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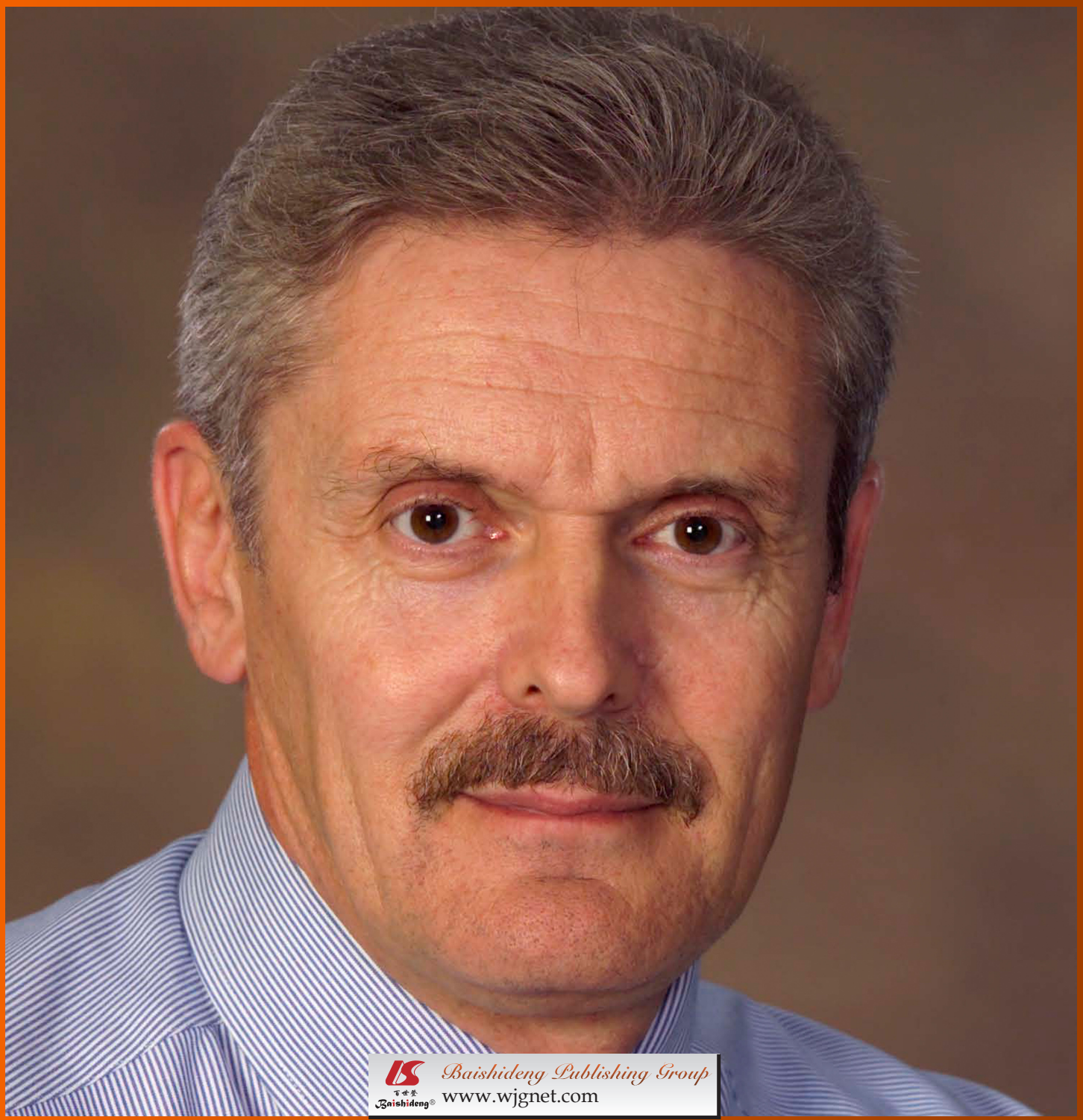

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BRIEF ARTICLE

Management practices of hepatitis C virus infected alcoholic hepatitis patients: A survey of physicians

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Abstract

AIM: To survey gastroenterologists and hepatologists regarding their current views on treating hepatitis C virus (HCV) infected alcoholic hepatitis (AH) patients.

METHODS: A sixteen item questionnaire was electronically mailed to gastroenterologists and hepatologists. A reminder was sent after 2 mo to increase the response rate. Participation of respondents was confidential. Accessing secured web site to respond to the questionnaire was considered as informed consent. Responses received on the secured website were downloaded in an excel sheet for data analysis.

RESULTS: Analyzing 416 responses to 1556 (27% response rate) emails, 57% respondents (56% gastroenterologists) reported HCV prevalence > 20% amongst AH patients. Sixty nine percent often treated AH and 46% preferred corticosteroids (CS). Proportion of respondents with consensus (75% or more respondents agreeing on question) on specific management of HCV infected AH were: routine HCV testing (94%), HCV not changing response to CS (80%) or pentoxifylline (91%), no change in approach to treating HCV infected AH (75%). None of respondent variables: age, specialty, annual number of patients seen, and HCV prevalence could predict respondent to be in consensus on any of or all 4 questions. Further, only 4% would choose CS for treating HCV infected AH as opposed to 47% while treating HCV negative AH.

CONCLUSION: Gastroenterologists and hepatologists believe that AH patients be routinely checked for HCV. However, there is lack of consensus on choice of drug for treatment and outcome of HCV positive AH patients. Studies are needed to develop guidelines for management of HCV infected AH patients.

Key words: Survey; Alcoholic hepatitis; Hepatitis C virus; Alcoholic liver disease

Core tip: Alcoholic hepatitis (AH) carries about 40%-50% mortality amongst patients with severe disease. Physicians usually shy away from treating AH in presence of concomitant hepatitis C virus (HCV). We surveyed gastroenterologists and hepatologists to assess their practice patterns on treating HCV infected AH patients. We found that although, physicians agree on screening for HCV in these patients, there is lack of consensus on treatment approach. There was no agreement on choice of drug and response to corticosteroids or pentoxifylline amongst HCV infected AH patients. Guidelines are needed on treating AH in presence of HCV.

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Anderson KE, Brunder D. Management practices of hepatitis C virus infected alcoholic hepatitis patients: A survey of physicians. *World J Gastrointest Pharmacol Ther* 2013; 4(2): 16-22 Available from: URL: http://www.wjgnet.com/2150-5349/full/v4/i2/16.htm DOI: http://dx.doi.org/10.4292/wjgpt.v4.i2.16

INTRODUCTION

Hepatitis C virus (HCV) infection and alcohol-related liver disease (ALD) either alone or in combination are responsible for more than two third of all patients with chronic liver disease in the United States[1]. Alcoholic hepatitis (AH), a distinct entity amongst patients with ALD, occurs in about 35% of heavy drinkers[2]. In its severe form, this disease is associated with significant morbidity, one month mortality of 30%-50%[3-8], and huge economic burden[9]. HCV, the most common bloodstream infection in the United States, affects approximately 3.9 million individuals with a higher prevalence amongst alcoholics[10]. Prevalence of HCV infection is higher amongst alcoholics with liver disease and correlates with its severity[11-20].

Alcohol and HCV together, present in about 10%-15% of patients with chronic liver disease in the United States[21], act synergistically resulting in higher prevalence of cirrhosis and hepatocellular carcinoma[22-24], cause more severe and rapid progression of fibrosis[25,26], and have poorer response to antiviral therapy compared to when either of these agents is present alone[27,28]. However, data on the interaction of HCV and AH are scanty. In a single center retrospective study of 76 patients with AH, presence of concomitant HCV infection emerged as an independent risk factor for a poor outcome at 6 mo (Cox proportional hazard ratio 8.45, $P = 0.01$) after controlling for patient demographics, disease severity at admission, and treatment[29]. Similar data have been reported on the in-hospital mortality in the large national inpatient database analyses[30]. In our retrospective study, we also observed that AH patients were less likely to be treated with specific treatments such as corticosteroids or pentoxifylline in the presence of concomitant HCV infection compared to patients without HCV despite similar disease severity (27% *vs* 54%, $P = 0.05$)[29]. This practice of physicians may reflect absence of guidelines for managing AH patients who are concomitantly infected with HCV. To further understand current practice, we conducted survey of gastroenterologists and hepatologists regarding their practice patterns on treating HCV positive AH patients.

MATERIALS AND METHODS

Survey questionnaire

A 16 item multiple choice questionnaire was designed with the aim to assess the responses to specific questions on the management of HCV infected AH patients. Questions specific to management of HCV infected AH patients were: (1) do you routinely test patients with acute AH for HCV infection; (2) does the presence of concomitant HCV infection change the way you treat AH; (3) which treatment option do you prefer for patients with acute AH and concomitant HCV infection; (4) in your opinion, does HCV infection alter the clinical outcome in patients with AH; (5) in your opinion, does HCV affect the response to treatment of AH with corticosteroids; and (6) in your opinion, does HCV affect the response to treatment of AH with pentoxifylline. In order to avoid bias, we mixed these questions with other questions on respondent characteristics and management of AH in general. These questions were: (1) what is your age; (2) what is your primary area of specialty; (3) how many patients of acute AH on an average do you see per year; (4) what percentage of your patients with acute AH are admitted to the hospital; (5) what percentage of those admitted are admitted through the emergency room; (6) among your patients with acute AH, what percentage have needed liver biopsy to establish diagnosis; (7) what percentage of your patients have associated HCV infection; (8) how often do you treat acute alcoholic patients with corticosteroids or pentoxifylline; (9) if you decide to treat, what drug you prefer; and (10) which of the following would make you chose pentoxifylline rather than corticosteroids. Questions were purposely kept simple so as to be able to complete the survey within 5-10 min.

Study population

Gastroenterologists and hepatologists who are members of the American gastroenterological association or American association for study of liver diseases members and involved in clinical patient care were randomly selected for the study. Physicians known to be involved with seeing only pediatric gastrointestinal diseases were also excluded. Similarly surgeons and paramedical staff (pathologists, radiologists, microbiologists and virologists) were excluded. As physicians could be members for both the associations, duplicate entries were excluded from the Microsoft excel sheet.

Administration of questionnaire

The questionnaire was placed on a secure website of the University of Texas Medical Branch intranet. Potential respondents were emailed a request letter explaining the reason and aim for the survey and the mail. The emails were sent out using the merge email option from the Microsoft Outlook Express. Using the individual email address and linking to the last name, it was assured that the email goes out as a personal email. The link to the website was included in the email request letter. Clicking to the link and taking the survey was considered as an informed consent of the respondent to take part in the survey. After completing the survey questions, responses were submitted to the central website by hitting the submission tab. Once in the website, responses were de-identified. To increase the response rate, a maximum of three additional reminder e-mails were sent at an interval

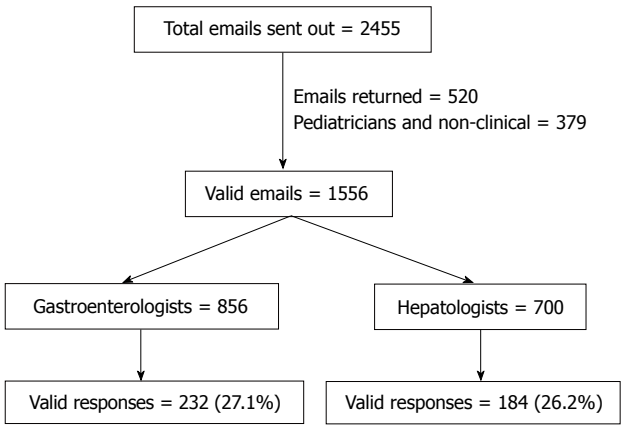

Figure 1 Attrition diagram of valid email responses analyzed for this study.

of 1 mo each.

