Effect of Phenformin on Glucose-Insulin Interrelationships

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SUMMARY

Phenformin was administered to nine male subjects with fasting plasma glucose levels below 110 mg./100 ml. and oral glucose tolerance levels ranging from clearly normal to mildly abnormal. Most of the subjects were slightly overweight, but weight was maintained constant throughout the study. Two weeks' administration of phenformin, 100 mg. per day, resulted in a fall in fasting plasma glucose levels both on a 45 per cent carbohydrate (mean change -4 per cent) and an 85 per cent carbohydrate diet (mean change -2 per cent). The glucose-lowering effect of the drug was not related to the initial glucose level, and the glucose-lowering effect of increased dietary carbohydrate was not altered by the drug. Both the total and the incremental glucose responses to oral glucose tended to be reduced by phenformin. Intravenous glucose tolerance (Kg) was improved by the drug, the mean change being similar to the mean change in oral glucose tolerance (-12 per cent). Basal insulin levels on both diets were lowered by phenformin (mean change -23 per cent) as were the total insulin responses to both oral and intravenous glucose (mean changes -18 per cent and -19 per cent respectively). It is suggested that phenformin's primary action is to enhance peripheral glucose assimilation, and that the changes in insulin secretion are secondary to this, having a counter-regulatory role in preventing profound hypoglycemia, and minimizing the changes in blood glucose in nondiabetic subjects. The absence of any drug effect on the acute insulin response to intravenous glucose (per cent basal) is consistent with the depressed insulin secretion being secondary to the drug's effect on glucose metabolism, rather than to a direct effect of phenformin on the pancreatic islets. The similar changes in the effect of the drug on oral and intravenous glucose tolerance suggest that impairment of intestinal glucose absorption is not an important effect of phenformin. DIABETES *23*:624-30, July, 1974.

Although phenformin has been used in the treatment of diabetes for more than a decade, it is still not clear whether it has different effects on diabetic and nondiabetic subjects. This is partly because effects of the drug on glucose concentrations are readily demonstrable in diabetic subjects, but have not usually been found in nondiabetic human beings.[1,2] On the other hand, glucose turnover[3,4] and lactate turnover[5] are increased in subjects with normal glucose tolerance treated with phenformin. Nondiabetic animals may show marked responses to phenformin administration.[6] This has led to the suggestion that phenformin may have different effects in man and animals, and different effects in nondiabetic and diabetic human beings. The conclusions, if true, prevent the extrapolation of data obtained in animal experiments to human metabolism.

Controversy also surrounds the mechanism of action of the biguanide drugs. Early suggestions were that phenformin enhanced glucose uptake in peripheral tissues, increased anaerobic glycolysis, and decreased gluconeogenesis.[7] More recently, studies in both diabetic[8] and nondiabetic[9] subjects suggested that biguanides may improve oral glucose tolerance without affecting intravenous glucose tolerance. This suggested that the drug might have an inhibiting effect on the intestinal absorption of glucose, a postulate that has received experimental support from animal studies.[10,11] However, it is not clear whether all the effects of phenformin can be attributed to impairment of glucose absorption.

It has also been reported that biguanides may lower elevated insulin levels after glucose assimilation.[12] However, the relationship of the changes in insulin secretion to the blood glucose changes is not clear.

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The present study was designed to answer some of these questions by studying the effect of phenformin on paired intravenous and oral glucose tolerance tests in a series of subjects whose glucose tolerance ranged from clearly normal to mildly abnormal.

METHODS

Nine male subjects with fasting plasma glucose levels less than 110 mg. per 100 ml. were admitted to the metabolic ward of the Seattle Veterans Administration Hospital or the Clinical Research Center of Harborview Medical Center, Seattle. The majority of the subjects (table 1) were above ideal body weight by the Metropolitan Life Insurance Company standards, and none was taking antidiabetic therapy or drugs, such as diuretics, which might affect carbohydrate metabolism. All subjects had hypertriglyceridemia, four had evidence of coronary artery disease, and one had peripheral vascular disease, but none had had any recent acute illness. The effect of phenformin on lipid metabolism in these subjects is being reported elsewhere.[13]

