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• *BRIEF REPORTS* •

^{14}C-urea breath test in patients undergoing anti-tuberculosis therapy

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Abstract

AIM: Urea breath test (UBT) is a non-invasive diagnostic test for detecting the presence of *Helicobacter pylori* (*H pylori*). In this study we evaluated the effect of anti-tuberculosis therapy on the results of ^{14}C-UBT.

METHODS: Patients, with the diagnosis of tuberculosis (TB) who had a positive UBT at the point of starting anti-TB therapy, were included. None had a history of peptic ulcer disease or had taken antibiotics, bismuth compounds and/or PPI in the previous month. ^{14}C-UBT was repeated at the end of the second month and the end of treatment period and one month after completion of treatment course.

RESULTS: Thirty-five patients (23 males) were enrolled. 14C-UBT was negative in all 35 patients (100%) at the end of the second month and remained negative in 30 cases (85.7%) at the end of the treatment course. One month after completion of treatment course, UBT remained negative in 13 patients (37.1%).

CONCLUSION: Our report underscores the need for caution while interpreting urea breath test results in patients undergoing anti-TB therapy. Furthermore, the combination of drugs used in this study resulted in *H pylori* eradication in a minority of patients.

Key words: Urea breath test (UBT); *Helicobacter pylori*; Tuberculosis

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INTRODUCTION

Helicobacter pylori (*H pylori*) is the most renowned factor among peptic ulcer risk factors[1]. Eradication of this germ has contributed to a significant reduction in the peptic ulcer prevalence[2-5]. Several drug regimens have been introduced for *H pylori* eradication[6,7]. Urea Breath Test (UBT) is currently the standard means of determining *H pylori* eradication. Some drugs, including antibiotics are known to lower the accuracy of this test. In the present study, we evaluated specifically the effect of a four-agent anti-tuberculosis therapy on the results of ^{14}C-UBT in a group of patients with tuberculosis and positive baseline UBT.

MATERIALS AND METHODS

All patients referred to Amir-Alam General Hospital from January 2002 to December 2003 with a diagnosis of tuberculosis (TB) were evaluated. TB had been documented based on clinical and laboratory findings and anti-tuberculosis treatment was ordered for all of them. Patients with a history of documented peptic ulcer before treatment or using Bismuth, proton pump inhibitors (PPIs), H_2 blocker agents or antibiotics in the month before were excluded from the study. None of the enrolled patients had ever been treated for *H pylori* eradication or undergone gastric resection. UBT test was done for all patients at the time of starting anti-TB therapy and patients with positive tests were enrolled. The anti-TB regimen in all patients consisted of Isoniazid, Rifampicin, Ethambutol and Pyrazinamide for two months, after which the latter two drugs were stopped and the treatment was carried on with Isoniazid/Rifampicin until the end of the treatment course. Cases of spinal tuberculosis were planned for a 12-mo course of therapy, whereas a 6-mo course was considered for other types of tuberculous organ involvement.

^{14}C-UBT was repeated three times for every enrolled patient: (1) at 2 mo (time of stopping Ethambutol/Pyrazinamide); (2) end of treatment course (mo 12 for spinal TB cases); (3) one month after completion of the anti-TB treatment course. The tests were all performed in the Nuclear Medicine Laboratory, Shariati Hospital, Tehran University of Medical Sciences, by a single team of specialized staff. Each overnight fasting patient was given 1 μCi (37 kBq) of ^{14}C-urea

dissolved in 250 mL water, after thorough brushing. Breath samples were collected once before ingestion of the tracer and subsequently at 15 min after ingestion. The breath samples were trapped in 1 mmoL ethanolic hyamine hydroxide in 10 mL toluene-based scintillation fluid. Carbon-14 content was measured in disintegration per minute (DPM) mode using a liquid beta-scintillation counter. A cut-off value of 200 was set for the positive test result. Intermediate test result was defined as 50-200 DPM, and test results of <50 DPM were considered negative.

RESULTS

During the study period, 44 patients with a definite diagnosis of tuberculous infection were planned for anti-TB therapy. Three patients revealed a history of antibiotic therapy during the month before and were therefore excluded. Six more patients had negative or intermediate UBT results and were also excluded. Thirty-five patients including 23 males (age 17-55 years; mean age: 38.5) and 12 females (age 16-39 years; mean age: 24) were eligible for the study. Among the enrolled patients there were 12 pulmonary and 23 extra-pulmonary cases of TB including 5 patients with a diagnosis of vertebral tuberculous osteomyelitis (Table 1). None were critically ill or under treatment with immunosuppressive drugs.