Statistical analysis

Responses on the website for each question were transmitted into a Microsoft excel sheet. If a particular question was not answered, it was assumed that the respondents did not know the answer to that question and was recorded as DNK. Responses were analyzed using the Statistical Analysis Software 9.2 (Cary Inc. Englewood NJ, United States). χ^2 student's *t*-tests were used for analyzing categorical and continuous variables respectively. Logistic regression analyses model was built to assess respondent variable for consensus on specific questions related to management of HCV infected AH. Consensus was defined as 75% or more respondents answering on a particular response option. *P* value < 0.05 was considered to be of statistical significance. The study was approved by the Institutional Review Board at the University of Texas Medical Branch, Galveston, TX, United States.

RESULTS

Respondent characteristics

There were 416 responses to 1556 valid emails with a response rate of 27% (Figure 1). Proportion of gastroenterologists was higher than hepatologists (56% *vs* 44%, $P = 0.028$) with about 75% of respondents < 55 years of age. About 72% reported seeing < 20 patients of AH per year. More than half responded to seeing over 75% of these patients as hospital admissions and through the emergency room.

Physician practice patterns for treating alcoholic hepatitis

About 15% reported need for liver biopsy for diagnosis, 68% would treat AH often with higher proportion reporting use of corticosteroids compared to pentoxifylline (47% *vs* 37%, $P < 0.0001$) and 14% using combination of both. The most common reason for choosing pentoxifylline over corticosteroids was presence or concern of infection or sepsis (72%) and 23% also reported concomitant HCV as a reason for choosing pentoxifylline.

Practice patterns on treatment for HCV infected alcoholic hepatitis patients

About 80% would screen AH patients for HCV infection with a higher proportion reporting HCV prevalence ≥ 20% compared to < 20% (49% *vs* 37%, $P = 0.015$). The poll was divided on the question of worse outcome of AH in the presence of concomitant HCV infection ($P = 0.51$). Majority responded that presence of HCV does not change approach to treatment policy and response to corticosteroids or pentoxifylline. However, only 3% would chose corticosteroids for treating HCV positive AH patients (Table 1).

On specific questions related to management of HCV infected AH patients, there was consensus (≥ 75% agreement on particular question) amongst respondents for screening of AH patients for HCV (341/363, 94%), concomitant HCV does not change treatment response to pentoxifylline (297/326, 91%), concomitant HCV does not change treatment response to corticosteroids (262/329, 80%), and no change in treatment approach to AH in the presence of concomitant HCV infection (249/332, 75%) (Table 1). On logistic regression analysis, none of the respondent variables of age (≤ 45 years *vs* > 45 years), specialty (gastroenterology *vs* hepatology), number of patients seen per year (≤ 20 *vs* > 20), and prevalence of HCV (≤ 20% *vs* > 20%) could predict the respondents to be in consensus on any of these 4 questions (Table 2). Further, only less than half of respondents were in agreement on all the four specific questions with lack of prediction by any of the respondent variables (Table 3).

DISCUSSION

About 14% of patients with chronic liver disease have combined alcohol abuse and HCV, and one-third of alcoholics with clinical symptoms of liver disease have been infected with HCV, which is four times the rate of HCV infection found in alcoholics who do not have liver disease[13,31,32]. Prevalence of HCV amongst patients with AH varies from 8% to 22.2%[16,19,33] and varies dependent on geographical areas and explains variation in the prevalence rates in our survey.

There was a lack of consensus on the outcome of AH in the presence of HCV infection. Our initial retrospective study showed HCV to be a strong predictor of mortality at 6 mo amongst AH patients[29]. These data have been confirmed using larger VA and Nationwide Inpatient Sample databases showing higher in-hospital mortality amongst HCV infected AH patients compared to AH patients without HCV infection[30,34]. Studies are suggested looking at the improvement of existing scoring systems with incorporation of HCV into the model. Further, with the availability of non-interferon based regimens for treatment of HCV infection, it would be worthwhile assessing feasibility of these options to improve outcome of HCV infected AH patients.

We found in a previous study that patients with concomitant AH and HCV received specific treatment for

Table 1 Respondent variables and responses on each question *n* (%)

Question	*n* (%)	DNK	*P* value
Age (yr)			0.190
< 35	85 (21)		
35-44	114 (27)		
45-54	112 (27)		
55-64	105 (25)		
Specialty			0.028
Gastroenterology	232 (56)		
Hepatology	184 (44)		
Patients (*n* per year)		23 (5)	< 0.001
< 10	141 (34)		
11-20	160 (38)		
⩾ 20	92 (23)		
Percent admitted to hospital		39 (9)	< 0.001
< 25%	46 (12)		
26%-50%	74 (18)		
51%-75%	94 (23)		
⩾ 75%	163 (38)		
Of admitted, percent through ER		44 (12)	< 0.001
< 50%	81 (19)		
51%-75%	69 (16)		
⩾ 75%	222 (53)		
Percent needing liver biopsy for diagnosis		48 (12)	< 0.001
< 25%	318 (76)		
26%-50%	29 (7)		
> 50%	21 (5)		
Test AAH patients for HCV		53 (13)	< 0.001
Yes	341 (82)		
No	22 (5)		
Percent positive for HCV		58 (14)	0.015
< 20%	156 (37)		
⩾ 20%	202 (49)		
Treatment for AH			< 0.001
Often	283 (68)		
Rarely	114 (27)		
Never	19 (5)		
Drug preference for treatment			< 0.001
Corticosteroids	197 (47)		
Pentoxifylline	150 (37)		
Combination	60 (14)		
No preference	9 (2)		
What makes you choose Pentoxifylline			> 0.05
Infection or sepsis	300 (72)		
GI bleeding	161		
Renal failure	125		
Hepatitis B	139		
Hepatitis C	94 (23)		
Change in treatment policy with HCV		84 (20)	< 0.001
Yes	83 (20)		
No	249 (60)		
Treatment preference with concurrent HCV		79 (19)	< 0.001
Corticosteroids	14 (3)		
Pentoxifylline	114 (27)		
Either	21 (5)		
Same as without HCV	180 (44)		
No treatment	8 (2)		
Does HCV alter outcome of AAH		80 (19)	0.510
No	174 (42)		
Worse	161 (39)		
Better	1 (0.2)		
Does HCV affect treatment response with CS		87 (21)	< 0.001
No	262 (63)		
Worse	65 (16)		
Better	2 (0.4)		
Does HCV affect treatment response with PTX		90 (22)	< 0.001
No	297 (71)		
Worse	3 (0.7)		
Better	26 (6)		

ER: Emergency room; HCV: Hepatitis C virus; AH: Alcoholic hepatitis; CS: Corticosteroids; GI: Gastrointestinal; PTX: Pentraxin; AAH: Acute alcoholic hepatitis.

AH less often compared with patients with AH alone for all the patients (28% *vs* 57%, $P = 0.014$) and for severe disease (41% *vs* 83%, $P = 0.0066$)[29]. This is also reflected by our survey where only 3% would chose corticosteroids for treating AH in the presence of HCV infection in contrast to 38% choosing this option for treating AH in general. The presence of HCV infection is not considered a contraindication for using steroids[35], and fear of using corticosteroids may be based on possible harmful effect of corticosteroids on the HCV replication[36-41]. An *in vitro* study showed lack of effect of steroids on the HCV-RNA level[42]. Data in HCV transplanted patients have shown association of steroids use with risk for increased recurrence, worse disease, and progression of fibrosis[43]. However, these effects are seen with bolus doses used for treatment of acute cellular rejection or when steroids are rapidly tapered after using them for long duration (6 mo or more)[44]. In AH, steroids are used for a short period of 1 mo with slow taper later. Randomized studies are suggested comparing slow to rapid taper of steroids on the HCV-RNA level and clinical outcomes.

Similar confusion and lack of consensus was also seen when choosing Pentoxifylline, a drug with excellent safety profile. Pentoxifylline has been used on long-term basis in cirrhotics including those with HCV cirrhosis[45]. Not only, the drug was found to be safe but was also beneficial for reducing the liver disease complications especially hepatorenal syndrome[46-48]. This is reflected by the 27% of the surveyed clinician who chose Pentoxifylline as a treatment option although there was general consensus that HCV does not affect AH treatment response.

To the best of our knowledge, this is the first study addressing current management of concurrent AH and HCV infection. Another strength of the study is limiting survey to gastroenterologists and hematologists who are usually involved to make decisions on management of severe AH. Lack of availability of data on gender and geographical area of respondents limited evaluation of these variables in the survey. Another limitation is keeping the survey anonymous which did not allow us to administer the survey again to check for reliability of the answers. However, this helped us to increase the response rate. Finally, some respondents did not answer to some of the questions and could have resulted in selection or non-response bias. However, we think that missing answers could be due to lack of sufficient AH population in clinical practices of respondents such as in China where HBV is endemic and or Middle East and Saudi Arabia where

Table 2 Effect of respondent variables on proportion of respondents being in consensus on each of the four specific questions related to management of hepatitis C virus infected alcoholic hepatitis patients

Respondent variable	Routine screening for HCV			HCV does not change treatment approach			HCV does not affect response to corticosteroids			HCV does not affect treatment response to pentoxifylline		
	n (%)	*P* value	OR (95%CI)	*n* (%)	*P* value	OR (95%CI)	*n* (%)	*P* value	OR (95%CI)	*n* (%)	*P* value	OR (95%CI)
Age (yr)		0.2			0.7			0.8			0.75	
< 35	68 (92)		1	51 (76)		1	54 (83)		1	59 (91)		1
35-44	85 (90)		0.8 (0.3-2.5)	66 (73)		1.3 (0.6-3)	69 (77)		0.6 (0.3-1.3)	79 (89)		0.9 (0.3-2.8)
45-54	99 (96)		2.1 (0.5-8)	73 (78)		0.9 (0.4-2)	75 (81)		0.7 (0.3-1.6)	85 (93)		1.7 (0.5-6)
⩾ 55	88 (97)		2.5 (0.6-11)	58 (72)		1.4 (0.6-3)	63 (79)		0.6 (0.3-1.5)	73 (91)		1.3 (0.4-4.2)
Specialty		0.37			0.5			0.2			0.55	
GE	183 (93)		1	135 (73)		1	135 (77)		1	160 (92)		1
HP	157 (95)		1.5 (0.6-3.7)	113 (77)		0.8 (0.5-1.4)	126 (83)		0.7 (0.4-1.2)	136 (90)		1.3 (0.6-2.7)
Patients (*n*/yr)		0.29			0.6			0.2			0.38	
< 30	299 (93)		1	221 (75)		1	232 (81)		1	259 (91)		1
⩾ 30	41 (98)		2.9 (0.4-22.0)	27 (71)		1.3 (0.6-2.7)	29 (73)		1.6 (0.7-3.3)	37 (95)		0.5 (0.1-2.3)
HCV prevalence		0.48			0.3			0.2			0.81	
< 20%	148 (95)		0.7 (0.3-1.8)	104 (72)		0.8 (0.5-1.3)	119 (83)		1.4 (0.8-2.5)	129 (91)		1.1 (0.5-2.4)
⩾ 20%	188 (93)		1	143 (77)		1	141 (77)		1	166 (91)		1

HCV: Hepatitis C virus; GE: Gastroenterology; HP: Hepatology. Also shown are results of logistic regression analyses for each respondent variable given as odds ratio (OR) with 95% confidence interval (CI).