During their eight-week hospitalization the patients were fed formula diets designed to maintain constant body weight throughout the study. The study was divided into four periods of two weeks each (table 2). In periods 1 and 4 the isocaloric formula diet contained 45 per cent of calories as carbohydrate, 40 per cent as fat and 15 per cent as protein. For periods 2 and 3 the diet contained no fat, 85 per cent of total calories as carbohydrate and 15 per cent as protein. Phenformin hydrochloride (DBI-TD) was administered as sustained-release capsules, 50 mg. twice daily during periods 3 and 4. In one subject (no. 9) the study was performed in reverse order, the drug being administered during periods 1 and 2 and discontinued during the latter half of the study. The subjects were weighed daily, and fasting samples for plasma glucose determination were taken thrice weekly.

TABLE 1

Characteristics of study subjects

Subject	Age	Body wt. (kg.)	Relative body wt.† (%)	Diagnosis‡
1	50	80.1	126	HT
2	41	68.4	117	HT, CAD
3	56	72.0	104	HT
4	47	88.0	123	HT, PVD
5	42	98.0	141	HT, CAD
6	57	83.3	146	HT, CAD
7	47	81.9	113	HT, CAD
8	47	79.0	128	HT
9*	61	92.7	137	HT

*Study performed in reverse order.
†Metropolitan Life Insurance Company tables.
‡HT—hypertriglyceridemia; CAD—coronary artery disease; PVD—peripheral vascular disease.

TABLE 2

Experimental design

	Period			
	1	2	3	4
40% fat diet	+			+
Fat-free diet		+	+	
Phenformin			+	+

At the end of periods 2 and 3, paired oral and intravenous glucose tolerance tests were performed on eight subjects. Intravenous glucose tolerance tests were also performed at the end of periods 1 and 4 in five subjects. On the day of the test, the morning dose of phenformin was not given until after the test had been completed.

Subject 1 was only studied during the two fat-free dietary periods and did not have glucose tolerance tests. The fasting plasma glucose results are the mean of the concentrations in the samples that were taken three times per week throughout the study, and blood samples for insulin were taken at the end of two fat-free dietary periods under basal conditions as described below.

Intravenous glucose tolerance tests were performed as previously described.[14] After an overnight fast (twelve hours), a slow intravenous infusion of 0.85 per cent saline was begun. Four samples at fifteen-minute intervals were obtained for measurement of basal plasma glucose and serum immunoreactive insulin (IRI) concentrations. Glucose, 20 gm. as 50 per cent dextrose in water, was given as a rapid (20 sec.) intravenous injection. After clearing the tubing of saline by removing and discarding a 3 ml. sample, an 8 ml. sample was taken at the following times: 3, 4, 5, 10, 15, 20, 25, 30, 45, 60, 90 and 120 minutes after injection, which was taken as the time when 50 per cent of the glucose had been given.

For the oral glucose tolerance tests, the subjects were prepared and the basal samples obtained in the same way. Glucose (100 gm.) was given as a flavored drink, and the subjects were encouraged to drink it as rapidly as possible. Samples were taken as described above at the following times: 5, 10, 15, 30, 45, 60, 90, 120, 150 and 180 minutes after ingestion of glucose.

A 5 ml. aliquot of each sample was delivered into a heparinized tube, mixed thoroughly and placed immediately in ice. Subsequently the plasma was sepa-

rated and frozen for later glucose determination by the AutoAnalyzer ferricyanide method. The 3 ml. aliquot was allowed to clot, then placed on ice, and subsequently the serum was frozen for determination of IRI by a modification of the Morgan and Lazarow method.[14] All samples from one subject were run on the same assay.

The basal glucose and insulin values were calculated from the mean of the four control samples. The acute insulin response to intravenous glucose was calculated from the mean of the increments of serum IRI at three, four and five minutes above the base line serum IRI concentrations (3′-5′ Δ IRI μU./ml.), and the acute insulin response relative to the basal level was calculated by expressing the acute response as a proportion of the basal level (3′-5′ Δ IRI per cent basal). The total insulin response to intravenous glucose or to oral glucose was calculated as the total incremental area above the base line (μU. min./ml.) or as the total area above zero. The glucose disappearance rate (Kg) was calculated by computer by the least squares analysis of the change of natural logarithm of plasma glucose levels between ten and thirty minutes after the glucose pulse. The glucose response to oral glucose was estimated as the total incremental glucose area above base line (mg.min./ml.) and as the total glucose area above zero (mg.min./ml.).