At the end of the second month of therapy, UBT became negative in all 35 patients (100%). The test results at the end of the treatment course were still negative in 30 cases (85.7%). One month after completion of anti-tuberculosis therapy, UBT turned positive in 17 of 30 patients, so 22 patients (62.9%) had positive results at this point, and the test remained negative in 13 patients (37.1%, Table 2).

DISCUSSION

H pylori is a slow-growing, microaerophilic, gram-negative bacterium, whose most striking biochemical characteristic is the abundant production of urease. This bacterium colonizes gastric mucosa and elicits both inflammatory and immune lifelong responses, with release of various bacterial and host-dependent cytotoxic substances[8]. *H pylori* eradication can be established reliably by histology, rapid urease testing and the urea breath test (UBT). The UBT uses labeled urea (^{13}C or ^{14}C) that, in the presence of *H pylori*, is metabolized by urease to yield CO_2. The labeled gas is absorbed across the gastric mucosa and subsequently measured in the patient's expired breath.

Analysis of the results reported in studies in which urea breath-tests were evaluated against an accepted gold standard, confirms the great accuracy (sensitivity 97%; specificity 95%) of this technique[9].

There is general consensus[10-13] regarding the adverse effect of proton pump inhibitors (PPIs) on the UBT (false negative results range from 17% to 61%). Moreover, antibiotics and bismuth compounds reduce *H pylori* load such that infection may be undetectable. Thus, urea breath-tests should not be performed within 4 wk of receiving such drugs, whether given specifically to treat the infection or not[14].

In 1992, Mitchell found that a history of pulmonary TB might be associated with an increased prevalence of *H pylori* infection[15]. More recently, Woeltje assessed the prevalence of tuberculin skin test (TST) positivity in a cohort of 346 newly hospitalized patients. A history of peptic ulcer disease was one of the identified risk factors for a positive TST test (odds ratio: 4.53, $P = 0.017$)[16]. Increased risk of TB for persons with a history of peptic ulcer disease has also been reported[17]. *H pylori* is seen in high prevalence in some populations around the world[18] especially in regions having lower socioeconomic status[19-21]. The same is true for the distribution of tuberculosis which is, to a great extent, clustered in some developing countries[22]. Rationally, there seems to exist a population of considerable size, potentially exposed to both microorganisms.

In-vitro studies of Rifampicin and Streptomycin, two drugs commonly used in anti-tuberculosis regimens have suggested the efficacy of these agents against *H pylori*[23-25] and a decrease in *H pylori* seroprevalence during anti-tuberculosis therapy has been reported[26]. There is no report of using Rifampicin in *H pylori* eradication regimens but recently Rifabutin from the same family of agents has been implemented as rescue therapy against resident species in combination with Pantoprazole and Amoxicillin[27]. Isoniazid is used in treating mycobacterial species and acts via inhibiting mycolic acid synthesis. There is no report so far of the efficacy of this agent on non-mycobacterial microorganisms[28].

To our knowledge, there has been no specific report of the effect of anti-tuberculosis therapy on the accuracy of UBT. Our report shows that anti-TB therapy causes negative UBT results in a considerable fraction of patients, and so underscores the need for caution while interpreting urea breath test results in patients undergoing anti-TB therapy.

Table 1 Patient characteristics

Gender	Male	23 (65.7%)
	Female	12 (34.3%)
	Total	35
Age (yr)	Male	17-55 (38.5±11.2)
	Female	16-39 (24.0±8.6)
Type of infection	Pulmonary TB	12
	TB adenitis	9
	TB enteritis	5
	TB osteomyelitis (vertebra)	5
	Meningeal TB	2
	Peritoneal TB	2
	Total	35

Table 2 ^{14}C-urea breath test results among 35 patients during the course of anti-tuberculosis therapy

	Baseline	End of 2nd mo of therapy	End of treatment course	One month after completion on therapy
Positive (%)	35 (100)	0 (0)	4 (11.4)	22 (62.9)
Negative (%)	0 (0)	35 (100)	30 (85.7)	13 (37.1)

Furthermore, the combination of drugs used in this study resulted in *H pylori* eradication in a minority of patients.

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