Hypoglycemic Action of Fenfluramine in Diabetes Mellitus

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SUMMARY

Fenfluramine has been demonstrated to have a biphasic effect on glucose removal by skeletal muscle during forearm perfusion. A prompt early increase in glucose removal by skeletal muscle, lasting 90 to 120 minutes, disappeared with the release of free fatty acids. The metabolic effect of fenfluramine on glucose removal occurred without increase in lactate release, suggesting complete oxidation of glucose by skeletal muscle.

The effect of fenfluramine on blood glucose was assessed in maturity onset and insulin-requiring diabetics. The drug was most suitable as a hypoglycemic agent when administered immediately before a meal in order that the maximum hypoglycemic action occurred during the period of post-absorption hyperglycemia. When administered before a meal fenfluramine consistently lowered blood glucose levels in maturity onset diabetes mellitus for at least two hours. A similar but less marked action was seen in insulin-requiring diabetics. Blood glucose levels were lowered by fenfluramine in diabetics who were maintained on diet alone or diet plus tolbutamide without the risk of lactic acidosis and without any direct effect on insulin secretion. DIABETES *22:* 858-67, November, 1973.

Hyperglycemia is a constant feature of overt or clinical diabetes mellitus. Although hyperglycemia may be produced by relative or absolute insulin deficiency, the precise metabolic defect in diabetes has not been elucidated. In the management of diabetes, therapy is directed toward maintenance of normal blood glucose levels and lipid metabolism and prevention of complications. Hyperglycemia can be controlled in most nonketotic diabetics by diet alone or diet plus oral hypoglycemic agents, such as the sulfonylureas and the biguanides.[1-3] Following the report of the University Group Diabetes Program 1970,[4] it has been suggested that there may be an increased risk of death from myocardial infarction in patients treated with sulfonylureas. Since 1970 these agents have been used with caution, particularly in patients with pre-existing coronary artery disease. Although the biguanides are effective hypoglycemic agents, they may cause nausea, anorexia and the occasional appearance of lactic acidosis.[5-8] In view of the disadvantages of these forms of therapy and the reluctance of patients to accept regular insulin injections, an alternative form of hypoglycemic therapy has become desirable.

Fenfluramine is an effective anorectic agent structurally resembling amphetamine.[9,10] Despite structural similarities, the metabolic actions of fenfluramine are quite different from those of amphetamine; it does not stimulate the central nervous system[11] and has not been used as an addiction drug.[12] Numerous investigators have demonstrated the efficacy of fenfluramine in the management of obesity[13-16] and acceleration of adipose tissue lipolysis in vitro,[17] but little attention has been paid to the actions of the drug on glucose metabolism. Butterfield and Whichelow[18] demonstrated that fenfluramine did increase glucose uptake by muscle, although no further observations on these properties have been made.

The present studies were undertaken to investigate the actions of fenfluramine on glucose metabolism in normal volunteers and in patients with maturity onset diabetes mellitus. Two parameters have been employed:

1. The effects of fenfluramine on human skeletal muscle and adipose tissue metabolism were examined by a modification of the forearm perfusion technic of Zierler and Rabinowitz.[19] This technic has been used to study differential metabolism of glucose, fatty acids, potassium and lactate in skeletal muscle and adipose tissue in the resting forearm and following intra-arterial infusion of

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fenfluramine and insulin. In other experiments glucose, free fatty acids, insulin and growth hormone response patterns were determined during prolonged intravenous infusions of fenfluramine.
2. The effect of fenfluramine on blood glucose was assessed in diabetic patients maintained on diet alone and diet plus a sulfonylurea or insulin.

METHODS

In the forearm perfusions and intravenous infusions, twenty normal male volunteers aged eighteen to twenty-three years were used. Each was within 5 per cent of the ideal weight for age and sex.

In the diabetes study, twenty-seven patients, including seventeen females and ten males, were used. All had maturity onset diabetes mellitus as diagnosed by glucose tolerance tests; sixteen were presenting for the first time, and eleven had been previously maintained by diet plus a sulfonylurea. In all patients previously treated with a sulfonylurea, the disease had not been satisfactorily controlled, with a fasting blood glucose above 120 mg./100 ml. and a two hour post-absorption blood glucose greater than 180 mg./100 ml. All patients were within 10 per cent of the ideal weight for height, age and sex. Patients outside this range were specifically excluded from the studies. In a separate study the effect of fenfluramine on blood glucose was assessed in ten insulin-requiring diabetics.