RESULTS

On the diet in which calorie distribution was similar to that of the average diet, phenformin administration resulted in a significant reduction in fasting plasma glucose levels (table 3). (Subject 9 was studied in reverse order, but, for simplicity, his results are presented in tables 3 to 9 as if he were studied in the conventional way.) On the fat-free diet, fasting glucose levels were reduced in seven of the nine subjects, and there was a reduction in the mean levels which did not quite reach significance. There was no correlation between the change in fasting glucose associated with phenformin administration and the initial glucose concentrations. The two subjects whose fasting glucose levels were not lowered by the drug had initial levels which were indistinguishable from those of the subjects who responded. As previously reported,[15] the fasting plasma glucose levels were lower when the subjects were taking high carbohydrate diets, and this effect occurred when they were taking phenformin (mean change -6.2 ± 0.7 mg./100 ml.; -7.0 ± 0.6 per cent, $t = 4.84$, $p < 0.01$) as well as during the control period (mean change -9.7 ± 2.2 mg./100 ml.; −10.0 ± 2.2 per cent, $t = 3.64$, $p < 0.02$).

TABLE 3

Effect of phenformin on fasting plasma glucose
mg./100 ml.

	40% fat diet		Fat-free diet	
	Control	Phenformin	Control	Phenformin
1	—	—	97	95
2	77	75	82	80
3	96	94	83	79
4	95	89	84	81
5	90	86	84	82
6	103	—	85	88
7	95	89	81	83
8	89	90	88	85
9*	105	98	97	90
Mean	92	89	87	85
	Mean change -3.7 ± 1.0 $t = 3.40$ $p < 0.02$ Mean % change -3.9 ± 1.0 $t = 3.57$ $p < 0.02$		Mean change -2.0 ± 0.9 $t = 2.22$; $0.1 > p > 0.05$ Mean % change -2.2 ± 1.1 $t = 2.00$; $0.1 > p > 0.05$	

*Study performed in reverse order.

The glucose responses to oral glucose are expressed as the total area under the glucose tolerance curves, and as the incremental glucose areas above basal levels (table 4). In both cases, there was a mean reduction in the glucose response when phenformin was administered (figure 1) which did not quite reach significance. Using data previously reported,[15] the total glucose response to oral glucose in nondiabetic subjects consuming fat-free diets was found to be 23,300 ± 3,200 (mean ± standard deviation). If two standard deviations above the mean is taken as the upper limit of normal, only one subject, no. 2, was clearly abnormal. Patients 6 and 9 had glucose responses greater

TABLE 4

Effect of phenformin on the glucose response to oral glucose
(fat-free diet)
mg. min./ml.

	Total Glucose Area		Incremental Glucose Area	
	Control	Phenformin	Control	Phenformin
2	33,690	26,580	18,660	12,180
3	17,420	18,880	2,655	5,018
4	24,720	22,460	9,329	8,055
5	21,000	22,350	5,610	7,770
6	27,130	23,060	12,010	7,215
7	22,760	21,650	8,717	7,065
8	22,360	19,830	6,517	4,350
9*	28,310	27,050	9,952	9,952
Mean	24,670	22,730	9,181	7,701
	Mean change -1,967 ± 927 $t = 2.12$ $p > 0.05$ Mean % change -6.5 ± 3.3 $t = 1.95$ $p > 0.2$		Mean change -2,020 ± 960 $t = 2.09$ $p > 0.05$ Mean % change -11.3 ± 15.1 $t = 0.74$ $p > 0.4$	

*Study performed in reverse order.

