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MEASUREMENT OF THE GASTRIC EMPTYING RATE IN INSULIN-DEPENDENT AND NON-INSULIN DEPENDENT DIABETIC MEN WITH AND WITHOUT NEUROPATHY AND THE EFFECT OF METOCLOPRAMIDE ON GASTRIC STASIS

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ABSTRACT

Gastric emptying rate was measured in 40 individuals both insulin dependent (IDDM) and non-insulin dependent (NIDDM) diabetic men with and without objective evidence of neuropathy and in 20 age-matched non-diabetic controls using double isotope scient-scanning technique which can differentiate between solid and liquid emptying. These studies revealed striking results in neuropathic group. Both IDDM and NIDDM diabetic patients with neuropathy exhibited a significant ($P<0.0005$) increase in the gastric emptying rate of liquid markers in comparison with the controls of same age group as a result of conventional upper alimentary barium examination. However both types of non-neuropathic patients showed no significant difference in the above mentioned parameters than their respective controls. In addition both IDDM and NIDDM diabetic neuropathics showed a loss of differentiation in between the movement of solid and liquid markers during the 120 minutes of scanning period after the meal.

Both intravenous and oral metoclopramide produced symptomatic improvement and restored solid and liquid emptying in these patients.

Gastric stasis in both IDDM and NIDDM diabetic neuropathics and an impaired pattern of the gastric emptying in both types of non- neuropathics thus suggests an abnormality of antral peristalsis may be associated with an increased frequency to neuropathy irrespective of the type of the diabetes.

INTRODUCTION

Disturbances of the digestive tract are common in diabetic patients. Most of these are not directly related to diabetes whereas others, such as those due to diabetic neuropathy, may be regarded as specific complications. Among the latter, hypotonia and altered motility of hollow viscera are the most frequently encountered abnormalities (Rundles, 1945; Feldman

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et al., 1979). Studies on the neuropathology of the diabetic esophagus have demonstrated degenerative changes in the nerve trunk of the esophageal plexus and above the cellist ganglia (Bergman et al., 1962; Mandelstam et al., 1967). These gastric motor abnormalities are reported to occur in 20 to 30% of diabetic patients (Soergel et al., 1964; Phyllips et al., 1992; Rosa et al., 1996). Diabetic gastric neuropathy occurs most frequently in the presence of other diabetic complications such as peripheral neuropathy and retinopathy. Most frequent symptoms are either markedly depressed antral motor function or ineffectual peristalsis (Campbell et al., 1977; Kershavarzian et al., 1987). However, the etiology of gastric stasis has not been fully elucidated. The delay in gastric emptying has been attributed to vagal damage as part of a more generalized autonomic neuropathy (Aylett, 1962; Wooten et al., 1971; Norwak et al., 1993). But other mechanism may also contribute to the etiology of this disorder. Drugs such as bethanechol and metoclopramide which increases gastric motility, have been proved somewhat helpful clinically (Raybould et al., 1988; Okano et al., 1996).

Gastric emptying abnormalities in diabetic patients suffering from nausea and vomiting have repeatedly been evaluated since Rundles (1945) who first proposed autonomic neuropathy as the cause of this gastrointestinal dysfunction. Diabetic gastric atony is believed to be similar to that seen after vagotomy (Oliveria et al., 1984; Foster et al., 1990) and has been attributed to a vagal neuropathy (Wooten et al., 1971). Conventional barium meal investigation reveals a dilated stomach with impaired peristalsis and delayed emptying (Bolondi et al., 1985; Byrne, 1996). Radiological and manometeric abnormalities of esophageal function commonly accompany gastric atony, but are more frequently asymptomatic with rare dysphagia (Marzio, 1989). Previous studies of gastric emptying using saline meals have shown that emptying is slower than normal in diabetics (Aylett, 1962). In addition studies on gastric emptying using the scanning and gamma camera methods based on the incorporation of gamma emitting radio active isotopes in the food offers a means of assessing emptying after ingestion of ordinary meals but the heterogeneity of such meals may present a problem, as liquids and solids ingested together are not emptied from the stomach at the same rate (Horowitz et al., 1986; Lehmann et al., 1996; Phillis et al., 1997). However available information on the emptying of solid and liquid meals in diabetic gastropathy is limited.

Although diabetic neuropathy is now believed to be multi factorial in origin, with chronic hyperglycemia, our knowledge regarding the pathological basis of diabetic gastrointestinal abnormalities are still incompletely understood. In the present study we have therefore employed the technique using two isotopes, one acting as a marker of liquid component and the other as the marker of solid component of the meal in both neuropathic and non-neuropathic diabetics which may be useful in defining diabetic gastropathy in such patients.