Forearm perfusion studies. After an overnight fast each volunteer was placed at rest for at least sixty minutes before the experiment. Xylocaine 1 per cent was infiltrated around a large vein in the antecubital fossa, a superficial vein on the dorsum of the forearm and the brachial artery 2 to 4 cm. proximal to the cubital fossa. A polyethylene cannula was introduced in retrograde fashion into the antecubital vein for a distance of 8 to 10 cm. toward the wrist. Providing the tip of the catheter in the antecubital vein lies between the radius and ulna, it will drain the deep muscular compartment of the forearm with approximately 15 per cent contribution from adipose tissue.[28] The second polyethylene cannula was introduced into a superficial vein on the dorsum of the forearm until its tip lay just beneath the skin 6 to 8 cm. distal to the cubital fossa. Venous catheters were kept patent with an infusion of physiologic saline at a rate of 2 ml. per minute.

A double lumen arterial cannula was introduced by percutaneous puncture into the brachial artery so that its tip lay proximal to the site of the arterial puncture. The needle had an 18 gauge inner collection channel which terminated 3 cm. above the outer infusion channel. The inner channel was kept patent by a constant infusion of physiologic saline at a rate of 0.1 ml. per minute. Test solutions were infused through the outer channel at a rate of 2.5 ml. per minute, using a Harvard constant infusion pump. Evans Blue (0.5 mg. per milliliter) was added to the test solution to measure forearm blood flow and to determine when steady state conditions had been established.[19] Five minutes before each collection period, a 5 cm. sphygmomanometer cuff was inflated around the wrist to at least 200 mm. Hg to exclude the hand from the circulation and to prevent mixing of superficial and deep venous blood. Using this procedure, arteriovenous differences of glucose, free fatty acids, potassium and lactate could be determined between the brachial artery and either deep or superficial veins, representing muscle and adipose tissue metabolism, respectively. The metabolic effect of a test substance could be evaluated by infusion into the brachial artery distal to the site of sampling. The forearm perfusion technic is illustrated in figure 1. Before fenfluramine was infused, five blood samples were obtained from each vessel during a thirty minute control period.

Two perfusion regimes were used. In the first, fenfluramine was infused into the brachial artery for fifteen minutes before the second sampling period. During the sampling period of thirty minutes, five blood samples were obtained from each vein and the brachial artery. An aliquot from each sample was placed in cold 5 per cent perchloric acid for lactate determination and the remainder was collected in a tube containing 1 per cent sodium fluoride. Serum was separated from the determination of glucose, potassium, free fatty acids and lactate. Subsequently, soluble porcine insulin (Novo) was infused at a rate of 18 mU.

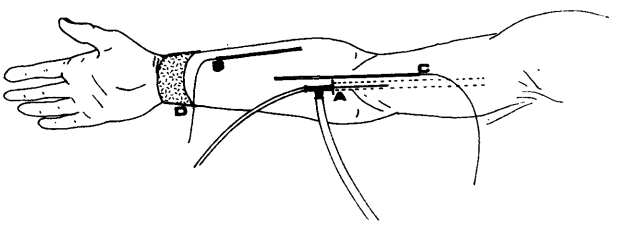

FIG. 1. Forearm perfusion procedure. The arterial cannula (A) is situated in the brachial artery. A superficial venous cannula (B) and a deep venous cannula (C) drain adipose tissue and skeletal muscle respectively. A sphygmomanometer cuff (D) is inflated above arterial pressure to prevent mixing of superficial and deep venous blood in the hand.

per minute to raise the arterial insulin concentration to approximately 250 μU. per milliliter (two to three times the peak insulin concentration following glucose absorption). A third sampling period was commenced after fenfluramine had been infused for one hour. Five samples were obtained from each vein and the brachial artery during the third thirty minute sampling period.

In the second series of experiments fenfluramine was infused into the brachial artery for ninety minutes before the second sampling period. Subsequently insulin was infused at a rate of 18 mU. per minute and the third sampling period was commenced after fenfluramine had been infused for two hours. Sampling was carried out during each period as in the previous experiments. In both the short (90 minutes) and the long (165 minutes) infusions, fenfluramine was administered at a rate of 5 μg. per minute, diluted in physiologic saline.

Intravenous fenfluramine infusion studies. After an overnight fast each volunteer was placed at rest for at least thirty minutes before the experiment. Fenfluramine, 40 mg., was injected intravenously, followed by a constant infusion of 1 mg. per minute for ninety minutes. Venous blood samples were obtained from an antecubital vein in the contralateral arm for determination of glucose, free fatty acids, immunoreactive insulin and growth hormone.

In separate experiments, the disappearance rate of glucose (50 gm.) injected intravenously was calculated (K value). This study was repeated on subsequent days following (1) injection of 40 mg. fenfluramine intravenously and (2) injection of 40 mg. fenfluramine intravenously plus constant infusion at a rate of 1 mg. per minute for 150 minutes.