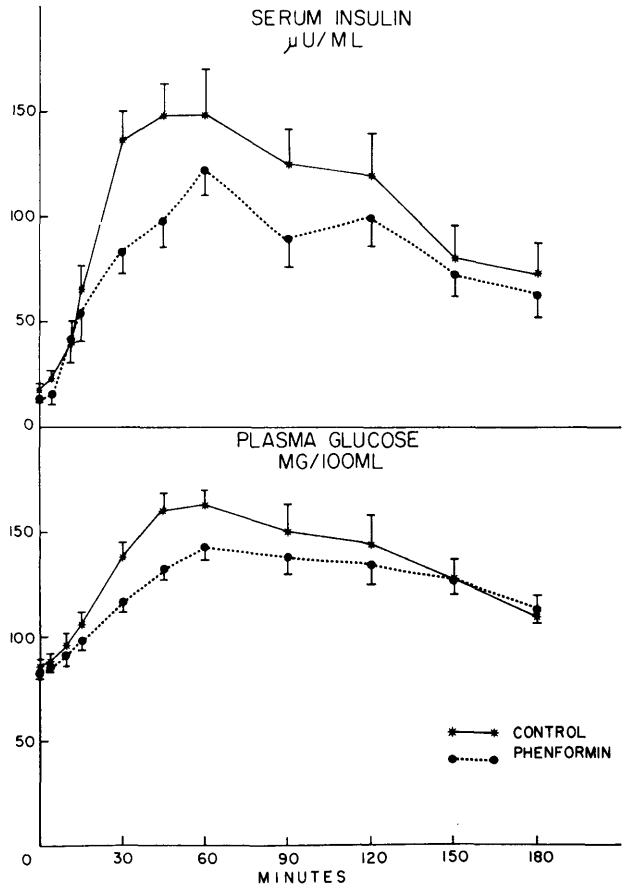

FIG. 1. Mean glucose and insulin responses to oral glucose in subjects before and during phenformin administration.

TABLE 5

Effect of phenformin on the glucose assimilation coefficient (Kg)

	40% fat diet		Fat-free diet	
	Control	Phenformin	Control	Phenformin
2			1.63	1.99
3			1.67	1.75
4	1.43	1.75	1.73	1.92
5	1.19	1.14	1.73	1.71
6	1.38	—	1.52	1.89
7	0.94	1.13	1.13	1.68
8	1.08	1.19	1.40	1.07
9*	1.03	1.14	1.46	1.66
Mean	1.13	1.27	1.50	1.71
	Mean change 0.14 ± 0.58		Mean change 0.18 ± 0.09	
	t = 2.41; 0.1 > p > 0.05		t = 2.00 p > 0.1	
	Mean % change 12.2 ± 4.3		Mean % change 12.5 ± 7.0	
	t = 2.82 p < 0.05		t = 1.79 p > 0.1	

*Subject studied in reverse order.

than one standard deviation above the mean for the normal group. The two subjects who did not have lower glucose responses when phenformin was administered (nos. 3 and 5) were the subjects with the lowest control values. On the other hand, three subjects with control glucose tolerance tests which were clearly normal responded to the drug with lower glucose responses. The changes in the incremental glucose responses were similar to the changes in the total glucose responses.

On each diet, the majority of subjects increased the glucose assimilation coefficient (Kg) when taking phenformin (table 5) with a mean increase which did not reach statistical significance. The subjects whose Kg was not increased by phenformin could not be distinguished by their control values from those who responded.

Basal insulin levels fell in all subjects (table 6) when phenformin was added to the fat-free diet, and in the majority of subjects on the 40 per cent fat diet. The incremental insulin response above basal levels, expressed as the area under the insulin curve following oral glucose (table 7), was also significantly reduced by phenformin on the fat-free diet (figure 1). The total insulin response to oral glucose was similarly reduced by phenformin.

The absolute acute insulin response to intravenous glucose, measured as the mean of the three, four and five minute samples above basal levels, was lower in all subjects when they were taking phenformin (table 8). However, the relative acute insulin response, measured as per cent change in insulin relative to basal levels, was not changed by the drug (table 8). The

TABLE 6

Effect of phenformin on basal insulin (μU./ml.)

	40% fat diet		Fat-free diet	
	Control	Phenformin	Control	Phenformin
1			11	8
2			18	15
3			11	9
4	20	13	20	17
5	19	11	17	14
6	28		23	15
7	23	18	19	17
8	6	7	11	7
9*	24	27	29	19
Mean	18	15	18	13
	Mean change -3.2 ± 2.2		Mean change -4.3 ± 0.9	
	t = 1.32 p > 0.2		t = 4.67 p < 0.01	
	Mean % change -13.9 ± 12.1		Mean % change -23.3 ± 3.0	
	t = 1.14 p > 0.2		t = 6.89 p < 0.001	

*Subject studied in reverse order.

