Potentiation of the Tolbutamide Effect by Dicoumarol

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SUMMARY

The administration of dicoumarol to four elderly diabetics who were daily receiving 500 mg. tolbutamide led to an increase in the tolbutamide concentration in the blood associated with a fall in blood sugar. The accumulation of tolbutamide was due to an increase in the half-life of tolbutamide in the blood from the normal average of 4.9 hours to an average of 17.5 hours. The mechanism responsible for this increase may be inhibition of tolbutamide metabolism in the liver by dicoumarol.

This accumulation may well increase the risk of hypoglycemia, such as has been demonstrated after administration of sulfaphenazole to diabetic patients receiving tolbutamide.

Phenindione does not seem to have a similar effect and, accordingly, would appear to be preferable in anticoagulant therapy in diabetics receiving tolbutamide. DIABETES *16*:211-14, April, 1967.

It is well recognized that the administration of one drug may diminish or increase the pharmacologic effect of a second, for example, by stimulation or inhibition of the metabolism of that drug in the liver. We have previously demonstrated[1] that the administration of sulfaphenazole and phenylbutazone to diabetics receiving tolbutamide may lead to accumulation of tolbutamide in the blood, with a consequent risk of hypoglycemia. The effect is presumably the result of inhibition of the oxidation of tolbutamide in the liver by the sulfaphenazole.

In connection with a study of the tolbutamide tolerance test our attention was drawn to dicoumarol, in that a patient developed hypoglycemia two hours after the administration of 1 gm. tolbutamide. Investigation did not otherwise suggest the presence of an insulinoma. The patient was receiving anticoagulant therapy with dicoumarol because of arteriosclerotic heart disease with previous coronary occlusion. Estimation of the half-life of tolbutamide in the blood revealed that this was fifteen hours, as compared with a normal value of four to six and one-half hours.[2,3] At the time of the investigation the prothrombin-proconvertin value was 12 per cent. The patient had no signs of liver or renal disease.

To ascertain whether there was any possible interaction between tolbutamide and dicoumarol we have carried out clinical experiments on volunteers.

METHODS

The plasma tolbutamide concentration was determined by the method described by Spingler.[4] It was found that the presence of dicoumarol in the serum did not interfere with the results.

Tolbutamide and its metabolites were identified by thin-layer chromatography using the following procedure: Four hundred μl. N HCl were added to 1 ml. plasma and extracted three times with water-saturated amylacetate. The extract was evaporated to dryness and the residue redissolved in absolute alcohol. The solution was placed on silica-gel plates and the chromatogram was run in a solution consisting of forty parts n-butanol, eleven parts ethanol, and nineteen parts phosphate buffer (1/15 M., *p*H 7.0). After drying, the chromatogram was developed with ninhydrin. By means of comparison with standards it was possible to determine the amount of tolbutamide present. In this system tolbutamide and its oxidation product, carboxytolbutamide, migrate with Rf values of 0.8 and 0.4, respectively.

Serum dicoumarol was determined by the method described by Axelrod et al.[5]

Blood sugar determinations were carried out on capillary blood using Hagedorn's method.[6]

RESULTS

Effect of dicoumarol on the plasma tolbutamide concentration

In four elderly diabetics, all of whom were receiving tolbutamide therapy, the dosage of tolbutamide was reduced to 500 mg. given in the morning. After the blood sugar level had remained stable for at least one week the patients were given dicoumarol in doses adjusted to give a prothrombin-proconvertin value of 30

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per cent. All the subjects were inpatients, and they had been receiving a controlled diet for at least eighteen days before the administration of dicoumarol. The blood sugar was determined three times daily: fasting, in the morning before the administration of the tablets; at 11 a.m.; at 5 p.m. The plasma tolbutamide was determined on about every third day at the same times as the blood sugar.

In all four patients there was an obvious increase in the tolbutamide concentration three days after the start of the administration of dicoumarol, and there was further increase during the following days. In figure 1 are shown the maximum tolbutamide concentrations in the four patients during treatment with 500 mg. tolbutamide daily, and during the combined treatment with tolbutamide and dicoumarol.