MATERIALS AND METHODS

Gastric emptying was studied in 20 insulin dependent (IDM) and 20 non-insulin dependent (NIDDM) diabetic men with and without an objective evidence of autonomic

neuropathy and in 20 age-matched non-diabetic men serving as controls using a double isotope scient-scanning technique which differentiates between solid and liquid emptying in 2 groups of diabetics by established methods (Bolondi et al., 1985). All diabetic patients were from 20 to 63 years old (mean 43) and the duration of onset of the disease was 1-33 years (mean 11.2).

In addition a preliminary study was made of the effect of metoclopramide on gastric stasis by intravenous and oral procedures.

All the neuropathic patients had abnormal cardiovascular reflexes, mainly an impaired heart rate response to the valsalva maneuver and abnormal blood pressure response to sustained hand grip and a postural fall in systolic blood pressure of at least 30 mm Hg. Non-neuropathic patients had no clinical evidence of autonomic neuropathy and had normal cardiovascular reflexes. The two groups of diabetics were matched for mean age and duration of diabetes. Twenty patients without known gastrointestinal disease formed a group of non-diabetic controls. One week before the gastric emptying study, all the diabetic patients had a conventional upper alimentary barium examination (swallow, meal, and follow-trough) performed. The time of ingestion of the meal was defined as the mid point of the period during which the meals was consumed, which on average was 5 minutes. Ten minutes thereafter, the patient was positioned under a double-headed rectilinear scanner (J & P Engineering Ltd., Reading, England) and a scan of the abdomen was performed. Four further scan were undertaken at intervals of approximately 30, 60, 90 and 120 minutes after the meals: Quantitation of the each isotope present in the stomach on successive scan was obtained by using automatic gamma counter with a silent-700-Data Terminal (Bio-Tech Inc. Texas, USA). Liquid marker emptying during the period 0-10 minutes was taken to represent the early phase of gastric emptying and this was measured in all diabetics and non-diabetic controls. Subsequent emptying of the liquid marker-that is during the period 10-120 minutes was measured in all patients and the emptying rates were expressed as half time (T 1/2). Comparison of solid and liquid marker emptying was initially undertaken during the period between the second and final scans that is, approximately 30-120 minutes after the meal ingestion with the intention of avoiding the early phase of emptying which might complicate interpretation of the data.

The effect of metoclopramide (Maxolon) on gastric emptying was assessed in all groups. Six weeks after the initial measurement the gastric emptying measurements were repeated with intravenous administration of 10mg metoclopramide five minutes before meal ingestion. After a further week patients started oral metoclopramide, one 10-mg tablet three times daily before meals, which was continued for two weeks. A third emptying study was then performed: on this occasion, the patients were given one 10- m metoclopramide tablet, 20 minutes before the meal. Statistical comparisons were performed using unpaired t-tests.

RESULT

A comparison of the measurement of the gastric emptying $T_{1/2}$ values for the liquid

marker in IDDM and NIDDM patients (with and without neuropathy) and their respective controls is presented in Table 1. This comparison revealed a significant ($P < 0.005$) increase in the $T_{1/2}$ values for gastric emptying in both types of diabetic neuropathics than non-diabetic controls. However both IDDM and NIDDM diabetics without neuropathy were found to have normal $T_{1/2}$ value. Gastric stasis with $T_{1/2}$ values greater than 100 minutes in both IDDM and NIDDM diabetic neuropathic patients clearly indicate a neuropathic involvement in the pathway of antral peristalsis in these patients.

A comparison of the gastric emptying between the solid and liquid markers during the period between the second and final scan in IDDM and NIDDM diabetic men with and without neuropathy and their respective non-diabetic controls is presented in Table II. This comparison reveled that in both types of non-neuropathics as well as in non-diabetic control group, there was a significant ($P < 0.005$) difference in the emptying pattern of the two markers, i.e. the gastric emptying of solid marker was more slow than the liquid marker. In the neuropathic group (both IDDM and NIDDM), however, the pattern of solid and liquid marker emptying were found to be much more alike with no significant difference.

