Brief Notes and Comments

Effect of Phenformin on Carbohydrate Absorption in Man

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SUMMARY

Recent studies have demonstrated that phenformin inhibits intestinal glucose absorption in man. In order to determine if carbohydrate malabsorption occurs during phenformin administration we used a breath hydrogen (H_2) test. This test depends upon fermentation of unabsorbed carbohydrate to hydrogen by colonic bacteria with subsequent absorption of H_2 and pulmonary excretion. H_2 excretion rates were measured in five normal subjects while fasting and two hours after the administration of 75 gm. of glucose. The study was repeated on the following day after the administration of 100 mg. of phenformin. There was no significant change in H_2 excretion. One subject was then studied several times a day while eating a normal diet; phenformin administration did not increase H_2 excretion. We conclude that the drug does not induce carbohydrate malabsorption. DIABETES *23*:716-18, August, 1974.

Although the precise mechanisms by which phenformin reduces blood glucose concentration in diabetic patients are unknown, it seems reasonably certain that part of the effect is mediated by inhibition of intestinal glucose absorption. The evidence for an intestinal effect includes the observation of decreased absorption in animals after phenformin[1-5] and studies in which a depression of blood glucose response to oral, but not to intravenous glucose, was found in both normal human subjects and patients with diabetes mellitus.[6,7] Finally, recent studies from our laboratory have confirmed an intestinal effect in man. We used a segmental perfusion technic in which intestinal absorption can be studied directly, and we found that phenformin markedly reduced jejunal glucose absorption in human volunteers.[8]

The purpose of the present study was to determine if phenformin results in glucose malabsorption. Is there a significant loss of glucose or is it all eventually absorbed by the small intestine even though the rate of absorption is diminished? In order to answer this question we used the method of Levitt and Donaldson;[9] this technic depends upon the production of hydrogen (H_2) by bacterial fermentation of unabsorbed carbohydrate in the colon. The H_2 produced is rapidly absorbed and then excreted by the lungs. Levitt and Donaldson found an inverse relationship between absorption as measured by blood sugar determination after oral carbohydrate and the rate of H_2 excretion by the lungs in patients with carbohydrate malabsorption and suggested the use of this technic to detect carbohydrate malabsorption.

MATERIAL AND METHODS

Five healthy volunteers, aged twenty-two to thirty-seven, were studied; three were female and two male. After an overnight fast, pulmonary H_2 excretion was determined at 8 a.m.; this was followed by the oral administration of 75 gm. of glucose. Two hours later (10 a.m.) a second H_2 excretion rate was measured. The change in H_2 excretion rate corresponds to malabsorbed glucose.[9] On the following day the study was repeated but with oral administration of 100 mg. of phenformin one-half hour prior to glucose.

One subject was studied for five days. During this period he received an 1838 calorie diet containing 78 gm. of protein, 86 gm. of fat, and 189 gm. of carbohydrate. Breakfast, containing 579 calories, was eaten at 8:15 a.m., lunch (687 calories) at 12 noon, and dinner (572 calories) at 5:30 p.m. H_2 excretion rates were measured at 8 a.m., 10 a.m., 12:30 p.m., 2:30 p.m. and 4:15 p.m. The first, second and fifth days were control periods. On the third and fourth days he was given 50 mg. of phenformin with breakfast, 25 mg. with lunch, and 25 mg. with dinner.

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Accepted for publication April 17, 1974.

Pulmonary H_2 excretion was measured by the following technic. After inhaling and exhaling several deep breaths of 100 per cent oxygen and expiring to residual volume the subject was switched to a Godart spirometer containing 9 L. of 100 per cent oxygen. A carbon dioxide absorber was incorporated into the system. After four minutes of breathing into this closed system, three vital capacity maneuvers were performed and the system was closed at the end of a forced expiration. The subject's residual volume was determined by a single breath neon method. Duplicate samples of spirometer gas were analyzed for H_2 concentration with a Tracor MT-150 gas chromatograph with an ultrasonic detector. Nitrogen was used as the carrier gas. 0.5 ppm. H_2 resulted in a deflection of 1 mm. H_2 excretion rate was determined by the following formula:

$$\frac{H \times (V + R)}{T}$$

where H equals H_2 concentration, V equals volume of gas in the spirometer at the end of rebreathing, R equals residual volume, and T equals time.

Informed consent was obtained from all subjects.