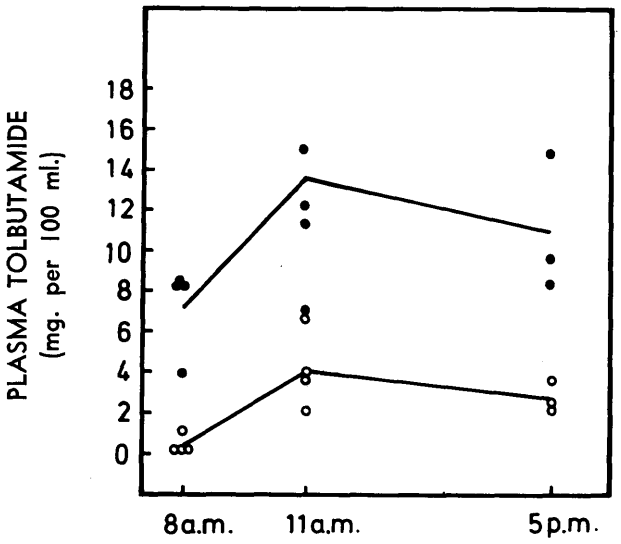

FIG. 1. Maximum tolbutamide concentrations in plasma in four patients during the administration of 500 mg. tolbutamide. ●—during dicoumarol treatment; O—without dicoumarol. The lines indicate the average concentrations.

During tolbutamide therapy the average concentrations of tolbutamide in the plasma at the different sampling times were: 8 a.m., 0.25 mg. per 100 ml.; 11 a.m., 4.0 mg. per 100 ml.; 5 p.m., 2.7 mg. per 100 ml. During the combined treatment these values rose to averages of 6.2, 13.6, and 10.8 mg. per 100 ml., respectively.

When Spingler's method is used the oxidation product, carboxytolbutamide, is determined together with tolbutamide. Normally the carboxytolbutamide in the plasma does not exceed a few per cent of tolbutamide, as it is very rapidly excreted via the kidneys. Thin-layer chromatography which, in the method used here clearly distinguishes between tolbutamide and its oxidation product, revealed that during the combined treatment the plasma contained exclusively tolbutamide in the amounts determined by Spingler's method.

In three of the patients the dicoumarol was withdrawn after eight days of treatment and, in the course of a week, the tolbutamide concentrations fell to "before dicoumarol" levels. The concentration of dicoumarol in the serum fell to zero in the course of three to four days.

Effect of the combination tolbutamide-dicoumarol on the blood sugar

In all the four patients a fall in blood sugar was observed three days after the start of the administration of dicoumarol. In figure 2 are shown the daily blood sugar concentrations and the plasma tolbutamide concentrations before and during treatment with dicoumarol in one patient. Simultaneous with the rise in tolbutamide concentration, which was seen after a few days, there was a fall in both fasting and mean blood sugar; additional increase of the dosage of tolbutamide to 1,500 mg. daily did not lead to any change in the

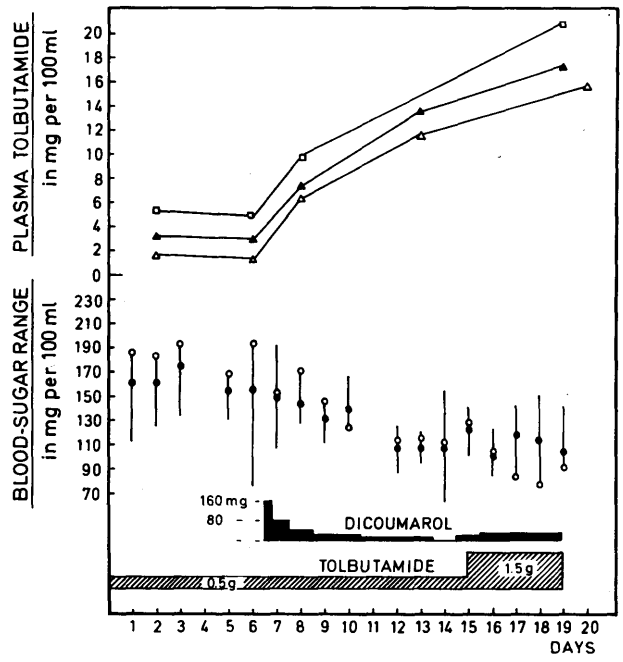

FIG. 2. Plasma tolbutamide concentrations and blood sugar concentrations in one patient before and during dicoumarol treatment. △—tolbutamide concentration at 8 a.m.; ▲—at 11 a.m.; □—at 5 p.m.; O—fasting blood sugar; ●—mean blood sugar.

mean blood sugar, whereas there was perhaps a slight fall in the fasting blood sugar.