Diabetes mellitus studies. Four studies were undertaken:

1. Oral glucose tolerance tests, 100 gm., were performed in sixteen maturity onset diabetics at the time of presentation. Testing was repeated after three weeks of treatment by a supervised diet containing 25 to 30 calories per kilogram of ideal body weight. A high carbohydrate diet (300 gm. daily) was given for three days before each test. Following the second glucose tolerance test, all patients were given 40 mg. of fenfluramine twice daily, thirty minutes before breakfast and thirty minutes before the evening meal. After three months of fenfluramine therapy, the glucose tolerance test was repeated in thirteen patients and also in three patients who had been maintained for the entire period by dietary regulation alone.
2. Eleven maturity onset diabetics in whom disease was inadequately controlled by diet plus tolbutamide (1 to 2 gm. daily) were examined by oral glucose tolerance tests. The sulfonylurea treatment was continued, and the patients were given 40 mg. of fenfluramine twice daily, thirty minutes before breakfast and thirty minutes before the evening meal. After three months the oral glucose tolerance test was repeated. The initial dietary management was continued throughout.
3. In five maturity onset diabetics the acute effects of fenfluramine on glucose tolerance were evaluated. Two glucose tolerance tests were performed five days apart on each patient. The second glucose tolerance test was preceded by an oral dose of 40 mg. of fenfluramine thirty minutes before the test.
4. In twenty-one maturity onset diabetics blood glucose was measured immediately before and one, two and three hours after a standard breakfast. The estimations were repeated on a separate day when the same breakfast had been preceded by an oral dose of 40 mg. of fenfluramine taken thirty minutes before eating. A similar study was undertaken on ten insulin-requiring diabetics who had received their usual dose of insulin on the morning of the test.

Analytical procedures. Serum glucose was estimated by a glucose oxidase method,[20] serum free fatty acids by the Dole extraction[21] followed by the Duncombe colorimetric procedure.[22] Serum potassium was determined by flame photometry and blood lactate by a spectrophotometric method that employs lactic dehydrogenase.[23] Serum immunoreactive insulin and growth hormone were determined by double antibody radioimmunoassay technic.[24,25] Insulin secretion was expressed as the insulinogenic index, in which the area subtended by the insulin response curve, measured by planimetry, was related to the corresponding glucose curve during an oral glucose tolerance test. Using this technic, an expression was obtained for the insulin response in terms of the glucose load.[26,27]

Forearm perfusion studies were accepted for analysis only when steady state conditions had been established. The concentration of Evans Blue in the brachial artery and superficial and deep veins was used to verify steady state conditions. In each serum sample the concentration of Evans Blue was determined from the optical density at 620 nm. Forearm plasma flow was calculated using the technic of Andres et al.[28] from the formula $F = 1/Co - Cr$, where F = plasma

flow (milliliters per minute), Co = the concentration of Evans Blue in venous plasma and Cr = the concentration of dye in recirculating plasma.

RESULTS

Effects of fenfluramine on glucose, free fatty acids, potassium, and lactate flux during forearm perfusion. The effects of fenfluramine and fenfluramine plus insulin on glucose, free fatty acids, lactate and potassium flux across forearm skeletal muscle and adipose tissue are shown in table 1. Fenfluramine infusion (5 μg. per minute) caused maximal glucose uptake by muscle, which could not be further increased by insulin (18 mU. per minute). Low rates of infusion of fenfluramine (2.5 μg. per minute) did not cause maximal glucose uptake by muscle, and this could be further increased by insulin. During short term perfusions (ninety minutes) there was no change in glucose flux in adipose tissue. Free fatty acid and potassium flux did not change in either muscle or adipose tissue. Although there was slight basal lactate release from muscle, this was not increased during fenfluramine perfusion.

During the long-term fenfluramine perfusions (165 minutes) there was no significant increase in glucose uptake by forearm skeletal muscle (table 2). The addition of insulin (18 mU. per minute) to fenfluramine (5μg. per minute) increased glucose uptake by muscle to a degree similar to that observed in the short-term perfusions. In contrast to the short-term perfusions, significant free fatty acid release occurred from the superficial vein and the deep vein during prolonged fenfluramine infusions. There was no significant change in lactate flux from either vein during prolonged fenfluramine perfusions.

Forearm blood flow was not altered by fenfluramine during either the short- or long-term perfusions (table 3).

Effects of intravenous fenfluramine on serum glucose, free fatty acids, immunoreactive insulin and growth hormone. Prolonged fenfluramine infusion did not alter serum glucose or serum immunoreactive insulin levels (figure 2). Serum free fatty acids rose from a fasting level of 560 ± 83 μEq. per liter to a peak of 1,150 ± 131 μEq. per liter at 140 minutes. No increase in serum free fatty acids occurred for the first seventy-five to ninety minutes after the start of the infusion. Serum immunoreactive growth hormone rose from a fasting level of 1.8 ± 0.5 ng. per milliliter to a maximum of 9.8 ± 2.4 ng. per milliliter at 160 minutes.