Table 3 Effect of respondent variables on proportion of respondents being in consensus on all four questions related to management of hepatitis C virus infected alcoholic hepatitis patients

Respondent variable	Consensus on all four questions related to management of HCV infected AH patients		
	n (%)	*P* value	OR (95%CI)
Age (yr)			
< 35	37 (44)		1
35-44	52 (46)		0.9 (0.5-1.8)
45-54	58 (53)	0.2	1.1 (0.6-3.1)
⩾ 55	44 (43)		1.9 (0.5-4.3)
Specialty			
GE	125 (56)		1
HP	84 (47)	0.37	1.4 (0.97-2.1)
Patients (*n*/yr)			
< 30	180 (52)		1
⩾ 30	22 (49)	0.29	1.1 (0.6-2.1)
HCV prevalence			
< 20%	71 (46)	0.48	0.9 (0.6-1.4)
⩾ 20%	97 (48)		1

HCV: Hepatitis C virus; GE: Gastroenterology; HP: Hepatology; AH: Alcoholic hepatitis. Also shown are results of logistic regression analysis for each respondent variable given as odds ratio (OR) with 95% confidence interval (CI).

alcohol is not often used due to religious reasons. There is no minimum acceptable response rate in a survey[49]. But we feel that 27% of response rate from a randomly selected group of gastroenterologists and hepatologists is adequate for the study results and avoid non-response bias.

In summary, our study showed a dissociated opinion amongst gastroenterologists and hepatologists on management of AH in the presence of concomitant HCV infection especially on the choice of drug and outcome of AH. Our findings suggest a clear need for studies to assess the response to treatment with corticosteroids amongst HCV infected AH patients and compare to AH patients without HCV infection in order to develop guidelines for management of AH patients who are also infected with HCV.

COMMENTS

Background

Recent data have shown worse outcome of AH in presence of concomitant hepatitis C virus (HCV) infection. Further, many physicians consider HCV to be a relative contraindication for treating alcoholic hepatitis (AH) especially with corticosteroids. Findings of lack of consensus on managing HCV infected AH patients as found in this survey analysis imply need for development of guidelines on management of these patients.

Research frontiers

There are two research frontiers: high prevalence of HCV in AH patients; lack of consensus amongst gastroenterologists and hepatologists on managing HCV infected AH patients.

Innovations and breakthroughs

Lack of data on managing HCV infected AH patients dictates need for studies in this group of patients.

Applications

Need for welld designed studies aiming to develop guidelines for management of HCV infected AH patients.

Peer review

Statistical tests using logistic regression analysis showing that none of respondent variables predicted respondent to be in consensus on questions related to managing HCV infected AH patients.

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BRIEF ARTICLE

Standard triple versus levofloxacin based regimen for eradication of *Helicobacter pylori*

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Abstract

AIM: To compare the eradication rates for *Helicobacter pylori* (*H. pylori*) and ulcer recurrence of standard triple therapy (STT) and levofloxacin based therapy (LBT).

METHODS: Seventy-four patients with perforated duodenal ulcer treated with simple closure and found to be *H. pylori* infected on 3 mo follow up were randomized to receive either the STT group comprising of amoxicillin 1 g *bid*, clarithromycin 500 mg *bid* and omeprazole 20 mg *bid* or the LBT group comprising of amoxicillin 1 g *bid*, levofloxacin 500 mg *bid* and omeprazole 20 mg *bid* for 10 d each. The *H. pylori* eradication rates, side effects, compliance and the recurrence of ulcer were assessed in the two groups at 3 mo follow up.

RESULTS: Thirty-four patients in the STT group and 32 patients in the levofloxacin group presented at 3 mo follow up. *H. pylori* eradication rates were similar with STT and the LBT groups on intention-to-treat (ITT) analysis (69% *vs* 80%, $P = 0.425$) and (79% *vs* 87%, $P = 0.513$) by per-protocol (PP) analysis respectively. Ulcer recurrence in the STT and LBT groups on ITT analysis was (20% *vs* 14%, $P = 0.551$) and (9% *vs* 6%, $P = 1$) by PP analysis. Compliance and side effects were also comparable between the groups. A complete course of STT costs Indian Rupees (INR) 1060.00, while LBT costs only INR 360.00.

CONCLUSION: *H. pylori* eradication rates and the rate of ulcer recurrence were similar between the STT and LBT. The LBT is a more economical option compared to STT.

Key words: *Helicobacter pylori*; Eradication; Peptic perforation; Levofloxacin regime; Randomized control trial; Standard triple therapy

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INTRODUCTION

Several studies have proved that the eradication of *Helicobacter pylori* (*H. pylori*) decreased the recurrence of ulcer in patients who had undergone simple closure for perforation[1,2]. A proton pump inhibitor with two antibiotics, amoxicillin and clarithromycin, is the commonly used regimen for *H. pylori* eradication[3]. Although it has been the recommended first line therapy for a long period of time[4-6], recent studies report unacceptably low eradication rates[7-9]. This is attributed to the development of resistance to clarithromycin. Levofloxacin based therapy

(LBT) has been recently reported to have higher and consistent eradication rates as a first line therapy in *H. pylori* eradication[10-12]. LBT represents a better alternative to clarithromycin therapy as it meets the criteria set for *H. pylori* treatment: effectiveness, simplicity and safety.

Limited studies have been reported comparing the eradication rates for *H. pylori* between standard triple therapy (STT) and LBT[10]. Hence, this study was done to compare the efficacy of STT to LBT as a first line therapy for the eradication of *H. pylori* and the prevention of ulcer recurrence in patients with perforated duodenal ulcer following simple closure.

MATERIALS AND METHODS

The study was conducted in the Department of Surgery, JIPMER, Puducherry, a tertiary care hospital in south India between September 2009 and August 2011, over a period of 23 mo. The study was conducted as an open-label prospective randomized trial. The study was cleared by the Institute Research Council and the Ethics Committee.

Patients

All consecutive patients who presented to the hospital with perforated duodenal ulcer were considered eligible for the study. Those patients who were found to have gastric ulcer perforation, upper gastro intestinal disorders, re-perforations or who had undergone any definitive surgery for perforated peptic ulcer were excluded from the study. At 3 mo follow up, following simple closure of the perforated duodenal ulcer, the patients found to be positive for *H. pylori* infection were included in the study.

Diagnosis of H. pylori infection

All recruited patients were subjected to upper gastro intestinal endoscopy using a video endoscope (EG 3400; Pentax, Montvale, NJ, United States) under topical anesthesia using 2% lignocaine viscous. Four gastric mucosal biopsies (two each from the gastric corpus and the antrum) were taken using standard endoscopic biopsy forceps. Two of these were used for urease test and the other two for histology after Giemsa staining. All endoscopies were done by an experienced endoscopist.

Diagnosis of *H. pylori* was made by urease test and histology by Giemsa stain. Urease test was done using a urea solution prepared and standardized in our institute[13]. The solution was observed at room temperature until 24 h of inoculation with two gastric mucosal biopsies. The change of color of the solution from yellow to pink was considered as a positive test for *H. pylori* infection. Histology was done by Giemsa stain of the biopsies for identification of *H. pylori*. If either or both the tests were positive, the patient was considered to have a positive *H. pylori* status. If both the tests were negative, the patient was considered to be negative for *H. pylori* infection.

Treatment regimes

Patients positive for *H. pylori* were randomized into two groups using the sealed envelope technique and computer generated random numbers. One group received the STT regimen while the other received LBT. The STT comprised of amoxicillin 1 g *bid*, clarithromycin 500 mg *bid* and omeprazole 20 mg *bid* and the LBT comprised of amoxicillin 1 g *bid*, levofloxacin 500 mg *bid* and omeprazole 20 mg *bid* for 10 d each.

Follow up

Follow up of these patients was done at 3 mo following therapy. Upper gastrointestinal endoscopy was done at the follow up visit to assess the eradication rates of *H. pylori* for both the groups. Urease test and histology were done on the gastric mucosal biopsies to diagnose *H. pylori* status. The presence or absence of ulcer in these patients was also noted in the follow up endoscopy. Patients who were found to have a positive *H. pylori* status, as evidenced by either a positive urease test or a positive histology, were considered as a treatment failure. The compliance to the regimens and the side effect profile were studied through a questionnaire in the patients' own language, handed over at the time of follow up.

Assessment of outcome

The primary outcome of the study was eradication of *H. pylori* infection. The secondary outcomes were ulcer recurrence, side effects, compliance and the cost of the regimen.

Statistical analysis

Study design is an open-label prospective randomized superiority trial. The sample size calculations were done based on our study with the eradication rates for STT[14]. A sample size of 35 in each group was determined for the power of the study to be 0.80. Statistical analysis for the observations were done using Graphpad Instat Software version 3 (Graphpad, San Diego, CA, United States). Fisher's exact test was used to analyze the statistical significance of the *H. pylori* eradication rates, ulcer recurrence rates, side effects of, and compliance to either regimen.

RESULTS

At 3 mo follow up, 130 patients presented for index endoscopy. Seventy four of these 130 patients were diagnosed to have *H. pylori* infection by urease test and/or histology. These 74 patients were randomized into two groups to receive either the STT ($n = 39$) or the LBT ($n = 35$).