The blood sugar concentrations in the remaining three patients before and during treatment are shown in figure 3. Only the blood sugar concentrations after more than two days of treatment with dicoumarol are included in the "during treatment" diagrams, as at this time the tolbutamide concentration was obviously increasing. Although only a few observations are shown it is apparent that there was a clear fall in blood sugar in all the patients, and that this fall was most obvious in the fasting blood sugar.

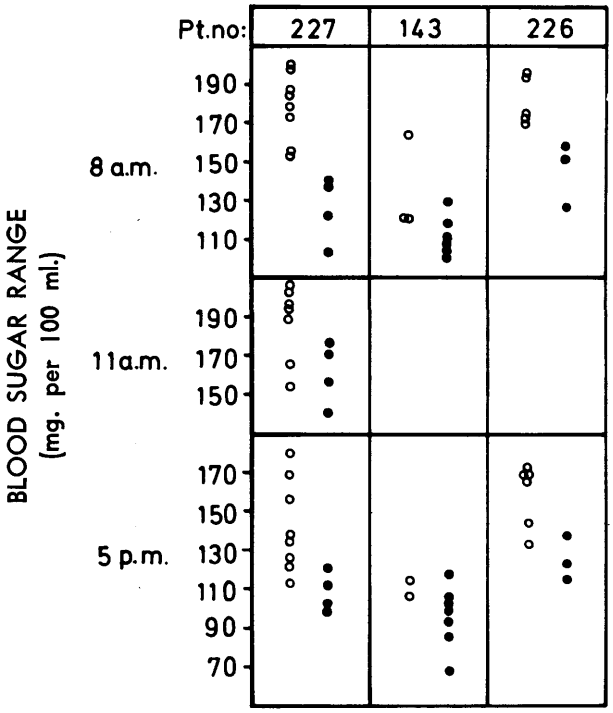

FIG. 3. Blood sugar concentrations in three patients. O—during administration of 500 mg. tolbutamide daily; ●—during combined treatment with tolbutamide-dicoumarol.

In the three of the patients in whom dicoumarol was withdrawn after one week there was no increase in the blood sugar during the following week, despite the fact that by this time the tolbutamide concentrations had fallen to "before dicoumarol" levels. None of the patients was followed up for more than one week after the withdrawal of dicoumarol.

Effect of dicoumarol on the half-life of tolbutamide in the blood

Eight volunteers each received 1 gm. tolbutamide intravenously before and after one week of treatment with dicoumarol. None of the subjects was fasting during the test. The tolbutamide concentration was determined at intervals during the twenty-four hours following the injections, the first sample being taken at two hours, and the remainder, a total of at least five samples, being equally distributed throughout the period. The half-life of tolbutamide in the blood was determined from these values. The results are shown in table 1, which also shows the dicoumarol concentration and the prothrombin-proconvertin values at the time of the injection after one week of administration.

Before the administration of dicoumarol the average half-life of tolbutamide was 4.9 hours, while during the administration this value was greatly increased to an average of 17.5 hours.

TABLE 1

Tolbutamide half-life before and during treatment with dicoumarol

Patient number	Tolbutamide half-life (in hours) Before dicoumarol	During dicoumarol	Serum dicoumarol in μg. per 100 ml.	Prothrombin-proconvertin per 100 ml.
6A	4.5	17.5	—	19
9	6.5	18.0	12.2	—
113	4.0	10.0	11.1	72
191	3.3	10.0	6.0	—
196	5.0	24.0	10.8	45
197	6.5	25.0	12.3	47
198	6.5	18.0	8.8	75
200	2.8	17.6	32.8	19
Average	4.9	17.5		

Effect of phenindione on tolbutamide

Three patients who were receiving treatment with phenindione were given 500 mg. tolbutamide daily. During this combined treatment the average tolbutamide concentration in the plasma, from several determinations, was found to be: 8 a.m., 1.8 mg. per 100 ml.; 12 noon, 4.7 mg. per 100 ml.; 5 p.m., 2.7 mg. per 100 ml. The tolbutamide half-life in the blood was determined in two volunteers before and after six days of treatment with phenindione; there was no alteration in the half-life. At the time of the determination of the tolbutamide half-life the prothrombin-proconvertin values in both subjects were 48 per cent, on phenindione dosages of 37.5 mg. and 50 mg., respectively.

