tolazamide. Diabetes *11*:216, 1962.

[14] Dulin, W. E., Oster, H. L., McMahon, F. G.: A new high potency antidiabetic sulfonylurea (N-1-hexahydro-1-acepinyl-N-p-tolylsulfonylurea). Proc. Soc. Exp. Biol. Med. *107*:245, 1961.

[15] Bauer, H. G.: Severe and prolonged hypoglycemic shock during sulfonylurea treatment. Metabolism *14*:220, 1965.

[16] Karon, E. H.: Severe, recurrent hypoglycemia due to chlorpropamide therapy. Minnesota Med. *48*:1,017, 1965.

[17] Hazard, J.: Two cases of hemiplegia indicative of severe hypoglycemia induced by hypoglycemic sulfonamides. Bull. Soc. Med. Hop. Paris *116*:473, 1965.

[18] Conte, M.: Two cases of hypoglycemia due to chlorpropamide in diabetic subjects. Bull. Soc. Med. Hop. Paris *116*:467, 1965.

[19] Zotti, G. C.: Recurring hypoglycemia and coma due to chlorpropamide administration. Policlinico (Prat) *72*:226.