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CASE REPORT

Acute Renal Failure After Massive Ingestion of Gliclazide in a Suicide Attempt

A. Barracca, O. Ledda, B. Michittu, G.F. Pili, O. Manca, A. Pani, and P. Altieri

Department of Renal Disease
Azienda Ospedaliera Brotzu
Cagliari, Italy

ABSTRACT

Gliclazide, a sulfonlyurea class molecule, is used to control glycaemic levels in non insulin-dependent diabetes mellitus. Acute and chronic toxicity studies, conducted in various animal species, have demonstrated a very low toxicity. We report a patient who developed acute renal failure due to acute tubular necrosis following a massive ingestion of gliclazide in an suicide attempt. The patient ingested 28 grams of gliclazide; the normal dose of gliclazide is 80 mg one or twice a day. At admission the patient was hypoglycaemia and in a few days became oliguric with an increase in the serum creatinine concentration, but with a normal blood urea nitrogen level. He underwent dialysis and ten days after ingestion of gliclazide, his renal function improved rapidly.

Key Words: Gliclazide; Acute Renal Failure; Hemodialysis.

INTRODUCTION

Gliclazide, a sulfonylurea class molecule, is used to control glycaemic levels in patients with non-insulin-dependent diabetes mellitus (NIDDM). Gliclazide has a molecu-

Address correspondence to: Dr. Antonio Barracca, Divisione di Nefrologia e Dialisi, Ospedale San Michele, Via Peretti, 09134 Cagliari, Italy. Tel: 39-70-539.491/496

lar weight of 324.4. Administration of a single dose of 40–120 mg of gliclazide results in a peak plasma concentration (C_{max}), at steady state, ranging from 0.3 to 8 μg/mL in patients with NIDDM and from 0.7 to 4.9 μg/mL in healthy volunteers (1–4). Steady state concentrations are obtained in NIDDM patients after 2 days of an oral administration of 40 to 120 mg of gliclazide. C_{max} values tend to increase after repeated administrations but drug accumulation does not occur (5).

Gliclazide, like other sulfonylureas, is highly bound to plasma proteins (94%, range 85–99%). The mean apparent volume of distribution in healthy volunteers and in patients with NIDDM is 19 L ranging from 13 to 24 L with an age-related increase (6). Gliclazide is extensively metabolized in humans to at least seven metabolites: the two major metabolites are oxidized while the remaining are hydroxylated. The metabolites have no hypoglycaemic activity. In the urine, only low levels of unchanged drug are present, whereas in the plasma more than 90% of the drug is in the parent form. The major route of elimination of gliclazide and its metabolites is via the urine. Studies using radiolabelled gliclazide have shown that 60–70% of the radioactivity is excreted in the urine and 10 to 20% in the feces. The plasma half life (t1/2) of gliclazide is approximately 11 hours, thus allowing once or twice dosing to maintain 24 hour blood glucose control (7).

Toxicity

Acute toxicity studies on gliclazide have been conducted by oral administration to four animal species of both sexes: rat, mouse, guinea pig, and dog. Toxicity was extremely low, the guinea pig being the more sensitive species. The overall LD_{50} was calculated to be greater than 1500 mg/kg and so 330 to 1300 times greater than the dose administered to humans.

Subacute studies were conducted after oral administration in two animal species: the guinea pig and the dog. In the guinea pig after administration of 25, 50 or 100 mg/kg 6 days out 7 for 8 weeks, neither change in body weight nor in organ weight occurred during the treatment. Histological studies did not reveal any lesions that could be associated with the treatment.

Similar results were observed in studies on chronic toxicity where doses of 25, 100 or 200 mg/kg were given orally 6 days out 7 for 26 weeks. These studies were conducted in three animal species the rat, the dog and the monkey. No target organs were detected. Doses without adverse effect (NOAEL) of 100 mg/kg/d for the rat and 180 mg/kg/d for the monkey were determined. A safety margin of 15–22 was calculated, based on drug plasma concentration.

A fall in blood urea was seen in all treated animals and a significant fall in blood glucose was observed in animals treated with 10 mg/kg/d. Histological studies did not reveal any lesion that could be associated with the treatment.

CASE REPORT

A 42 year old male was admitted to our hospital because he ingested 350 tablets (roughly 28 grams) of Gliclazide in a suicide attempt. The patient was not diabetic. At admission, the patient was hypoglycaemic (blood glucose < 20 mg/dL) and a 10% i.v.

glucose solution was administered. The patient was otherwise well. Blood urea nitrogen (BUN) and creatinine values were 18 mg/dL and 0.8 mg/dL, respectively. The temperature was 36.8 °C and the blood pressure was 130/80 mmHg. Table 1 shows blood chemicals findings.

On the second hospital day, glucose infusion was continued (glycaemia 60 mg/dL) and the renal function appeared normal. On the third hospital day, the patient was oliguric and diuretic agents were started (Furosemide 3–4 mg/kg/h and Dopamine 2–3 μg/kg/min) but on the fourth hospital day the patient had become anuric. Table 1 shows blood chemicals findings. The kidneys were normal at echografic scanning. A TC99m DTPA scan showed a good perfusion. BUN was within normal range values (20 mg/dL), but creatinine levels were high (8 mg/dL) while low levels of sodium and potassium were noted.