It is thus apparent that phenindione does not affect the metabolism of tolbutamide.

DISCUSSION

Tolbutamide is oxidized in the body, presumably mainly in the liver, to the nonhypoglycemic carboxy-

tolbutamide, and nearly all of the tolbutamide which is administered may be recovered in this form in the urine.[2] The excretion of carboxytolbutamide in the urine is a very rapid process, the half-life in the blood averaging 0.48 hours.[2] The half-life of tolbutamide in the blood will, therefore, principally be determined by the rate at which tolbutamide is converted to carboxytolbutamide in the liver.

Our investigations have revealed that the administration of dicoumarol to diabetic patients receiving tolbutamide leads to an increase in the tolbutamide concentration in the plasma as determined by Spingler's method. Thin-layer chromatography has demonstrated that it is tolbutamide, and not carboxytolbutamide, which accumulates. This presumption is further supported by the fact that after the administration of dicoumarol there is a fall in blood sugar in diabetics who are maintained on a small, and presumably insufficient, dosage of tolbutamide. The accumulation of tolbutamide in the blood is due to the fact that the normal half-life in the blood, which averages 4.9 hours, is increased to an average of 17.5 hours.

It would seem reasonable to assume that dicoumarol inhibits the conversion of tolbutamide to carboxytolbutamide in the liver.

Since the observations described above were made, we have been able to demonstrate that dicoumarol also causes accumulation of diphenylhydantoin in man, and it has been demonstrated that this is presumably due to inhibition of the parahydroxylation of diphenylhydantoin in the liver.[7] The present study suggests that dicoumarol also inhibits the enzymatic conversion of the methyl group in tolbutamide to the carboxyl group.

It has previously been demonstrated that the administration of sulfaphenazole to diabetics treated with tolbutamide may lead to unexpected attacks of hypoglycemia, and that these are due to accumulation of tolbutamide in the blood.[1] There must be a similar risk associated with the administration of dicoumarol to diabetics receiving tolbutamide. Insofar as we have been able to ascertain, dicoumarol has no inherent hypoglycemic effect.

As we have demonstrated, phenindione does not have any similar effect on the metabolism of tolbutamide, and this must therefore be the anticoagulant of choice in the treatment of diabetics receiving tolbutamide.

REFERENCES

[1] Christensen, L. K., Hansen, J. M., and Kristensen, M.: Sulfaphenazole-induced hypoglycemic attacks in tolbutamide-treated diabetics. Lancet *2*:1298-1301, 1963.

[2] Nelson, E., and O'Reilly, I.: Kinetics of carboxytolbutamide excretion following tolbutamide and carboxytolbutamide administration. J. Pharm. Exper. Therap. *132*:103-09, 1961.

[3] Hicha, U., Sakurai, T., Ota, M., Nakajima, A., Kamii, K., and Maezawa, H.: The disappearance rate of tolbutamide in normal subjects and in diabetes mellitus, liver cirrhosis and renal disease. Diabetes *12*:414-19, 1963.

[4] Spingler, H.: Über eine Möglichkeit zur colorimetrischen Bestimmung von N-(4-Methyl-Benzolsulfonyl)-N'-Butyl-Harnstoff in Serum. Klin. Wschr. *35*:533-35, 1957.

[5] Axelrod, A., Cooper, J. R., and Brodie, B. B.: Estimation of dicoumarol, 3,3-Methylene bis (4-hydroxycoumarin) in biological fluids. Proc. Soc. Exper. Biol. Med. 70:693-95, 1949.

[6] Hagedorn, H. C., Halstrøm, F., and Jensen, B. N.: Reports of the Steno Memorial Hospital and the Nordisk Insulinlaboratorium *1*:29-41, 1946.

[7] Hansen, J. M., Kristensen, M., Skovsted, L., and Christensen, L. K.: Dicoumarol-induced diphenylhydantoin intoxication. Lancet *2*:265-66, 1966.