TABLE 7

Effect of phenformin on the insulin response to oral glucose (fat-free diet)
μU. min./ml.

	Total area		Incremental area	
	Control	Phenformin	Control	Phenformin
2	18,530	14,670	15,470	11,880
3	7,440	7,730	5,370	5,930
4	24,330	14,890	21,090	11,920
5	20,010	19,250	17,130	16,640
6	30,180	18,590	26,950	16,610
7	20,190	15,320	16,950	12,980
8	10,260	9,202	8,460	7,942
9*	26,120	22,310	20,540	19,430
Mean	19,630	15,240	16,420	12,920
	Mean change -4,389 ± 1,394		Mean change -3,499 ± 1,407	
	$t = 3.15$ $p < 0.05$		$t = 2.48$ $p < 0.05$	
	Mean % change -18.5 ± 5.1		Mean % change -16.4 ± 6.5	
	$t = 3.64$ $p < 0.01$		$t = 2.49$ $p < 0.05$	

*Subject studied in reverse order.

TABLE 9

Effect of phenformin on the insulin response to intravenous glucose
μU. min./ml.

	Total area		Incremental area	
	Control	Phenformin	Control	Phenformin
2	5,598	4,173	3,318	2,373
3	2,333	1,959	1,133	999
4	5,875	4,213	3,355	2,533
5	5,370	4,613	3,330	2,693
6	7,024	4,602	4,084	2,802
7	6,579	8,465	4,419	5,945
8	3,297	2,172	1,616	1,092
9*	6,877	5,063	3,457	2,543
Mean	5,369	4,408	3,089	2,623
	Mean change -962 ± 435		Mean change -466 ± 308	
	$t = 2.21$ $p < 0.05$		$t = 1.51$ $p > 0.2$	
	Mean % change -18.8 ± 6.8		Mean % change -17.5 ± 7.8	
	$t = 2.76$ $p < 0.05$		$t = 2.22$; $0.1 > p > 0.05$	

*Subject studied in reverse order.

total amount of insulin secreted during the two hours of the intravenous glucose tolerance test was also reduced by phenformin (table 9), but the incremental response was not significantly affected.

The correlation coefficient between the changes in fasting glucose levels and the change in the acute insulin response to intravenous glucose was -0.684 ($t = 2.30$; $0.1 > p > 0.05$). There was a significant correlation ($r = 0.588$, $t = 2.72$, $p < 0.02$) in the combined control and phenformin groups, between the Kg and the acute insulin response to intravenous glucose (per cent basal).

TABLE 8

Effect of phenformin on the acute (3′-5′) insulin response to intravenous glucose (fat-free diet)

	Absolute response μU./ml.		Relative response % basal	
	Control	Phenformin	Control	Phenformin
2	231	213	1,333	1,495
3	85	77	910	1,063
4	237	186	1,243	1,404
5	203	149	1,294	1,033
6	222	126	1,007	955
7	151	122	954	839
8	113	63	889	823
9*	159	155	660	828
Mean	175	136	1,036	1,055
	Mean change -37.5 ± 9.9		Mean change 18.8 ± 54.4	
	$t = 3.79$ $p < 0.01$		$t = 0.34$ $p > 0.5$	
	Mean % change -21.2 ± 5.1		Mean % change 2.8 ± 5.3	
	$t = 4.16$ $p < 0.01$		$t = 0.53$ $p > 0.2$	

*Subject studied in reverse order.

DISCUSSION

The results of these studies show that, under carefully controlled conditions, an effect of phenformin on glucose regulation in nondiabetic subjects can be demonstrated. The effect on fasting glucose levels was small, variable, and not related to the initial glucose level. The reported effects of the drug in diabetic subjects are also very variable.[1] The effect of phenformin on oral glucose tolerance was similar to its effect on intravenous glucose tolerance. Thus, the results are in contrast to many reports of the drug in both diabetic and nondiabetic subjects.[8,9] Two features of the design of the experiments may have contributed to the different results obtained in this study. First, the patients spent the whole of the study period under the carefully supervised conditions of a metabolic ward, consumed liquid formula diets and maintained constant body weight. The majority of the studies reported were performed on outpatients (e.g.[2,16]), and several reports stated that the weight of the subjects changed during the course of the study (e.g.[16]). Secondly, the drug was administered for ten to fourteen days before the measurements of glucose and insulin were made, and no drug was administered in the fifteen hours before the test. In most of the studies which report different effects of phenformin on oral and intravenous glucose tolerance, the drug was administered only on the day of the study[9] or for three days prior to the study, with a complete daily dose being taken just before the glucose tolerance test.[8] Thus the earlier studies may have been complicated by an acute toxic effect on the gastrointestinal tract, a well known side effect of the biguanides,[17] and may

