Brief Notes and Comments

Failure of Induction of Liver Microsomal Enzymes by Tolbutamide in Maturity-Onset Diabetics

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SUMMARY

Plasma tolbutamide half-life was measured in nine previously untreated mature onset diabetics before and after a minimum of two weeks treatment with 1.0 to 1.5 gm. of tolbutamide daily. The tolbutamide half-life was shortened in six patients, but the mean reduction in mean half-life from 5.7 to 5.3 hours was not statistically significant. Five patients then took phenobarbital, 60 to 90 mg. daily, for two weeks. There was no further reduction in mean tolbutamide half-life. Self-induced stimulation of tolbutamide metabolism is unlikely to be an important factor in the secondary failure of treatment of diabetics with this drug. DIABETES 22:210-11, March, 1973.

Many drugs are known to stimulate their own metabolism through induction of the liver microsomal enzymes.[1,2] It has been shown that tolbutamide has this property in dogs,[2-5] and self-induced drug inactivation is marked at plasma tolbutamide concentrations comparable to those observed in diabetic patients. On the other hand, tolbutamide does not induce its own metabolism in rats and rabbits.[5]

Stimulation of tolbutamide metabolism during prolonged therapy in diabetics could conceivably contribute to secondary failure of treatment; Südhof et al.[6] observed a reduction in the mean plasma tolbutamide half-life from 7.8 to 6.5 hours in ten diabetics during the first two to five months of treatment. However, others have stated that tolbutamide metabolism is not increased in man during long-term treatment.[2,7] Because of these discrepancies, further studies of tolbutamide metabolism have been carried out during extended treatment of diabetes. In addition, the effect of phenobarbital (a potent microsomal enzyme inducer) on the plasma tolbutamide half-life was studied.

METHODS

Nine patients with previously untreated maturity-onset diabetes were selected at their first attendance at a diabetic clinic. A diagnosis of diabetes was based on a raised fasting (> 120 mg./100 ml.) or postprandial blood glucose concentration (> 180 mg./100 ml.). Five patients were receiving other drug therapy (table 1). Blood urea, serum electrolytes, bilirubin, alkaline phosphatase, and alanine transaminase were measured on each occasion that tolbutamide metabolism was investigated. There was slight elevation of the serum bilirubin (up to 1.4 mg./100 ml.) in patients 5 and 7, and alkaline phosphatase (up to 23 K.A. units) in patient 8.

The plasma half-life of tolbutamide was measured before and after treatment with oral tolbutamide, 1.0 or 1.5 gm. daily, for at least two weeks. The half-life was measured again in five of the patients following administration of 60 to 90 mg. of phenobarbital daily for two weeks in addition to tolbutamide.

The plasma tolbutamide half-life was measured as follows: 1.0 gm. of tolbutamide was given intravenously and five blood samples were taken at intervals over a period of twelve hours. The first sample was taken one hour after the injection. Oral tolbutamide therapy was discontinued on the day of each test. Tolbutamide concentrations in plasma were estimated by a gas-liquid chromatographic method[8] which is not subject to interference by metabolites or phenobarbital. The half-life values were calculated by the least squares method using the logarithms of the plasma tolbutamide concentrations.

RESULTS

The mean plasma tolbutamide half-life in the patients before oral therapy ranged from 3.6 to 10.5 hours (mean 5.7 hours). After chronic administration of tolbutamide, the half-life was shortened in six patients and unchanged in one (table 1). Although the mean value after treatment fell to 5.3 hours, the difference was not statistically significant. There was a further slight reduction in the tolbutamide half-life in four out of five patients after taking phenobarbital for two weeks. However, the mean half-life was unchanged in the group receiving phenobarbital. In each patient, the plasma concentrations of tolbutamide one hour after administration were similar on each occasion that the half-life was measured. The mean values (± S.E.) before and after oral tolbutamide therapy, and after treatment with phenobarbital were 114 ± 7.6, 118 ± 9.6, and 102 ± 15.6 μg. per milliliter, respectively.

DISCUSSION

Although the plasma half-life of tolbutamide was shortened

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TABLE 1

Clinical details and plasma tolbutamide half-life before and after treatment with tolbutamide and phenobarbital

Patient Age and sex	Other drug therapy	Daily dose of tolbutamide (gm.)	Tolbutamide half-life (hours) Before treatment	Time interval (weeks)	After tolbutamide	After tolbutamide and phenobarbital
62 M	Guanethidine, amytal, KCl, hydrochlorothiazide, reserpine, propranolol, meprobamate	1.5	5.7	14	7.6	—
67 M	Reserpine bendrofluazide	1.0	7.9	3	6.5	8.7
66 F	Prednisolone	1.0	10.5	2	8.1	—
63 F	α Methyl dopa	1.0	4.2	2	3.9	—
46 M	Nil	1.0	5.4	2.5	4.9	4.5
54 M	Nil	1.0	3.6	2.5	4.1	3.6
68 M	Nil	1.0	4.5	2	4.5	3.6
61 F	Nil	1.0	4.0	2	3.8	3.6
64 F	Nil	1.5	5.3	2	4.7	—
Mean			5.7		5.3	4.8

following prolonged administration in six of the nine patients, the change is of no therapeutic significance. Larger doses of tolbutamide and/or phenobarbital given for a longer period might have had a greater effect, but induction of liver microsomal enzymes is unlikely to be an important factor in the development of secondary failure of treatment in diabetics. The 17 per cent reduction in tolbutamide half-life observed by Südhof et al.[6] could possibly be explained by the longer interval between half-life measurements.

Once distribution equilibrium has been reached, the plasma half-life of a drug depends on the plasma clearance and the apparent volume of distribution. In the case of tolbutamide, metabolism is the major route of elimination in man, since negligible amounts of drug appear unchanged in the urine.[9] It was not possible to exclude changes in the volume of distribution after starting treatment because of residual drug from oral therapy on the day prior to the test.

The present results are surprising in view of the marked self-induction of tolbutamide metabolism in dogs, and the established inducing effect of phenobarbital in man.

Tolbutamide is metabolized in dogs by N-dealkylation, while in man, rats, and rabbits oxidation of the 4-methyl group occurs.[5] The latter reaction is presumably carried out by the oxidative enzymes of the liver microsomes and should, therefore, be influenced by treatment with inducing agents. It is possible that other enzyme systems are involved in tolbutamide metabolism in man.

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