RESULTS

Table 1 shows the results using glucose as the carbohydrate source. During the control period H_2 excretion declined from fasting values despite glucose. This decline was also found by Levitt and Donaldson in normal subjects after glucose and in fasting subjects; they ascribed it to the decreasing availability of fermentable substrate in the colon.[10] On the day in which phenformin was given, post glucose H_2 excretion was slightly greater than fasting values but not in the range reported with significant carbohydrate malabsorption; Bond and Levitt observed an H_2 excretion of 0.2 ml. per minute after ingestion of as little as 6.5 gm. of lactulose, a nonabsorbable sugar.[11] ΔH_2, the change in H_2 excretion produced by glucose, was not significantly different after phenformin.

Figure 1 shows the results of the five-day study. Clearly phenformin given in divided dosage did not increase H_2 excretion in this subject ingesting normal meals.

TABLE 1

Effect of phenformin on H_2 excretion after oral glucose

	Control ml. per min.	Phenformin ml. per min.
Fasting	0.0662 ± 0.0234	0.0242 ± 0.0086
Postglucose	0.0266 ± 0.0141	0.0300 ± 0.0083
ΔH_2	−0.0395 ± 0.0178	0.0058 ± 0.0118

Mean ± SE are given.

ΔH_2: the difference between fasting and postglucose excretion rates. Mean ΔH_2 during the control period was not different statistically from that during the phenformin period (Student *t* test).

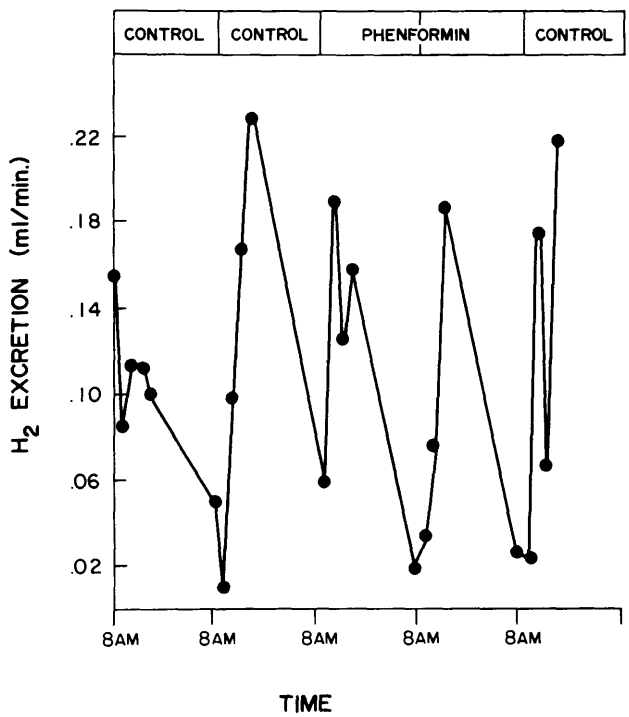

FIG. 1. H_2 excretion in one subject over a five-day period. Two days on phenformin were preceded by two control days and followed by one control day.

DISCUSSION

Phenformin has been shown to diminish the rate of glucose absorption from human jejunum[8] and to depress blood sugar response to oral but not intravenous glucose in normal subjects and in patients with diabetes.[6,7] Because of the considerable absorptive capacity of the small intestine and because of the infrequency of diarrhea in patients on phenformin, it seemed possible that ingested carbohydrate might be completely absorbed despite the effect of the drug upon absorption rates. In an elegant series of experiments[9-11] Levitt's group has demonstrated the usefulness of the breath H_2 test for detecting carbohydrate malabsorption. They have shown that H_2 production is limited to the colon, increases substan-

tially when only a small amount of carbohydrate reaches the colon, and that pulmonary H_2 excretion is a good reflection of colonic production. They have demonstrated that administration of poorly absorbed sugar such as xylose or lactulose in normal subjects and well absorbed sugar such as glucose to patients with carbohydrate malabsorption results in a substantial increase in pulmonary H_2 excretion. This technic then seemed ideal for determining if carbohydrate malabsorption occurs as a consequence of phenformin administration. Because breath H_2 is maximal at about two hours after the administration of poorly absorbed carbohydrate[10] we studied our subjects two hours after a glucose load, but found no significant effect of phenformin. Since it seemed possible that carbohydrate malabsorption might be intermittent, we studied one subject on a normal diet with multiple H_2 determinations. Again there was no increase in H_2 excretion during phenformin administration. This drug then, although it decreases rates of intestinal glucose absorption in man thereby at least contributing to an alteration in glucose tolerance curves, does not appear to result in significant carbohydrate malabsorption.

ACKNOWLEDGMENT

We are grateful to Dr. Edna M. Cree for advice and for the use of equipment in the Pulmonary Function Laboratory.

This work was supported in part by Grant no. AM 13927 from the National Institutes of Health, Bethesda, Maryland, and Veterans Administration Research Funds.

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