TABLE 1

Effects of fenfluramine and insulin during short-term perfusion (90 minutes)

	Glucose		Free fatty acids		Lactate		Potassium	
	A	A-DV	A-SV	A	A-DV	A-SV	A	A-DV	A-SV	A	A-DV	A-SV
	Micromoles per milliliter											
Control	4.85 ± .01	0.15 ± .02	0.20 ± .02	0.42 ± .02	−0.15 ± .01	−0.30 ± .05	0.60 ± .01	−0.12 ± .02	−0.17 ± .01	4.00 ± .03	−0.21 ± .04	−0.03 ± .04
Fenfluramine 5 μg./min.	4.86 ± .03	*1.15 ± .21	0.41 ± .08	0.41 ± .01	−0.17 ± .02	−0.33 ± .05	0.60 ± .02	−0.10 ± .02	−0.19 ± .02	4.02 ± .02	−0.17 ± .04	−0.02 ± .04
Fenfluramine 5 μg./min. + Insulin 18 mU./min.	4.85 ± .01	1.25 ± .30	0.50 ± .06	0.42 ± .02	0.22 ± .03	0.29 ± .04	0.61 ± .02	−0.13 ± .02	−0.19 ± .02	4.02 ± .03	0.20 ± .03	0.01 ± .02

Short-term forearm perfusion in six subjects. A = arterial, A-DV = arteriovenous difference between brachial artery and deep vein (muscle), A-SV = arteriovenous difference between brachial artery and superficial vein (adipose tissue). Each value represents the mean ±S.E.M. of six studies with five determinations during each sampling period. Negative values indicate that lipolysis, lactate or potassium release occurred, whereas positive values indicate uptake during forearm perfusion.

*$p < 0.01$

TABLE 2

Effects of fenfluramine and insulin during prolonged perfusion (165 minutes)

	Glucose			Free fatty acids			Lactate		
	A	A-DV	A-SV	A	A-DV	A-SV	A	A-DV	A-SV
	Micromoles per milliliter								
Control	4.90 ± .06	0.16 ± .02	0.21 ± .03	0.39 ± .02	−0.12 ± .04	−0.28 ± .05	0.61 ± .02	−0.12 ± .02	−0.18 ± .03
Fenfluramine 5 μg./ml.	4.84± .02	0.20 ± .03	0.24 ± .04	0.40 ± .02	*0.26 ± .05	*1.36 ± .24	0.59 ± .01	−0.12 ± .02	−0.20 ± .02
Fenfluramine 5 μg./ml. + Insulin 18 mU./min.	4.84 ± .08	*1.16 ± .20	0.50 ± .08	0.41 ± .03	0.21 ± .05	0.29 ± .05	0.60 ± .02	−0.12 ± .02	−0.19 ± .02

Long-term perfusion in six subjects. A = arterial, A-DV = arteriovenous difference between brachial artery and deep vein (muscle), A-SV = arteriovenous difference between brachial artery and superficial vein (adipose tissue). Each value represents the mean ± S.E.M. of six studies with five determinations during each sampling period. Negative values indicate that lipolysis, lactate or potassium release occurred, whereas positive values indicate uptake during forearm perfusion.

* $p < 0.01$.

Effect of fenfluramine on glucose disappearance. The disappearance rate of glucose injected intravenously was accelerated immediately following fenfluramine (figure 3). After injection of 40 mg. fenfluramine plus a constant infusion at 1 mg. per minute for ninety minutes, the disappearance rate of glucose was markedly delayed. This delay in glucose removal coincided with the increase in serum free fatty acids during fenfluramine infusion (figure 2).

Effects of diet and fenfluramine on glucose tolerance in maturity onset diabetes mellitus. The glucose and immunoreactive insulin (IRI) responses and the insulinogenic indices calculated during glucose tolerance tests were all markedly abnormal in the sixteen maturity onset diabetics studied at the time of presentation (table 4). Dietary regulation alone for three weeks or three months significantly reduced the glucose and IRI responses but did not alter the insulinogenic index. Although glucose tolerance was improved, dietary management alone did not improve the relative insulin deficiency. A marked reduction in glucose and IRI responses was seen in those patients maintained on diet plus fenfluramine for three months, although the insulinogenic index had not changed significantly.

The mean body weight on presentation was 73.5 kg., and after three months of fenfluramine was 72.9 kg., the difference being not statistically significant. In this group of patients the reduction in the glucose response from 754 ± 27 mg.-min. per milliliter to 540 ± 18 mg.-min. per milliliter was significant ($p < 0.01$) and could not be explained by weight reduction due to diet alone.