The data for an other comparative study of gastric emptying between the solid and liquid markers over full 0-2 hours time period in IDDM and NIDDM diabetics (with and without neuropathy) and in non-diabetic controls is presented in Table III. This comparison again revealed an obvious solid-liquid differentiation in both types of non-neuropathic diabetic as well as in non- diabetic controls. The difference being significant ($P < 0.005$) statistically. Both IDDM and NIDDM diabetics with neuropathy, however did not attained a significant difference in solid-liquid emptying rate.

An impaired pattern of solid-liquid marker emptying in both IDDM and NIDDM diabetic neuropathic patients thus suggest gastric stasis probably due to an abnormality of antral peristalsis as a result of a defect in motor nerve function in this disease.

The data for the effect of metoclopramide on the pattern of gastric emptying in both IDDM and NIDDM diabetics (with and without neuropathy) and in age matched non-diabetic controls is summarized in Table IV. Both intravenous and oral metoclopramide was found to restore the $T_{1/2}$ values of the liquid-solid markers to normal in IDDM and NIDDM diabetic neuropathic patients. There results thus suggest that metoclopramide may be helpful in clinical management of gastric stasis in these patients.

DISCUSSION

In the present study an attempt has been made to determine the pattern of gastric emptying in IDDM and NIDDM diabetic men (with and without neuropathy) and their age-matched non-diabetic control subjects.

None of our non-neuropathic diabetic patients (both IDDM and NIDDM) exhibited gastric stasis, however the normal differentiation between solid and liquid emptying in this

group was found to be impaired.

Very interestingly both intravenous and oral therapy of metoclopramide produced symptomatic improvement in both types of diabetic neuropathic patients showing the symptoms of gastric stasis and restored the pattern of gastric emptying to normal.

As in the previous studies of diabetes (Campbell et al., 1977; Schade et al., 1985; Lipp et al., 1996), radiological abnormalities of esophageal motility were also found in some of our patients, (data not shown) although none had symptom suggesting esophageal dysfunction. In our studies we found these abnormalities to be associated in the diabetic patients with an objective evidence of autonomic neuropathy, whereas non- neuropathic diabetic patients showed normal esophageal motility. Clinical and experimental studies have suggested that loss of normal vagal innervation of the stomach results in accelerated gastric emptying (Sandhu et al., 1987; Brown et al., 1988; Bornet et al., 1990). In our studies, we could not identify any rapid early emptying of liquid marker corresponding to this pattern. However an unexpected finding in our diabetics without gastric stasis was the loss of solid-liquid differentiation. It would seen that this can not be directly attribute to loss of vagal integrity, as such differentiation is oftenly preserved after truncal-vagotomy and pyloroplasty (Elashoff et al., 1982; Herowitz et al. 1989), whereas it is impaired by antrectomy in cats (Feng et al., 1990), and by partial gastrectomy in man (Feldman et al., 1979; Marzio et al., 1989). While we do not doubt the existence of auto vagotomy in the diabetics with gastric stasis, the present findings suggest that diabetics without neuropathy may have an abnormality of antral peristalsis, as we observed an impaired differentiation of gastric emptying in these patients without stasis, which was found to be more rapid for solid emptying particularly during the first hour. In the present study we have used metoclopramide both intravenously and orally for the treatment of gastric stasis. Regarding the treatment of gastric stasis in diabetics our knowledge is still unsatisfactory. Cholinergic agents such as bethanechol (Wotten et al., 1971), and cholinesterase inhibitors such as ambenonium chloride (Talman et al., 1993), and neostignine (Pfeifer et al., 1984) have been used, but the results were variable. Metoclopramide has been only referred to as being of possible therapeutic benefit (Schade et al., 1985). In the non-diabetic subjects it is known to increase the strength of gastric interactions and to accelerate gastric emptying (Moore et al., 1985). The drug has also been shown to reduce gastric stasis associated with surgical vagotomy (Siegel et al., 1988; Turconi et al., 1993). Our data indicated symptomatic improvement in both IDDM and NIDDM diabetics with neuropathy during the two weeks of oral therapy. Similarly we also found restoration of solid and liquid emptying in the patients without gastric stasis. We therefore suggest that oral metoclopramide may be helpful in the clinical management of gastric stasis in these patients.

A loss of differentiation between the movement of liquid and solid markers and delayed gastric emptying rate in both IDDM and NIDDM diabetic patients with neuropathy, thus provides the possibility of a defect in the motor nerve function in this disease. However a detailed and thorough investigation of neuropathic diabetic patients seems extremely necessary for the understanding of probable defect in the autonomic and peripheral nerve pathway

in these patients. Such studies may be directed towards the development of an important diagnostic test for the diabetic gastropathy.

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