In the STT group, 2 patients were non-compliant and 3 were lost to follow up. In the LBT group, 1 patient was non-compliant and 2 patients were lost to follow up. Sixty-six patients presented for the 3 mo follow up, which included 34 patients in the STT group and 32 patients in the levofloxacin group. These 66 patients were included in the per-protocol analysis, as shown in Figure 1. The eradication rates for *H. pylori*, ulcer recurrence rates,

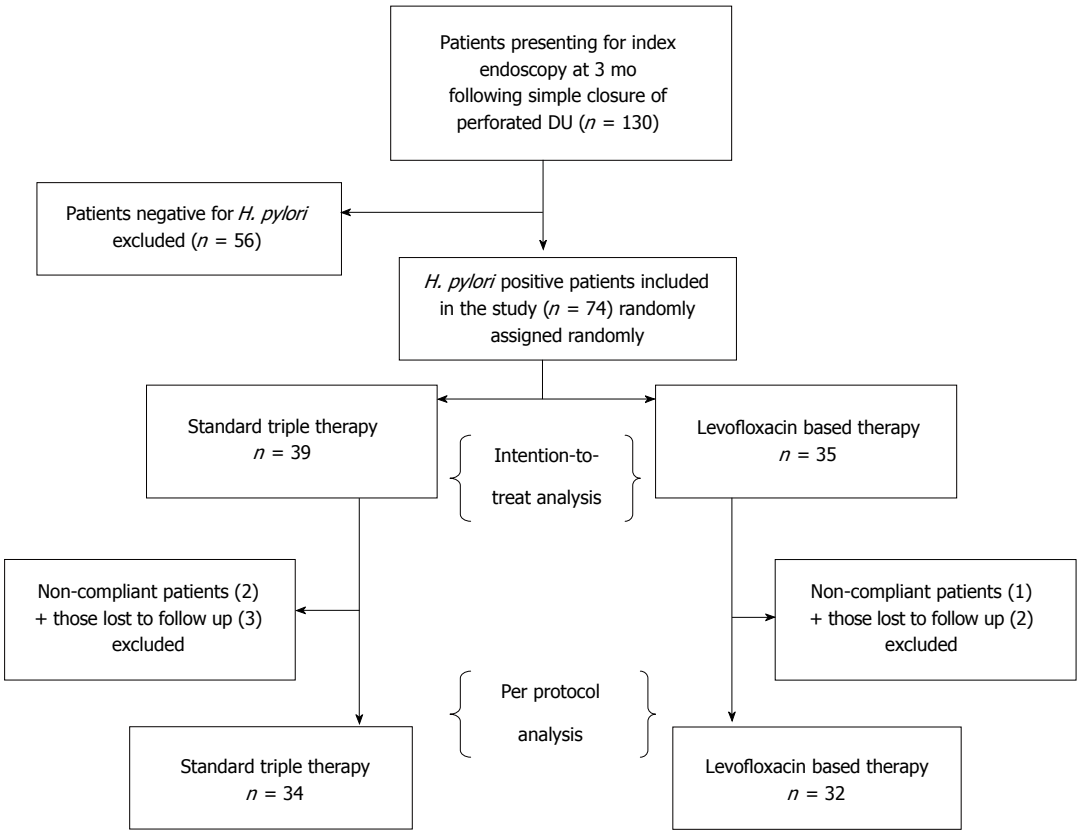

Figure 1 Schematic representation of the design of the study. DU: Duodenal ulcer; *H. pylori*: *Helicobacter pylori*.

side effects and compliance to the two treatment regimes were analyzed in these patients. The patients in the STT group were in the age group of 19-65 years, with a mean and standard deviation of 38 ± 11.99 years, and the LBT group had patients between 20 and 75 years, with a mean and standard deviation of 43.00 ± 12.25 years. The mean of the ages of the patients in both the groups were statistically comparable (P = 0.0822). The gender distribution in the groups also did not show any significant difference with 37/39 (95%) in the STT and 34/35 (97%) in the LBT being male (P = 1.00). The eradication rates for *H. pylori* infection by intention-to-treat (ITT) analysis for STT group was 27/34 (79%) and for the LBT group it was 28/32 (87%). The difference was not significant (69% *vs* 80%, P = 0.425). There was no difference in the eradication rates by per protocol (PP) analysis either (79% *vs* 87%, P = 0.513). The rate of ulcer recurrence between the groups was also analyzed at the follow up endoscopy. There were only 3 cases with recurrent ulcer in the standard therapy arm and only 2 in the LBT arm. The rate of ulcer recurrence between the groups were not significant by ITT or PP analysis (20% *vs* 14%, P = 0.551; 9% *vs* 6%, P = 1.00, respectively). Both the groups showed good compliance to therapy (94% in the STT group and 97% in the LBT). There was no significant difference between the groups in both ITT and PP analysis (P = 0.713, respectively). Side effects of both the treatment regimens were analyzed (Table 1).

In the STT arm, diarrhea was the most common side effect, with a prevalence of 26%. Other side effects reported were epigastric pain, bloating, nausea, vomiting and rashes, in the decreasing order of frequency. In the LBT arm, the most common side effect complained of was nausea and vomiting (22%), followed by diarrhea, bloating, epigastric pain and rashes. There was no significant difference between the side effect profiles of the two groups. The cost of the complete course of STT was 1060.00 Indian Rupees (INR) and 360.00 INR for the LBT.

DISCUSSION

H. pylori has been identified as the most important risk factor for peptic ulcer disease[15,16]. Significant decrease in the rate of ulcer recurrence was reported in patients with perforated peptic ulcer following simple closure and eradication of *H. pylori*[2,15]. However, the choice of the optimal regimen for *H. pylori* eradication is debated[17]. The STT, using amoxicillin, clarithromycin and omeprazole, is one of the widely used regimens for *H. pylori* eradication[17]. Different studies have shown different rates of eradication with this regimen, ranging between 76% and 90%[18]. The emergence of resistance of the organism to clarithromycin has urged researchers to look for alternatives to the STT. The sequential therapy and levofloxacin based regimens are two of the newly recommended combinations[18-22]. Levofloxacin based regimens were used as rescue regimens in case of failure with standard regimen[23]. The efficacy of this combination as a first line regimen has not been studied exten-

Table 1 Comparison of side effects between the two regimens

Side effect	Standard triple therapy	Levofloxacin based therapy	*P* value[1]
Diarrhea	26%	19%	0.3096
Nausea/vomiting	12%	22%	0.0892
Bloating	18%	19%	1.0000
Epigastric pain	21%	12%	0.1871
Rashes	6%	3%	0.4977

[1]Fisher's exact test.

sively. Data regarding the efficacy of this regimen in the Indian setting is lacking.

The present study showed an eradication rate of 79% and 69% with the STT and 87% and 80% with the LBT in PP and ITT analysis respectively. Gisbert *et al*[10] studied the efficacy of LBT as the first line treatment of *H. pylori* and found eradication rates of 88% and 84% under PP and ITT analysis respectively, which are comparable to the results of our study. Schrauwen *et al*[24] from the Netherlands found that therapy with the levofloxacin regimen was very effective in the eradication of *H. pylori*. There are no reports to date of STT being superior to the former. The resistance to fluoroquinolones, including levofloxacin, has been reported to be low in most populations across the globe[25]. This is one reason that encourages the use of this drug in eradication regimens.

Bose *et al*[2], in a study conducted in our institute, found that eradication of *H. pylori* infection decreases the rate of ulcer recurrence significantly. At 3 mo follow up, they found that ulcer recurrence in patients in whom *H. pylori* was eradicated was only 18.6% compared to a 70% in the non-eradicated patients ($P = 0.003$).

In the present study, ulcer recurrence rates in both groups were comparable under both PP and ITT analyses. The STT group had ulcer recurrence rates of 20% and 9% under ITT and PP analysis respectively, while the levofloxacin group had ulcer recurrence rates of 14% and 6% respectively. The ulcer recurrence rates observed at 3 mo follow up in the STT group were comparable to that seen in the earlier study from the same center[2].

The side effect profile in both groups did not show any significant difference with regard to any of the symptoms. The more common side effects of the individual agents were chosen, assessed using a questionnaire and analyzed. Diarrhea (26%), followed by epigastric pain (21%), was the most reported side effect in the STT group. The levofloxacin group complained mostly of nausea and vomiting (22%), with diarrhea and bloating occurring in 19% of patients. The irritant effect of amoxicillin on the gastrointestinal tract and the alteration of the native gut flora by the high dosage can explain the high incidence of diarrhea in both treatment groups[26]. One of the major side effects of clarithromycin therapy is mild to moderate epigastric pain. This can explain the relatively high incidence of this symptom in the STT group.

Both study groups had comparable compliance to treatment in our study. The STT group had compliance rates of 94% and 87% in the PP and ITT analysis respectively, compared to 97% and 91% in the levofloxacin group by PP and ITT respectively. These compliance rates are comparable to those seen in western studies. Vaira *et al*[20] reported a compliance rate of 94% in patients receiving STT. Gisbert *et al*[10] reported similar adherence to treatment in his study among patients receiving both STT and LBT.

Clarithromycin is the costliest component of the STT. Replacing it with less expensive levofloxacin helps to reduce the cost of treatment significantly. The cost analysis done as a part of the present study has shown that a complete course of the STT costs 1060.00 INR compared to 360.00 INR of the LBT, as on August 1, 2011. This economical convenience also favors the use of the latter treatment regimen.

The results of the present study show a higher trend of eradication of *H. pylori* and prevention of ulcer recurrence in patients who received LBT when compared to those who were administered STT, but statistical analysis failed to show any significance in these differences.

Thus, from the observations of this study, we conclude that LBT is an equally effective alternative to the STT with regard to *H. pylori* eradication rates, prevention of ulcer recurrence, compliance and side effect profile. The lesser cost of the LBT makes it an economical option for treatment of *H. pylori*.

COMMENTS

Background

Standard triple therapy (STT), with a proton pump inhibitor and two antibiotics, amoxicillin and clarithromycin, is the commonly used regimen for *Helicobacter pylori* (*H. pylori*) eradication. Recent studies report low eradication rates due to the development of resistance to clarithromycin.

Research frontiers

Levofloxacin based therapy (LBT) has been recently reported to have higher and consistent eradication rates as a first line therapy in *H. pylori* eradication.

Innovations and breakthroughs

Limited studies have been reported comparing the eradication rates for *H. pylori* between STT and LBT.

Applications

LBT represents a comparable alternative to clarithromycin therapy as it meets the criteria set for *H. pylori* treatment: effectiveness, simplicity and safety.

Peer review

This is an interesting study comparing the use of clarithromycin and levofloxacin based eradication therapy for *H. pylori* infection.

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BRIEF ARTICLE

Interaction of insulin with prokinetic drugs in STZ-induced diabetic mice

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Abstract

AIM: To study the possible interactions of metoclopramide, domperidone and erythromycin in streptozotocin-induced diabetic mice treated with insulin by various parameters.

METHODS: Effects of the individual as well as combined drugs were studied in diabetic mice *via* estimation of the blood glucose and serum insulin levels, small intestinal transit (SIT), gastric emptying (GE), xylose absorption and glucose tolerance tests. Groups were given insulin 2 IU/kg *s.c.*, metoclopramide 20 mg/kg *p.o.*, domperidone 20 mg/kg *p.o.* and erythromycin 6 mg/kg *p.o.* individually and in combination. There were also normal and diabetic control groups. The first set of experiments was carried out to investigate the subchronic effect on blood glucose and serum insulin levels in diabetic mice of one week of daily dose administration of the tested drugs individually as well as the combination of insulin with each prokinetic drug. The other five sets of experiments were carried out to investigate the acute effect of a single dose of each drug individually and in combination on blood glucose and serum insulin levels, SIT, GE, oral xylose absorption and glucose tolerance tests.