Effect of fenfluramine on glucose tolerance during tolbutamide therapy. The glucose and IRI responses to oral glucose were markedly abnormal in the eleven maturity onset diabetics treated with tolbutamide (table 4). In these patients the insulinogenic index was higher than it was in the untreated maturity onset diabetics, indicating some improvement in the relative insulin deficiency during sulfonylurea treatment ($p < 0.05$).

Fenfluramine further lowered the glucose and insulin responses ($p < 0.01$ in each case) although there

TABLE 3

Forearm blood flow during fenfluramine perfusion

Subjects		Forearm blood flow	
		Before fenfluramine	After fenfluramine
		ml. blood /100 ml. forearm per min.	
Short-term perfusion	1	5.3	5.4
	2	4.3	4.4
	3	4.5	4.8
	4	5.1	5.1
	5	4.2	4.5
	6	5.1	5.3
Long-term perfusion	7	4.3	4.5
	8	5.2	5.3
	9	4.5	4.7
	10	3.9	4.4
	11	4.4	4.7
	12	4.9	5.1

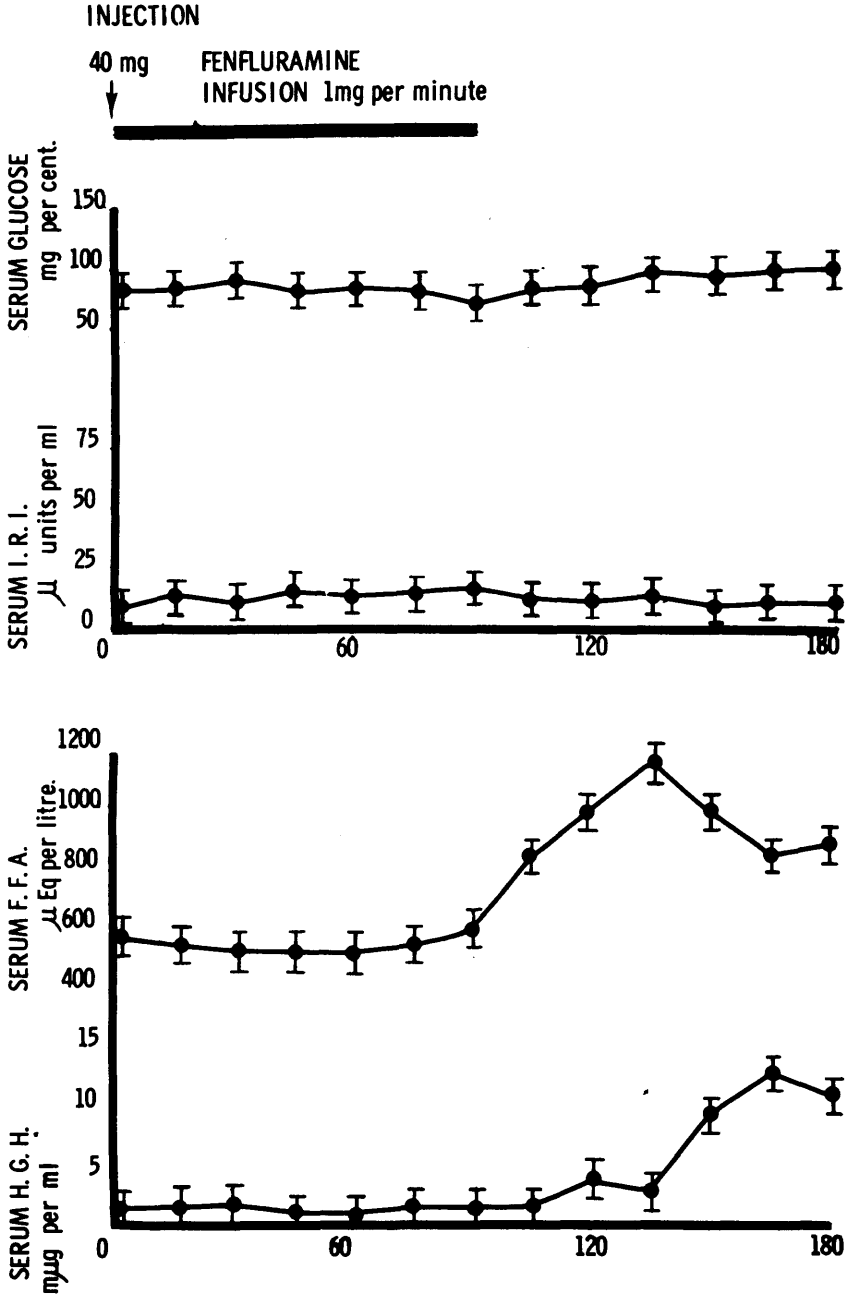

FIGURE 2

Serum glucose, insulin (IRI) FFA and growth hormone (HGH) in eight volunteers after intravenous injection of 40 mg. fenfluramine and a constant infusion of 1 mg. per minute for ninety minutes. Each point represents the mean ± S.E.M. of eight determinations.

was no change in the degree of insulin deficiency. Mean body weight did not change significantly (75.6 to 74.9 kg.) during the three months of fenfluramine treatment.