Renal failure was diagnosed and hemodialysis started on the sixth day of hospitalization, to correct fluid overload and hyponatraemia. Blood samples were collected before and after the first and the second hemodialysis treatment to determine gliclazide levels. Figure 1 shows the results of these determinations. With the first dialysis, the pre- and post-dialysis gliclazide levels were 1444 and 1251 μg/mL, respectively. With the second dialysis, the pre-and post-dialysis levels were 439 and 335 μg/mL, respectively. Hemodialysis was repeated on the eight and ninth hospital day.

On the tenth hospital day renal function improved rapidly, the patient became polyuric, hemodialysis was stopped. The urinalysis showed the presence of glucose; hyaline and granular casts were also present. The patient was discharged on the twentieth hospital day. At the time of discharge, the BUN was 10 mg/dL and the serum creatinine concentration was 2.4 mg/dL) (Table 1).

DISCUSSION

The present case confirms the low toxicity of gliclazide already demonstrated in animal studies and above all the absence of target organs seen in toxicity studies. The overall LD_{50} was calculated to be greater than 1500 mg/Kg and so 330 to 1300 times greater than the dose administered for clinical use.

This man has taken a dose of 400 mg/Kg. This dose is 400 times greater than the dose used in humans. Couturier (8) presented a case of ingestion of an unknown dose of gliclazide in an suicide attempt. In his work, Couturier documents the procedure for the detection of gliclazide in plasma, several days after ingestion of the drug. The author shows how the peak concentration, after intake 80 mg in normal subjects averaged 4.76 ± 0.63 μg/mL and was reached 4.17 ± 0.65 h after ingestion of the drug. In our case the high drug plasma levels are consequent on the large dose taken by the patient. Based on a mean half life of 10 hours and assuming that no saturation of absorption and hepatic metabolism occurred (which is unlikely), we can estimate that plasma levels have been as high as 1.800 μg/mL on day 1. This is consistent with the calculation we can make from the levels obtained at the therapeutic doses (2.2 to 8 μg/mL after 160 mg). Assuming that kinetics is linear, levels would have been raised up to 350 to 1400 μg/mL after 28.000 mg.

In chronic studies, hyponatraemia is frequently found. This situation is present in diabetic patients treated with sulphonamides. These drugs have an antidiuretic action. For

Table 1

Values Obtained after Gliclazide Overdose

	1st HD	4th HD	Discharge
BUN, mg/dL	18	20	10
Creatinine, mg/dL	0.8	8	2.4
AST, U/L	234	230	23
ALT, U/L	267	210	42
Na, mEq/L	130	105	135
K, mEq/L	3	2.1	3
CPK, U/L	164	180	75
RBC $\times 10^6$	4.14	3.88	
WBC $\times 10^3$	8.91	7.26	

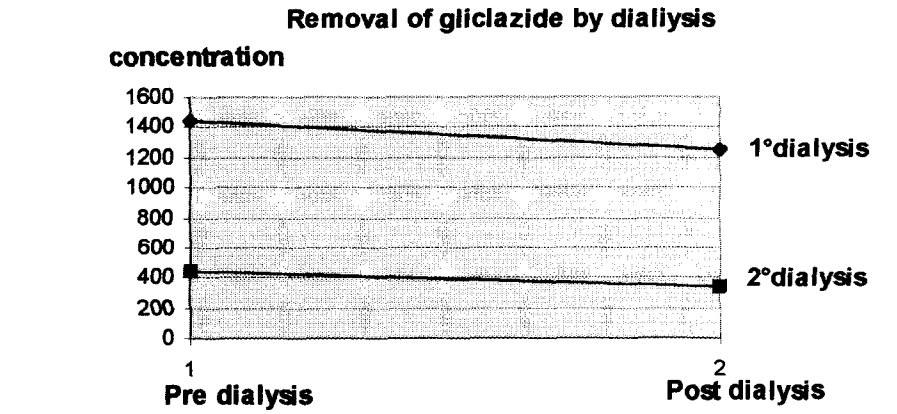

Figure 1. Removal of gliclazide by dialysis.

example, chloropropamide was the most important drug for the treatment of diabetes insipidus. The same drugs have a little diuretic action.

In diabetic patients treated with sulphonamides, we can find low levels of sodium in 33% of patients treated with gliclazide; in those treated with chloropropamide, the frequency of hyponatraemia is of 23%, and only in 6% of patients treated with glibenclamide is there hyponatraemia (9). Also in our patient hyponatraemia was observed during hospitalization.

In conclusion, our patient had cellular damage expressed by an elevation of the liver enzymes, and acute renal failure due to acute tubular necrosis. The high protein binding

of Gliclazide in the plasma (94%) could account for the inability of dialysis to remove excess Gliclazide in spite of a low molecular weight and an apparent clearance of 24 mL/min in humans (Figure 1).

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