not have allowed enough time for the drug to exert its full effects on carbohydrate metabolism.

The more marked effect of phenformin on diabetic subjects could be explained by its effect on insulin secretion, which may have a counterregulatory function, as suggested by the negative correlation between the change in fasting glucose and the change in the acute insulin response. It has been shown that there is a relationship between the fasting blood glucose levels and the acute insulin response to an intravenous glucose pulse, and that fasting hyperglycemia is associated with a diminished or absent acute insulin response with normal basal insulin levels.[18] Thus, diabetic subjects with no acute insulin response may not be able to compensate for the hypoglycemic action of phenformin, and a profound effect on glucose levels could result. Similarly, there is a linear relationship between the Kg and the acute insulin response in both normal[14] and diabetic subjects,[18] and this was confirmed in this study. Diabetic subjects with a diminished acute insulin response may thus respond to phenformin with a greater improvement in Kg and a lesser change in insulin response than nondiabetics. This is supported by the data of a study of the effect of metformin in obese subjects,[19] which showed that diabetic subjects with no acute insulin response increased their Kg in response to the drug, while nondiabetic subjects had no change in Kg but lowered their acute insulin response.

These studies provide some information on the importance of impaired intestinal absorption of glucose in the effect of phenformin on carbohydrate metabolism. The lowering of basal glucose and insulin levels suggests that effects other than those on glucose absorption must be operating. Further support for this comes from the lowering of the insulin response to intravenous glucose brought about by the drug. Despite the lower insulin response, the Kg tended to increase. As there is a linear relationship between the Kg and the acute insulin response, a lowering of the acute insulin response with an increase or even no change in Kg, must mean that phenformin either exerts its own effect on the assimilation of glucose, or increases the tissue sensitivity to insulin. Studies in which only the glucose response to intravenous glucose[8] was measured are thus misleading in suggesting that biguanides have no effect on glucose assimilation. If phenformin's major action on carbohydrate metabolism is to impair intestinal absorption of glucose, a more marked effect of the drug on oral than intravenous glucose tolerance would be expected, but this was not found. Also, any reduction in the glucose response to oral glucose would be more prominent in the incremental area than the total area if malabsorption was the cause. The changes in the total insulin responses to oral (table 7) and intravenous glucose (table 8) are almost identical. This is in agreement with a previous study of the effect of phenformin on insulin secretion[12] and does not support the proposal that phenformin's major action is 'nonperipheral'.[9] The present results are consistent with the results of glucose turnover studies[3,4] which found that phenformin had little effect on the blood glucose levels of nondiabetic subjects, but increased glucose turnover by increasing both hepatic output and peripheral utilization of glucose. Insulin concentrations were not measured in either of the turnover studies.

Although it has been suggested that the depressed insulin response which occurs when phenformin is administered is secondary to the effect of the drug on glucose metabolism, a direct effect of the drug on the pancreatic islets cannot be excluded. However, the fact that the acute insulin response to intravenous glucose, expressed in relation to basal levels (table 8), was unchanged suggests that the insulin secretory mechanisms were intact. A preliminary study of the effect of phenformin on the perfused rat pancreas showed that the drug stimulated insulin secretion.[20] Thus there is no evidence that the function of the insulin secretory cells is depressed by phenformin.

Thus this study shows that, contrary to what is stated in many standard texts,[21] phenformin has mild effects on the plasma glucose and marked effects on the plasma insulin in nondiabetic subjects. Theories of the mode of action of phenformin must take account of this fact and of the observations that many of the actions of the drug cannot be explained in terms of impaired intestinal absorption.

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