Acute effects of fenfluramine on glucose tolerance. Improvement in glucose tolerance could be demonstrated immediately after fenfluramine was commenced (figure 4, table 5). A single oral dose of 40 mg. fenfluramine significantly reduced the blood glucose concentration thirty, sixty and ninety minutes after the glucose. The effect of fenfluramine on blood glucose could be demonstrated only during the post-absorptive phase, and there was no change in fasting blood glucose.

The pattern of glucose response was not altered by fenfluramine, and the peak postabsorption level occurred at the same time before and after fenfluramine, suggesting that the rate of glucose absorption re-

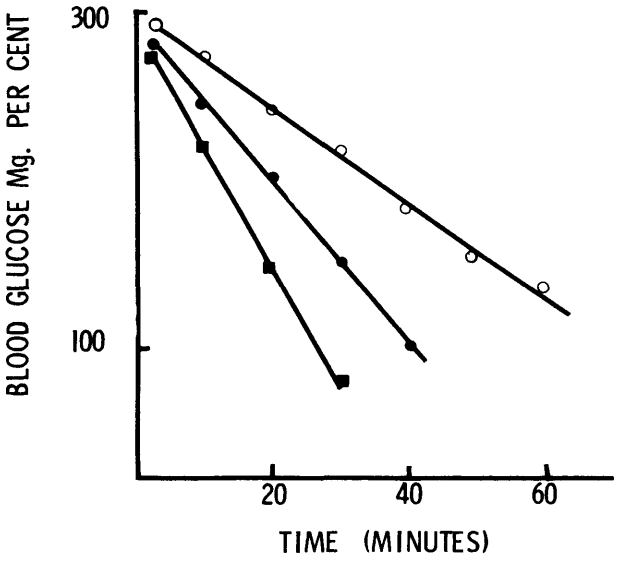

FIG. 3. Glucose disappearance (K value) in three volunteers after 50 gm. glucose by intravenous injection on three occasions: (1) Control •—• K = 2.75, (2) Immediately after injection of 40 mg. fenfluramine ▪—▪, K = 2.93 and (3) ninety minutes after injection of 40 mg. fenfluramine plus a constant infusion of 1 mg. per minute for ninety minutes o—o, K = 1.78.

mained unaltered. The single oral dose of fenfluramine did not significantly reduce serum IRI levels.

Effect of fenfluramine on postabsorption hyperglycemia. In twenty-one maturity onset diabetics managed by diet alone or by diet plus tolbutamide, fenfluramine lowered the postabsorption blood glucose by 35 per cent at one hour and 32 per cent at two hours after the standard meal (figure 5). The lowering of blood glucose by fenfluramine could not be detected after three hours and was confined to the first two hours after food ingestion.

A similar reduction in postabsorption blood glucose was seen after fenfluramine in ten insulin-requiring diabetics, but the change was less marked than that seen in diabetics maintained on diet alone or diet plus a sulfonylurea (figure 6).

Clinical data and side effects. Only diabetics whose body weight was within 10 per cent of the ideal weight for age and sex were included in this study to eliminate any bias due to obesity. The diet of 25 to 30 calories per kilogram was given in order that variation in body weight should be minimal during the study. No significant loss of weight occurred in any of the fenfluramine-treated patients during the study.

Side effects were infrequent and minimal. One patient experienced mild depression and vertigo which necessitated withdrawal of fenfluramine. All other patients completed the study, and four have been receiving fenfluramine for three years or more. A total of 486 patient months of fenfluramine treatment have been completed.

DISCUSSION

Although there are many published reports on the anorectic actions of fenfluramine and its use in the treatment of obesity, little attention has been paid to the action of this drug on glucose metabolism in man. Butterfield and Whichelow[18] observed that fenfluramine does increase glucose uptake by forearm skeletal muscle and suggested that it has an action similar to that of mild exercise, diverting glucose utilization to muscle rather than adipose tissue.