RESULTS: The study included the prokinetic drugs metoclopramide (20 mg/kg), domperidone (20 mg/kg) and erythromycin (6 mg/kg), as well as insulin (2 IU/kg), which was individually effective in decreasing SIT, enhancing GE and increasing xylose absorption significantly in diabetic mice. Erythromycin tended to decrease blood glucose level and increase serum insulin level after 1 wk of daily administration in diabetic mice. Erythromycin potentiated the effect of insulin on blood glucose level and serum insulin level whereas other prokinetic agents failed to do so after repeated dose administration in diabetic mice. Metoclopramide or erythromycin in combination with insulin significantly decreased SIT, in diabetic mice, to lower levels than with insulin alone. Administration of prokinetic drugs along with insulin antagonized the action of insulin on xylose absorption. These combinations also increased the rate of glucose absorption from the gut.

CONCLUSION: The present study suggests that prokinetic drugs could potentially improve glycemic control in diabetic gastroparesis by allowing a more predictable absorption of nutrients, matched to the action of exogenous insulin. The use of prokinetics, such as erythromycin, may be interesting in the clinic in decreasing the need for insulin in diabetic patients. The dose of insulin may be safely decreased with erythromycin in chronic treatments.

Key words: Streptozotocin; Gastrointestinal motility; Insulin; Prokinetic drugs; Intestinal absorption

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INTRODUCTION

Diabetes mellitus is the most common cause of gastroparesis and disturbed gastric and small intestinal intestine motility. Gastroparesis is a syndrome characterized by delayed gastric emptying (GE) in the absence of mechanical obstruction of the stomach. The cardinal symptoms include postprandial fullness (early satiety), nausea, vomiting, bloating, or epigastric pain. Symptoms attributable to gastroparesis are reported by 5% to 12% of patients with diabetes[1,2]. There is an association between self-reported glycemic control and psychological distress, and the development of gastrointestinal symptoms in diabetics[3]. Impaired function of the gastrointestinal tract related to diabetes mellitus results from diabetic autonomic neuropathy, impaired sensory innervation and the direct effect of persistent hyperglycemia[4]. Once established, diabetic gastroparesis tends to persist, despite amelioration of glycemic control. Thus, GE and symptoms are stable over ⩾ 12 years follow-up, despite improved glycemic control[5]. Gastroparesis affects nutritional state and, in diabetics, it also has deleterious effects on glycemic control and secondary effects on organs, leading to increased mortality[6]. First-line treatment includes restoration of nutrition and medication using prokinetic drugs. Therefore, searching for therapeutic interventions with prokinetic drugs that will improve the specific alterations associated with diabetic gastroparesis represents the most important aim of the present study. Prokinetic drugs have been used for gastroparesis in diabetic patients for a relatively long time and some data about the interactions with insulin in the clinic should be available. It seemed of interest to investigate the possible drug-drug interactions, which may develop from co-administration of insulin and the prokinetic drugs metoclopramide, domperidone and erythromycin. Also, the study aims to highlight the possibility that prokinetics might increase the hypoglycemic effect of insulin.

Prokinetic drugs, commonly used to treat delayed GE, have variable effects on small intestinal motility, and little is known about their effects on glucose absorption. The prokinetic drugs act primarily through neurons since peristalsis is based on neural reflexes. Dopamine antagonists such as metoclopramide and domperidone[7] are used in this study. Motilides such as erythromycin enhance peristalsis by acting on motilin receptors[8].

In the present study, streptozotocin (STZ)-induced diabetic mice were treated with insulin and prokinetic agents (metoclopramide, domperidone, erythromycin) individually and in combination. Acute and subchronic studies were carried out to determine whether the prokinetic drugs could improve the blood glucose level and neuropathy changes in diabetic conditions treated with insulin. This was achieved by measuring some of the biochemical parameters affected by persistent hyperglycemia *via* estimation of blood glucose and serum insulin levels. The acute study were carried out to determine the effect of the test drugs on the gastrointestinal tract motility represented by small intestinal transit (SIT) and GE, in the knowledge that all of the prokinetic drugs used produce acute actions on the gut. The rate of GE is an important determinant of carbohydrate absorption and thus of the blood glucose profile[9]. Oral xylose absorption and glucose tolerance tests were used as representative indices of carbohydrate absorption changes.

MATERIALS AND METHODS

Drugs and reagents

Insulin (Regular insulin, Novonordisk, Denmark), Metoclopramide (Memphis Pharmaceutical Co., Cairo, Egypt), Domperidone (El Kahira Pharmaceutical Co., Cairo, Egypt) and Erythromycin ethylsuccinate (Abbott Laboratories, Cairo, Egypt) were obtained. Glucose Reagent Kit (Biomerieux, France), Insulin IRMA Kit IM3210 (Immunotech Beckman coulter, Czech Republic), STZ (Sigma Aldrich Chemie, Germany), Phloroglucinol (Sigma chemical Co., United States) and *D*-xylose (Acros Organics, United States) were used. Insulin was diluted with normal saline solution to obtain a suitable strength for injection. Hydroxypropylmethylcellulose (1%) was used as vehicle to administer prokinetic drugs. The other reagents were the highest grade of commercially available products.

Animals

Healthy adult male albino mice weighting between 20-30 g were used in the present study. They were obtained from the animal house of the research department of Kahira pharmaceutical company, Cairo, Egypt. All animals were fed a standard pellet chow and had free access to water. They were maintained under controlled laboratory conditions (temperature, humidity) throughout the study. New groups of mice were recommended for each test caried out. Animals were sacrificed under mild ether anesthesia. Experiments were conducted in accordance with the guidelines set by the animal health research ethics training initiative, Egypt.

Drug treatments

Control groups received equal volumes of vehicle through corresponding routes. Groups were given insulin 2 IU/kg *s.c.*, metoclopramide 20 mg/kg *p.o.*, domperidone 20 mg/kg *p.o.* and erythromycin 6 mg/kg *p.o.* individually and in combination. There were also normal and diabetic control groups. The doses were selected based on the earlier reports, recommended clinical doses and prior pilot experiments[10-12]. Metoclopramide, domperidone or erythromycin in the dose mentioned above were given alone 15 min before the administration of insulin/ve-

hicle. Insulin was given 50 min before determination of blood glucose and serum insulin levels. Six main sets of experiments were carried out. The first set of experiments was carried out to investigate the subchronic effect on blood glucose and serum insulin level in STZ-induced diabetic male mice of one week of a daily dose of insulin, metoclopramide, domperidone and erythromycin individually as well as the combination of insulin with metoclopramide, domperidone or erythromycin. The other five sets of experiments were carried out to investigate the acute effect of a single dose of insulin, metoclopramide, domperidone and erythromycin individually as well as the combination of insulin with metoclopramide, domperidone or erythromycin on blood glucose and serum insulin level, SIT, GE, oral xylose absorption and glucose tolerance tests.

Experimental induction of diabetes

Diabetes mellitus was induced in overnight fasted mice by a single intraperitoneal injection of freshly prepared solution of STZ (100 mg/kg body weight) in 0.1 mol/L cold citrate pH 4.5[13,14]. The animals were allowed to drink 5% glucose solution to overcome STZ-induced hypoglycemia[15]. The control mice were injected with citrate buffer alone. Two weeks after STZ injection, blood samples were collected by tail venopuncture of the mice and used for the estimation of blood glucose levels using an advanced Glucometer ACCU-CHEK (Roche, Germany)[16,17]. Overnight fasted mice with blood glucose level above 200 mg/dL were selected and used in the present study.

Measurement of blood glucose and serum insulin levels

Blood was collected from the reto-orbital venous plexus according to the method of Cocchetto *et al*[18]. Blood was collected into Wassermann tubes using heparinized microhematocrit capillaries. Blood glucose level was measured using advanced a Glucometer ACCU-CHEK. Serum was separated by centrifugation at 11000 *g* for 2 min and serum glucose level was determined immediately using a glucose kit[19]. There was no significant difference in glucose levels between the two methods. The remaining amount of serum was kept frozen at -20 ℃ for insulin determination. Serum insulin was estimated by immunoradiometric assay (IRMA)[20] using an insulin IRMA Kit. This estimation was done 2 min before drug/vehicle administration and 50 min after insulin/vehicle administration.

Small intestinal transit

The passage of a charcoal meal through the gastrointestinal tract of mice was used as parameter for intestinal motility[10,21]. Overnight fasted mice were treated with test prokinetic drug orally 45 min and/or insulin subcutaneously 30 min before administration of charcoal meal (0.3 mL of a 5% suspension of charcoal in 2% hydroxypropylmethylcellulose solution). After 20 min, animals were killed by cervical dislocation just after mild ether anesthesia. The abdomen was opened, the charcoal marker was identified in the small intestine and tied immediately to avoid movement of marker. The entire intestine was removed by cutting at the pyloric and ileocaecal ends and then washed in water. The distance the meal had traveled through the intestine as indicated by the charcoal was measured and expressed as percent of the total distance from the pylorus to the caecum. SIT = (distance travelled by charcoal/total length of the small intestine) × 100.

Gastric emptying

GE was determined by the phenol red method[12,22]. The test prokinetic drug was given alone 45 min before administration of phenol red meal. Insulin (*s.c.*) was injected 30 min before the administration of the meal. A solution of 1.5% hydroxypropylmethylcellulose containing 0.05% phenol red as a marker was given intragastrically (0.5 mL/mouse) to overnight fasted mice. Fifteen minutes later, animals were sacrificed by cervical dislocation just after mild ether anesthesia. The abdominal cavity was opened, the cardiac and pyloric ends of the stomach were clamped, and the stomach was then removed and washed with normal saline. The stomach was cut into pieces and homogenized with 25 mL of 0.1 mol/L NaOH. The suspension was allowed to settle for 1 h, 5 mL of the supernatant was then added to 0.5 mL of 20% trichloroacetic acid (w/v) and centrifuged at 3000 *g* for 20 min. 4 mL of 0.5 mol/L NaOH was added to 1 mL of supernatant. The absorbance of this pink colored liquid was measured using a spectrophotometer at 560 nm (Model: Shimadzu 150-20). Phenol red recovered from animals that were sacrificed immediately after administration of the test meal was used as a standard (0% emptying). GE (%) in the 15 min period was calculated according to the following equation: GE (GE)% = 100 - (x / y × 100), x = absorbance of phenol red recovered from the stomach of animals sacrificed 15 min after test meal, y = mean (n = 5) absorbance of phenol red recovered from the stomach of control animals (killed at 0 min following test meal).

Oral D-xylose loading test

This test measures intestinal carbohydrate absorption by calculating the plasma concentration of *D*-xylose after ingestion of a known amount of *D*-xylose[23,24]. The test prokinetic drug was given alone 45 min before administration of xylose. Insulin (*s.c.*) was injected 30 min before the administration of xylose. A 30% solution containing *D*-xylose (0.8 g/kg body weight) was administrated by oral gavage to overnight fasted mice. After 60 min of xylose administration, blood samples were drawn from the retro-orbital venous plexus and centrifuged at 11000 *g* for 2 min. Plasma xylose concentrations were measured using a colorimetric assay. The assay involved incubation for 4 min at 100 ℃ of 20 μL of plasma with 1 mL of colored reagent containing 1 g phloroglucinol in 200 mL glacial acetic acid and 20 mL concentrated HCl, followed by

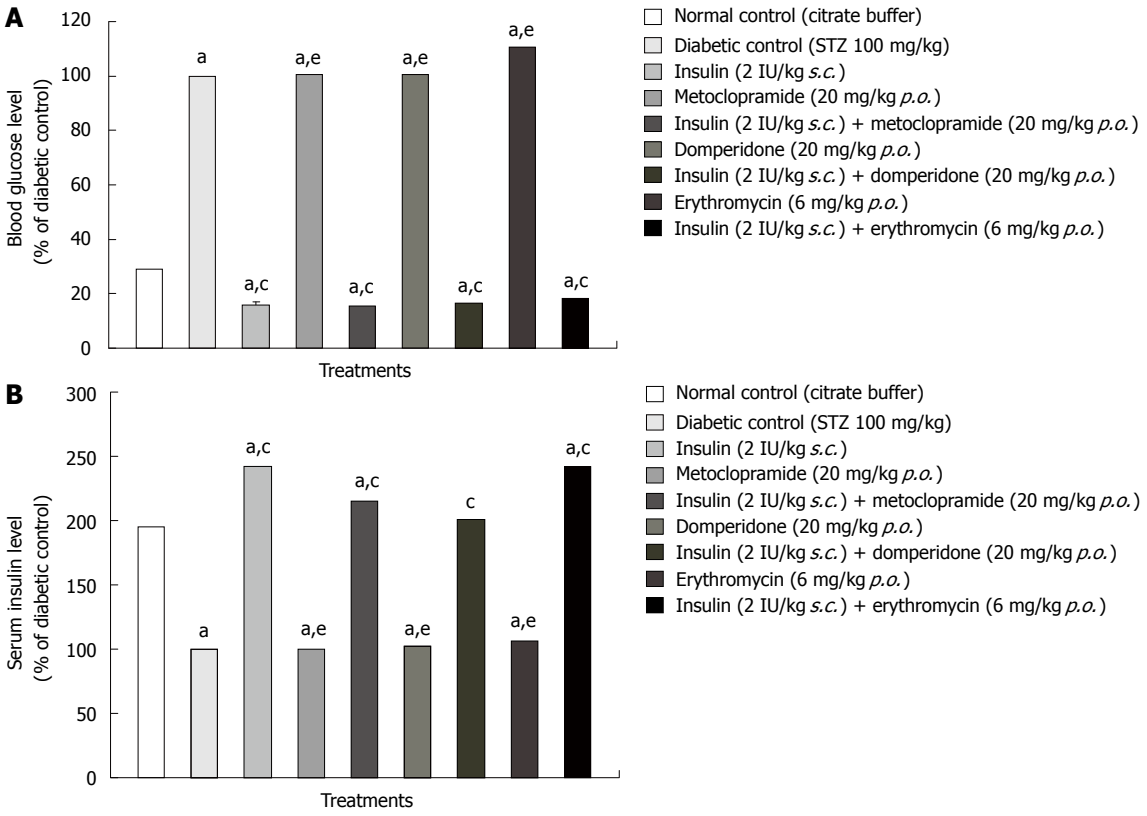

Figure 1 Acute effect in streptozotocin-induced diabetic mice of single doses of insulin, metoclopramide, domperidone and erythromycin individually as well as the combination of insulin with metoclopramide, domperidone or erythromycin. A: Blood glucose level; B: Serum insulin level. Values represent the mean ± SE of eight mice per group. Significantly different from the normal control value at $^{a}P < 0.05$; Significantly different from the diabetic control value at $^{c}P < 0.05$; Significantly different from insulin value at $^{e}P < 0.05$.

reading of the absorbance at 554 nm using spectrophotometer (Model: Shimadzu 150-20).

Oral glucose tolerance test

The oral glucose tolerance test (OGTT) was used to evaluate intestinal absorption. The test was carried out according to the method of Stümpel *et al*[25] and Badole *et al*[26]. After the mice were fasted for 12 h, the test compound was administered half an hour before glucose loading. A 50% glucose solution (2.5 g/kg of body weight) was orally administered, and blood was taken from the tail vein at 0, 30, 60 and 120 min afterward. Blood glucose concentrations were determined immediately using an Accu-chek (Roche Diagnostics, Germany). The difference between the value of the diabetic control group and the diabetic treated groups represent the amount of glucose absorption from the intestine affected by the different drugs used in this study in addition to other factors. The extent of absorption of glucose was estimated using the total area under the curve, which represents blood glucose level from t_0 to t_{120}. AUC_{total} is calculated using the trapezoidal rule from t_0 to t_{120}.

Statistical analysis

All data were expressed as the mean ± SE with 6 to 10 mice per group. Statistical analysis was performed using two way analysis of variance (ANOVA) followed by Tukey-Kramer multiple comparisons test. For all the statistical tests, the level of significance was fixed at $P < 0.05$.

RESULTS

Effects of insulin and prokinetic drug individually or combined on blood glucose and serum insulin levels in STZ-induced diabetic mice

Figure 1 show the antihyperglycemic effect of insulin against STZ-induced diabetic mice. Acute administration of insulin (2 IU/kg) significantly ($P < 0.05$) decreased blood glucose level to 45.37 ± 4.57 mg/dL and increased serum insulin level to 1.96 ± 0.10 μIU/kg in diabetic mice close to hypoglycemic value. The acute administration of a single dose of metoclopramide (20 mg/kg), domperidone (20 mg/kg) or erythromycin (6 mg/kg) individually did not affect blood glucose level or serum insulin level in diabetic mice. Acute administration of metoclopramide, domperidone or erythromycin did not affect the action of insulin on blood glucose and serum insulin level (Figure 1). Erythromycin tended to decrease blood glucose level and increase serum insulin level after one week of daily dose administration in diabetic mice. Daily dose administration of insulin (2 IU/kg) for one week significantly ($P < 0.05$) decreased blood glucose level to 45.94 ± 2.60 mg/dL and increased serum insulin level to 2.01 ± 0.02 μIU/kg in diabetic mice close

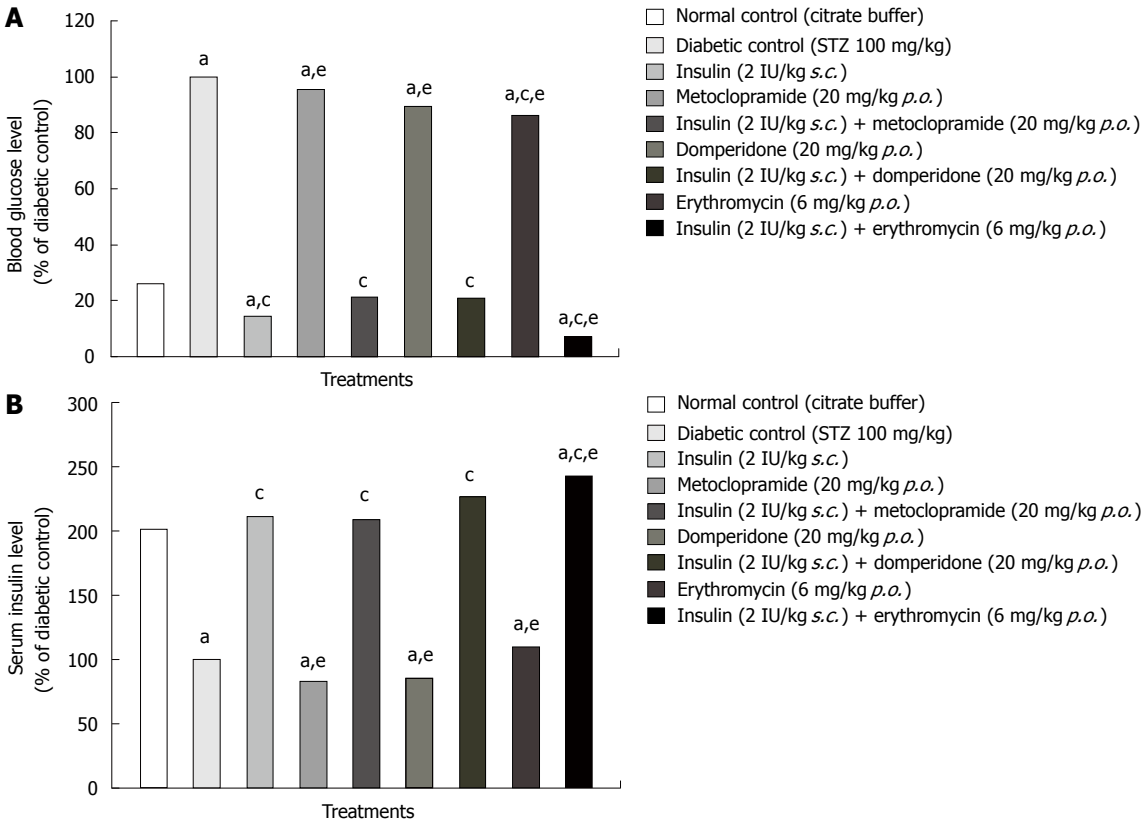

Figure 2 Subchronic effect in streptozotocin-induced diabetic mice of one week of daily administration of insulin, metoclopramide, domperidone and erythromycin individually as well as the combination of insulin with metoclopramide, domperidone or erythromycin. A: Blood glucose level; B: Serum insulin level. Values represent the mean ± SE of eight mice per group. Significantly different from the normal control value at $^{a}P < 0.05$; Significantly different from the diabetic control value at $^{c}P < 0.05$; Significantly different from insulin value at $^{e}P < 0.05$.

to hypoglycemic value. There is no interaction between insulin and the test prokinetic, metoclopramide or domperidone, on blood glucose level and serum insulin level after one week of daily administration in diabetic mice. On the other hand, combination of insulin and erythromycin significantly ($P < 0.05$) decreased blood glucose level to 22.9 ± 1.91 mg/dL and increased serum insulin level to 2.18 ± 0.12 μIU/kg (Figure 2).

Small intestinal transit

The normal control value of the SIT was 56.61% ± 2.58% of the total length of the small intestine. Induction of diabetes in mice significantly ($P < 0.05$) increased SIT to 76.90% ± 6.12%. Insulin (2 IU/kg) significantly ($P < 0.05$) decreased SIT in diabetic mice to 61.05% ± 3.85% as compared to diabetic control group. The test prokinetic drugs, metoclopramide (20 mg/kg), domperidone (20 mg/kg) and erythromycin (6 mg/kg), significantly ($P < 0.05$) decreased SIT in the diabetic mice to 50.04% ± 2.42%, 48.70% ± 4.53% and 43.05% ± 3.50% respectively. Either metoclopramide or erythromycin in combination with insulin significantly ($P < 0.05$) decreased SIT in diabetic mice and this effect was less than that of insulin alone. Domperidone did not affect the action of insulin on SIT in diabetic mice (Table 1).