TABLE 4

Effect of diet and fenfluramine on blood glucose, serum IRI and insulinogenic index in maturity onset diabetes mellitus

	Glucose Response (mg.-min. per ml. mean ± S.E.M.)	IRI Response (μU.-min. per ml. mean ± S.E.M.)	Insulinogenic Index (μU.-mg. per ml.)
Normal (10)	244 ± 12	6,010 ± 135	24.6
Untreated maturity onset diabetics (16)	1,210 ± 236	18,327 ± 390	15.1
Treated diabetics:			
Diet: 3 weeks (16)	780 ± 25	13,327 ± 333	16.8
3 months (3)	754 ± 27	12,607 ± 203	16.7
Diet + fenfluramine: 3 months (13)	540 ± 18	9,234 ± 154	17.1
Diet + tolbutamide (11)	633 ± 23	12,849 ± 170	20.3
Diet + tolbutamide + fenfluramine: 3 months (10)	451 ± 33	9,290 ± 136	20.6

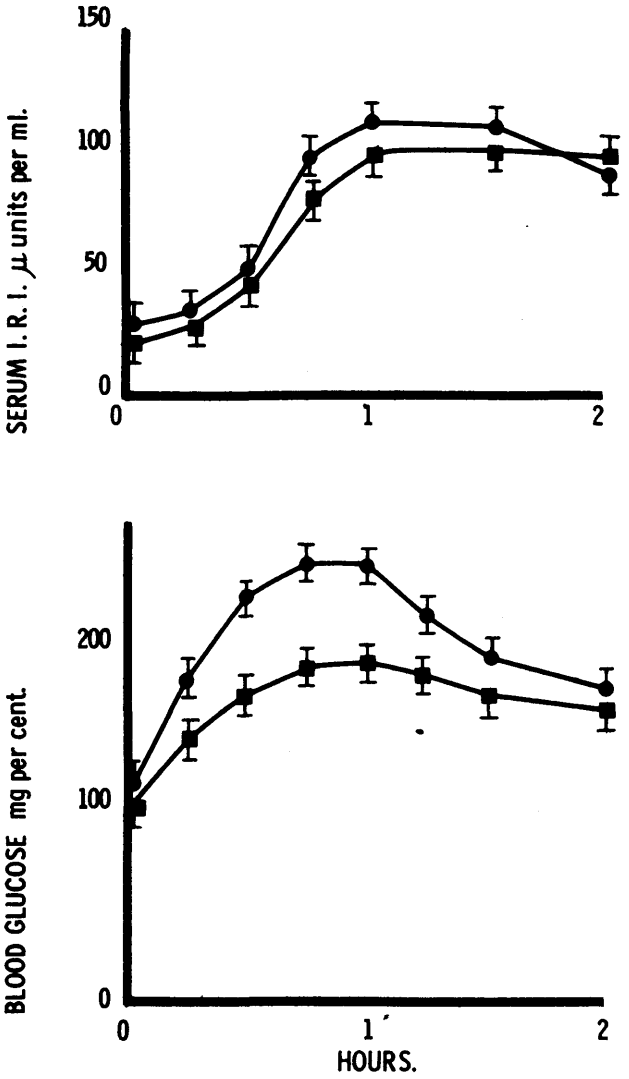

FIG. 4. Effect of a single dose of 40 mg. fenfluramine given thirty minutes before an oral glucose load in five maturity onset diabetics. The two glucose tolerance tests in each patient were five days apart. Each point represents the mean ± S.E.M. of five determinations. The fenfluramine-induced reduction in blood glucose is statistically significant at thirty minutes ($p < 0.01$), sixty minutes ($p < 0.01$) and ninety minutes ($p < 0.05$). (See table 5). Control •—•; after fenfluramine ■—■.

In forearm perfusion fenfluramine increased the glucose uptake by skeletal muscle for at least sixty minutes after administration. During this time there is no evidence of free fatty acid release from muscle or adipose tissue. When fenfluramine infusion was prolonged, free fatty acid release did occur after a delay of ninety minutes, and at this stage the effect of fenfluramine on glucose uptake was abolished. It is likely that the increased concentration of free fatty acids in serum and muscle was directly responsible for the loss of the effect of fenfluramine on glucose uptake. A similar action of free fatty acids on glucose uptake by muscle has been reported by Schonfeld and Kipnis.[29,30]

The effect of fenfluramine on glucose uptake by muscle is marked. In high doses, fenfluramine can increase glucose uptake to the maximum that can be achieved with insulin. Smaller doses of fenfluramine are potentiated by insulin. The action of fenfluramine on glucose uptake is similar to that of phenformin. In contrast to phenformin, it did not cause lactate release from muscle even when infused for two and one-half hours in a dose which produced maximal glucose uptake.

The delayed increase in serum free fatty acids during forearm perfusion and after prolonged intravenous infusion of fenfluramine was notable. Although the pattern of delayed free fatty acids release was similar to that produced by injection of human growth hormone, immunoreactive growth hormone should have been detectable in the serum for sixty to ninety minutes before the increase in serum free fatty acids if growth hormone were responsible for the lipolysis.[31] The delayed increase in growth hormone coincided with the rise in free fatty acids and this could not be related to coincidental stress or hypoglycemia. As suggested by Tsushima et al.,[32] it is likely that the rise in serum free fatty acids was directly responsible for the increase in growth hormone.