Gastric emptying

The normal control value of the GE was 72.50% ± 1.68 % of the total amount of the phenol red meal given. The high blood glucose level in diabetic control mice delayed GE significantly ($P < 0.05$) to 55.23% ± 9.30%. Insulin (2 IU/kg), metoclopramide (20 mg/kg), domperidone (20 mg/kg) or erythromycin (6 mg/kg) in the doses employed increased GE significantly ($P < 0.05$) to 95.87% ± 2.41%, 76.38% ± 7.67%, 90.92% ± 4.92% and 84.77% ± 2.11%, respectively, compared with diabetic control mice. Administration of prokinetic drugs (metoclopramide, domperidone or erythromycin) along with insulin (2 IU/kg) did not affect the action of insulin on GE (Table 1).

Oral D-xylose absorption test

The normal control value of serum *D*-xylose concentration was 1.63 ± 0.10 mg/mL after 60 min of *D*-xylose administration (0.8 g/kg).The amount of xylose absorbed from the GIT significantly ($P < 0.05$) decreased in the diabetic mice, to 0.606 ± 0.030 mg/mL, as compared to normal control group. Insulin (2 IU/kg), metoclopramide (20 mg/kg), domperidone (20 mg/kg) and erythromycin (6 mg/kg) individually increased xylose absorption to 1.64 ± 0.16 mg/mL, 0.989 ± 0.030 mg/mL, 1.162 ± 0.030 mg/mL and 1.469 ± 0.030 mg/mL, respectively. Administration of prokinetic drugs, along with insulin

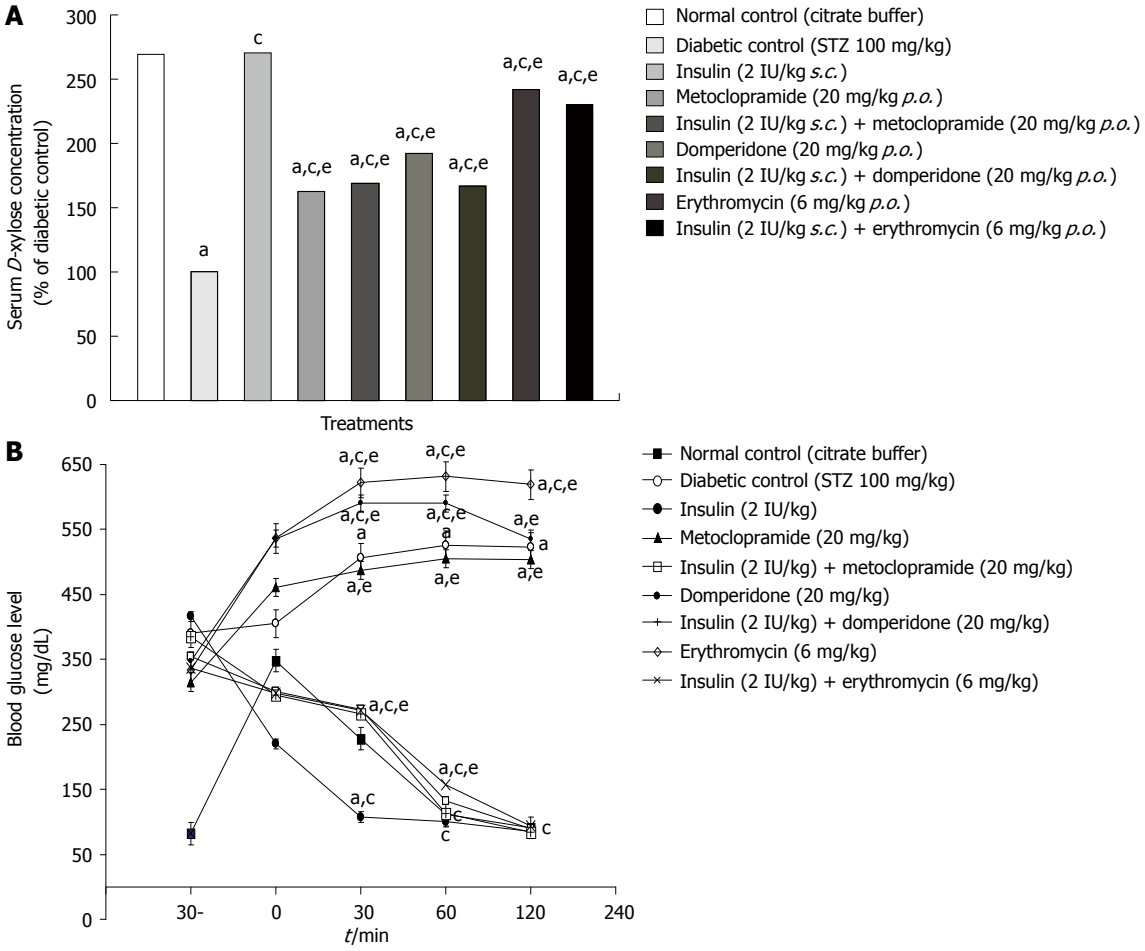

Figure 3 Effect on oral *D*-xylose absorption and tolerance test in streptozotocin-induced diabetic mice of single doses of insulin, metoclopramide, domperidone and erythromycin individually as well as the combination of insulin with metoclopramide, domperidone or erythromycin. A: Oral *D*-xylose absorption test; B: Oral *D*-glucose tolerance test. Values represent the mean ± SE of eight mice per group. Significantly different from the normal control value at $^{a}P < 0.05$; Significantly different from the diabetic control value at $^{c}P < 0.05$; Significantly different from insulin value at $^{e}P < 0.05$.

antagonized the action of insulin (2 IU/kg) on xylose absorption (Figure 3A) in diabetic mice.

Oral D-glucose tolerance test

The OGTT can be used to evaluate blood glucose homeostasis and also indirectly evaluate glucose absorption. As shown in Figure 3B, glucose load (2.5 mg/kg) in normal mice produced rapid increase in blood glucose levels at 30 min and returned to baseline values within 120 min. In contrast, STZ-induced diabetic mice demonstrated basal hyperglycemia (399 ± 14 mg/dL) which remained above 400 mg/dL during all time points determined. The peak increase in serum glucose concentrations in diabetic mice was observed after 60 min of glucose treatment, while that of normal mice observed after glucose loading, indicating delayed glucose homeostasis in diabetic mice. STZ significantly ($P < 0.05$) increased the area under the curve (Figure 4). Insulin (2 IU/kg) significantly ($P < 0.05$) decreased blood glucose level to 107.16 ± 8.51 mg/dL and 100 mg/dL after 30 min and 60 min of glucose loading, respectively, and the effects persisted until 120 min (Figure 3B). The area under the curve was significantly reduced to 226.53 ± 12.28 mg/dL after 120 min (Figure 4). Metoclopramide (20 mg/kg) did not affect blood glucose level where BGL was 487.5 ± 13.6 mg/dL and 505.50 ± 14.55 mg/dL after 30 min and 60 min of glucose loading, respectively. Domperidone (20 mg/kg) and erythromycin (6 mg/kg) produced significant ($P < 0.05$) increases in blood glucose level to 590 ± 13 mg/dL, 590.8 ± 17.4 mg/dL and 622.00 ± 23.11 mg/dL, 631.50 ± 21.48 mg/dL after 30 min and 60 min of glucose loading, respectively (Figure 3B). In addition, domperidone and erythromycin significantly ($P < 0.05$) increased the area under the curve (Figure 4). Administration of metoclopramide, domperidone or erythromycin along with insulin significantly ($P < 0.05$) increased blood glucose levels as compared to insulin treated values (Figure 3B). Combination of insulin with metoclopramide, domperidone or erythromycin significantly ($P < 0.05$) increased the area under the curve as compared to insulin treated value (Figure 4).

DISCUSSION

Findings of the present investigation revealed that STZ-induced diabetes resulted in a significant increase in SIT and a significant decrease in GE. Abnormalities in GE and small intestinal motor functions were also reported

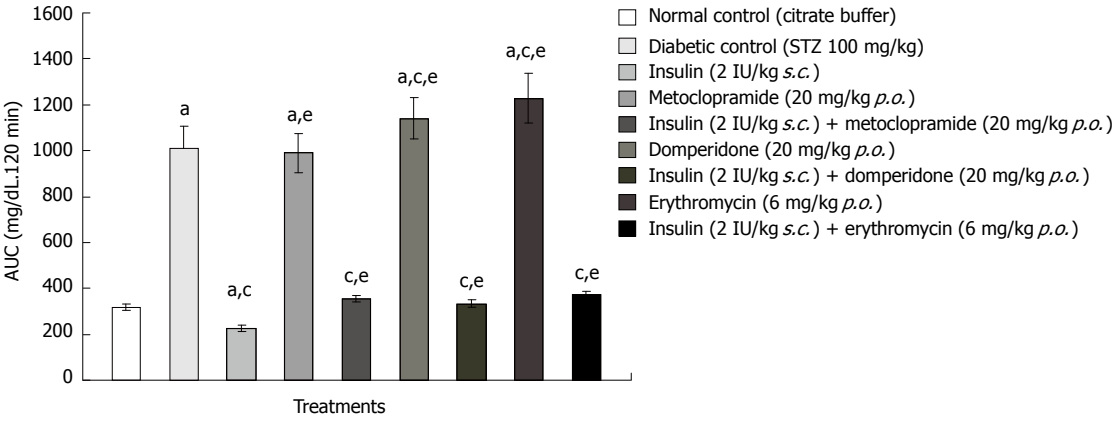

Figure 4 Effect on the area under the curve of blood glucose concentrations during oral glucose absorption test in streptozotocin-induced diabetic mice of single doses of insulin, metoclopramide, domperidone and erythromycin individually as well as the combination of insulin with metoclopramide, domperidone or erythromycin. Values represent the mean ± SE of eight mice per group. Significantly different from the normal control value at $^{a}P < 0.05$; Significantly different from the diabetic control value at $^{c}P < 0.05$; Significantly different from insulin value at $^{e}P < 0.05$. AUC: Areas under the curve.

in diabetic mice[27,28]. Increased intestinal transit may be partially due to increased cholinergic and decreased beta-adrenergic receptor activities in diabetic animals[29]. The delay in GE could be partially attributed to the decrease in the number of myenteric neurons in the stomach as a result of diabetes[30-32]. Similarly, the increase in intestinal transit could be mediated through the same mechanism. All of the stomach's smooth muscle cells have the ability to produce electric depolarizations "slow waves" from resting potential. These rhythmic contractions are thought to originate in the non-smooth muscle pacer cells in the interstitial cells of Cajal (ICCs)[33]. GE is delayed because the number of ICCs is markedly diminished in diabetes[34]. Data of the current study showed that insulin-induced hypoglycemia significantly attenuated SIT and accelerated GE in diabetic mice. These results are partly in agreement with earlier reports[35-38]. The obtained results might be partially due to the direct effect of insulin and not only due to the antidiabetic effect of insulin in decreasing blood glucose level, thereby leading to decreased SIT. This effect could be due to counter-regulation of hypoglycemia. The actions of insulin on the stomach could be mediated via an insulin stimulant effect on the vagus nerve, as reported by Quigley *et al*[39].

Data from the present investigation showed that STZ-induced diabetes resulted in a significant decrease in xylose absorption, in agreement with the finding of Fuessl[40]. The decrease in xylose absorption could be mediated the decreased rate of GE, which resulted from elevation in BGL, as reported by the present study. This explanation coincides with that given by Rayner *et al*[9] and Chapman *et al*[41].

Recent studies have shown that modifications of systemic glycemia in OGTT reflect the activity of the intestinal glucose transporter SGLT1[42]. In the present study, STZ-induced diabetic mice demonstrated basal hyperglycemia, which remained above 400 mg/dL during all time points determined. The capacity of the small intestine to absorb glucose increases in experimentally induced diabetic animals as a consequence of the enhanced activity and abundance of SGLT1, as shown by Fedorak *et al*[43], suggesting SGLT1 as a potential target for glycemic control in diabetic animals. STZ-induced diabetic mice exhibited severe hyperglycemia with increased Na^+ dependent glucose uptake activity, compared with normal mice[44]. Acute insulin-induced hypoglycemia increased xylose absorption and glucose absorption from the GIT in the diabetic mice. In the present study, the effects of insulin on the intestinal absorption of sugar did not differentiate between an effect of insulin on the absorption capacity of the mucosa and other factors that may affect total sugar absorption. Some studies have shown that insulin causes increased Na^+ dependent glucose carrier activity in the small intestine, which leads to increased glucose absorption[45]. Some studies reported that insulin-induced hypoglycemia accelerates gastric empting in type 1 diabetes[37]. The decreased time for movement of sugar from stomach to the small intestine, in addition to its therapeutic effect, decreases the rate of glucose production and increases the rate of glucose utilization by cells[46].

By studying the prokinetic drugs individually in the current study, domperidone (20 mg/kg *p.o.*) was found to be the most effective agent in the diabetic mice both when compared to diabetic control group and to the other prokinetic drugs. Domperidone, metoclopramide and erythromycin significantly ($P < 0.05$) decreased small intestine transit and accelerated GE in STZ-induced diabetic mice. Similar results have recently been reported from other studies[47-51]. The inhibitory effect of domperidone on SIT is probably mediated *via* its action on dopamine since it is a dopamine antagonist[52]. Dopamine has an indirect inhibitory effect through inhibition of cholinergic transmission in the myenteric plexus, which regulates the gastrointestinal tract[53]. It could be suggested that metoclopramide produces its action through inhibition of presynaptic and postsynaptic D_2 receptors, stimulation of presynaptic excitatory 5-HT_4 receptors and/or antagonism of presynaptic inhibition of muscarinic receptors, in accordance with the conclusions of Valenzuela *et al*[54]. The action of erythromycin is prob-

Table 1 Effects of insulin and prokinetic drugs alone and in combination on small intestinal transit and gastric emptying in diabetic mice

Treatments	SIT (%)	GE (%)
Normal control (citrate buffer)	56.61 ± 2.58	72.50 ± 1.68
Diabetic control (streptozotocin 100 mg/kg)	76.90 ± 6.12[a]	55.23 ± 9.30[a]
Insulin (2 IU/kg *s.c.*)	61.05 ± 3.85[c]	95.87 ± 2.41[ac]
Metoclopramide (20 mg/kg *p.o.*)	50.04 ± 2.42[ce]	76.38 ± 7.67[ce]
Insulin (2 IU/kg *s.c.*) + Metoclopramide (20 mg/kg *p.o.*)	54.30 ± 3.46[c]	94.91 ± 1.01[ac]
Domperidone (20 mg/kg *p.o.*)	48.70 ± 4.53[ce]	90.92 ± 4.92[ac]
Insulin (2 IU/kg *s.c.*) + Domperidone (20 mg/kg *p.o.*)	62.60 ± 3.07[c]	92.87 ± 1.14[ac]
Erythromycin (6 mg/kg *p.o.*)	43.05 ± 3.50[ce]	84.77 ± 2.11[c]
Insulin (2 IU/kg *s.c.*) + Erythromycin (6 mg/kg *p.o.*)	49.14 ± 4.57[ce]	90.86 ± 3.20[ac]

Values represent the mean ± SE of eight mice per group. Significantly different from the normal control value at [a]$P < 0.05$; Significantly different from the diabetic control value at [c]$P < 0.05$; Significantly different from insulin value at [e]$P < 0.05$. SIT: Small intestinal transit; GE: Gastric emptying.

ably mediated *via* its agonistic activity to motilin receptors, which accelerates GE[8,33].

Metoclopramide significantly increased xylose absorption but did not affect glucose absorption in STZ-induced diabetes. These finding are in agreement with those of Kuo *et al*[55]. The action of metoclopramide is mediated through increased plasma concentrations of glucagon like peptide-1 and glucose dependant insulinotropic polypeptide, which are responsible for delay in glucose absorption, although this action does not affect rate of xylose absorption. Domperidone (20 mg/kg) and erythromycin (6 mg/kg *p.o.*) significantly increased xylose absorption and glucose absorption in the diabetic mice as compared to diabetic control group. The effect of erythromycin could be mediated through the action of erythromycin on motilin receptors in the GIT. The action of erythromycin is probably mediated *via* its agonistic activity to motilin receptors, which accelerates GE and increases the rate of sugar absorption.

Combination of domperidone (20 mg/kg), metoclopramide (20 mg/kg) or erythromycin (6 mg/kg) with insulin (2 IU/kg) decreased the amount of xylose absorbed from the GIT when compared to insulin given alone in the diabetic mice. This indicates antagonistic interaction between each two drugs on xylose absorption. It is difficult to explain this action satisfactorily on the basis of the limited information available on the two drugs in this respect. Combination of insulin with metoclopramide, domperidone or erythromycin increased glucose absorption from the intestine when compared to the effect of insulin alone in the diabetic mice. These results suggest that combination of prokinetic drugs with insulin may lead to increased Na^+ dependent glucose carrier activity in the small intestine. In addition to treating symptoms, prokinetic drugs could potentially improve glycemic control in diabetic gastroparesis by allowing a more predictable absorption of nutrients, matched to the action of exogenous insulin.

The present study suggested that prokinetics may increase the hypoglycemic effect of insulin. Erythromycin tended to decrease the blood glucose level and increase the serum insulin level after one week of daily administration in STZ-induced diabetic mice. Erythromycin at a dose of 6 mg/kg *p.o.* potentiated the effect of insulin on blood glucose and serum insulin levels after one week of daily administration in diabetic mice where other prokinetic agents failed to do so after repeated administration. Similar results have been reported by Ueno *et al*[56]. The action of erythromycin on insulin could be mediated *via* its action as a motilin agonist. It is to be noted that motilin controls cyclic release of insulin through vagal cholinergic muscarinic pathways, as reported by Suzuki *et al*[57]. Itoh *et al*[58] found that there are no motilin receptors in the pancreas. Therefore, the action of erythromycin on insulin secretion is probably mediated *via* vagal-cholinergic muscarinic pathway stimulation linking to serotonergic receptors. This is a common mechanism in the stimulatory effect of motilin on muscle contraction in the stomach and on pancreatic polypeptide secretion from the endocrine pancreas[59,60].

The action of erythromycin on gastrointestinal motility in the present study is contradictory to some studies which claim that active motilin receptors do not exist in rodents, and that they only exist as pseudogenes[61,62]. However, the present results are in agreement with other studies[63-65]. It is suggested that the action of erythromycin is mediated by binding to central motilin receptors which might be involved in regulation of gastric motility in diabetic rats.

This study dealt with an important issue concerning the use of prokinetic drugs in insulin-treated diabetic individuals. Not all diabetic patients develop gastrointestinal motility disorders or gastroparesis. However, the use of prokinetic drugs might be also relevant in these patients. Erythromycin potentiates the effect of insulin on blood glucose levels and serum insulin levels after repeated administration in diabetic mice. This seems to suggest that the use of prokinetic drugs, such as erythromycin, might be useful in the clinic for decreasing the need of insulin.

In conclusion, combination of insulin with metoclopramide, domperidone or erythromycin increases glucose absorption. This leads to the suggestion that such prokinetic drugs may guard against the risk of sever hypoglycemia associated with diabetic mice treated with insulin. The present study suggests that the use of prokinetic drugs, such as erythromycin, may be useful in the clinic for decreasing the need for insulin in diabetic patients. Use of erythromycin may allow the dose of insulin to be safely decreased in chronic treatments.

COMMENTS

Background

Diabetes mellitus is the most common cause of gastroparesis and disturbed gastric and small intestine motility. Gastroparesis is a syndrome characterized by delayed gastric emptying (GE) in the absence of mechanical obstruction of the stomach. Prokinetic drugs have been used for gastroparesis in diabetic pa-

tients for a relatively long time and some data about the interactions with insulin in the clinic should be available.

Research frontiers

Searching for therapeutic interventions with prokinetic drugs that will improve the specific alterations associated with diabetic gastroparesis was the most important aim of the present study. The research focus was to study the possible effects of metoclopramide, domperidone or erythromycin combined with insulin on different parameters in streptozotocin (STZ)-induced diabetic mice and to highlight the possibility that prokinetic drugs might increase the hypoglycemic effect of insulin.

Innovations and breakthroughs

Diabetic gastroparesis has been managed most successfully with drugs that stimulate GE. Previously prokinetic agents have generally been prescribed in order to relieve symptoms associated with diabetic gastroparesis. The prokinetic drugs metoclopramide, domperidone and erythromycin are all reported to reduce disturbance of gastrointestinal motility. This study deals with an important issue concerning the use of prokinetic agents in insulin-treated diabetic individuals. Not all diabetic patients develop gastrointestinal motility disorders or gastroparesis, but the use of prokinetic drugs might be also useful in these patients. In the present study, erythromycin potentiated the effect of insulin given on blood glucose levels and serum insulin levels after repeated administration in diabetic mice. Combination of insulin with metoclopramide, domperidone or erythromycin increased glucose absorption from the intestine.

Applications

The present study suggests that prokinetic drugs could potentially improve glycemic control in diabetic gastroparesis by allowing a more predictable absorption of nutrients, matched to the action of exogenous insulin. The use of prokinetic drugs, such as erythromycin, may be useful in the clinic for decreasing the need for insulin in diabetic patients. Use of erythromycin may allow the dose of insulin to be safely decreased with in chronic treatments.

Terminology

Gastroparesis is a syndrome characterized by delayed GE in the absence of mechanical obstruction of stomach. Prokinetic drugs enhance gastrointestinal motility by increasing the frequency of contractions in the small intestine or making them stronger, but without disrupting their rhythm. They are used to relieve gastrointestinal symptoms such as abdominal discomfort, bloating, constipation, heart burn, nausea, and vomiting.

Peer review

This manuscript deals with an important issue concerning the use of prokinetic drugs in insulin-treated diabetic individuals. Different prokinetic agents are used alone or in combination with insulin in STZ-induced diabetic mice in order to determine whether there exists any interaction between these drugs in different parameters. The study is interesting and the design is adequate.

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16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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