The early glucose uptake by muscle disappeared coincident with free fatty acid release. This change in the rate of glucose removal was demonstrated by the effect of fenfluramine on glucose disappearance from the circulation when free fatty acid release had occurred.

TABLE 5

Effect of fenfluramine on postabsorption blood glucose

Time	Control	Fenfluramine	Decrement	Per cent reduction
	mg. per cent			
0	105	103	2	1.9
30	223	151	72	32.3
60	241	163	78	32.3
90	185	149	36	19.5
120	173	140	33	19.0
150	143	137	6	4.0

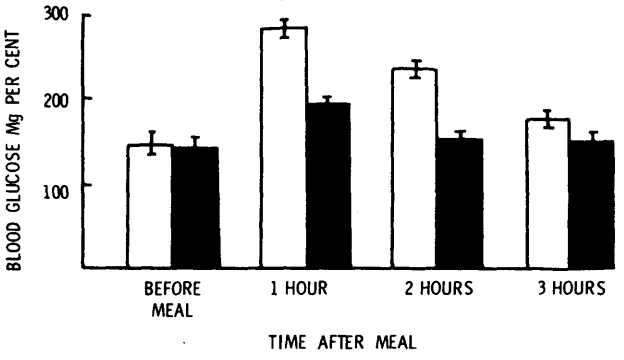

FIG. 5. The effect of fenfluramine before a standard meal in twenty-one maturity onset diabetics treated by diet alone or diet plus tolbutamide. Blood glucose was estimated during fasting and one, two and three hours after the meal (□). The test meal was repeated three days later following an oral dose of 40 mg. fenfluramine (■). Each histogram represents the mean ± S.E.M. of twenty-one determinations. The fenfluramine-induced fall in blood glucose is statistically significant at one hour ($p < 0.005$) and two hours ($p < 0.01$).

It was possible to use the short-term action of fenfluramine in lowering blood glucose to advantage in the management of diabetes mellitus, particularly to prevent the postabsorption rise in blood glucose which commonly occurs in diabetics who have achieved marginal control by diet alone or diet plus sulfonylureas. Fenfluramine given thirty minutes before breakfast consistently lowered the postabsorption blood glucose levels one and two hours after the meal. This change was seen without reduction in fasting blood glucose and had disappeared three hours after the meal. The ability of fenfluramine to lower blood glucose was demonstrated when body weight and food intake remained constant.

The effect of fenfluramine on blood glucose is different from that of the sulfonylureas as it does not improve the relative insulin deficiency characteristic of maturity onset diabetes mellitus. Although the insulinogenic index did not change during treatment with fenfluramine in diet-treated or sulfonylurea-treated diabetics, the abnormal glucose and insulin responses were both significantly reduced by fenfluramine. As there was no change in the efficiency of insulin secretion and no increase in serum insulin during fenfluramine infusion, ability of fenfluramine to lower blood glucose appears to be due to direct removal of glucose from the circulation. In this action, fenfluramine is similar to phenformin, however the latter drug inhibits glucose oxidation and leads to an accumulation and release of lactate from muscle with the risk of lactic acidosis.[5-8] Fenfluramine does not increase lactate production, and lactic acidosis has not been reported in patients treated with fenfluramine for obesity.

As the effect of fenfluramine on glucose removal is most marked for 90 to 120 minutes after administration of the drug, it is most beneficial as a hypoglycemic agent in the management of diabetes mellitus if it is administered immediately before a meal to achieve its maximum effect during the postabsorption period. When given before meals, fenfluramine will consistently lower postabsorption blood glucose levels in maturity onset and insulin requiring diabetics.

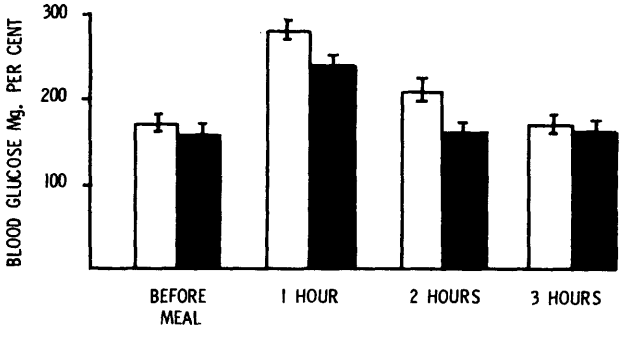

FIG. 6. The effect of fenfluramine before a standard meal in ten insulin-requiring diabetics. Blood glucose was estimated during fasting and one, two and three hours after the meal (□). The test meal was repeated three days later following an oral dose of 40 mg. fenfluramine (■). Each histogram represents the mean ± S.E.M. of ten determinations. The fenfluramine-induced fall in blood glucose is statistically significant at one hour ($p < 0.05$) and two hours ($p < 0.05$).

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