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SHORT COMMUNICATION

Point-of-care Arkansas method for measuring adherence to treatment with isoniazid

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Summary
We evaluated the accuracy of a point-of-care test designed to measure adherence to isoniazid (INH) preventive therapy in a hospital setting in Rio de Janeiro, Brazil. Patients on treatment with daily INH and patients not receiving INH were included. Sensitivity and specificity of the test were 84%/98% at the first minute, and 95%/98% at the fifth minute, respectively. Among smokers, sensitivity and specificity was reduced (80%/89% at the fifth minute, respectively), but only 17% smoked. This test accurately detected INH metabolites 24 h following directly observed INH intake, though sensitivity and specificity may be compromised by tobacco smoke exposure.

Introduction

Treatment of latent tuberculosis (TB) infection with isoniazid (INH) preventive therapy (IPT) as a TB control strategy has been limited predominantly to developed countries, though in settings with high rates of HIV co-infection, this strategy is being re-visited.[1] Ensuring adherence to IPT is a significant challenge. Although measuring patient adherence is essential, it is often limited to patient report.[2]

The Arkansas color method of detecting INH metabolites in the urine relies on a colorimetric assay test performed in a laboratory.[3–6] A recently developed test, IsoScreen (GFC Diagnostics Limited, Oxfordshire, UK), utilizes the reagents of the Arkansas method in a patented

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plastic testing device (SafeTube), allowing test evaluation in the field. However, IsoScreen has only been tested in small groups of patients.[7]

The objective of this study was to determine, under routine conditions, the sensitivity and specificity of the IsoScreen test in measuring adherence to IPT among an outpatient hospital population with high prevalence of TB in Rio de Janeiro, Brazil.

Methods

We recruited two patient groups: patients currently on treatment with daily INH were classified as the INH group; and individuals attending the hospital for initial evaluation for active or latent TB therapy initiation were considered the control group. For the INH group, a first visit was a routinely scheduled appointment in which the subjects took INH under supervision, and a second visit was scheduled after 24 h for urine specimen collection. The control group had only one visit to provide the urine specimen. All patients were ≥18 years. Exclusion criteria were non-daily INH use for the INH group, and INH intake within the last 30 days for the controls. Urine specimens were aspirated using the syringe connected to the device, then injected into the dried chemicals within the device and shaken. The urine color was recorded 1 and 5 min after mixing. The test was considered positive when urine turned green or dark blue and negative if no change in color. The McNemar test was used to analyze the difference between test sensitivities at first and fifth minutes.

This project was approved by the Clementino Fraga Filho University Hospital and the Johns Hopkins School of Medicine institutional review boards.

Results

From June 2007 to July 2008, a total of 146 subjects were included in the study. Two patients were excluded from the INH group because they did not return to provide a urine specimen. There were 94 patients in the INH group and 50 in the control group.

In the INH group, 65 (69%) patients were on IPT while 29 (31%) were on active TB treatment. The median time from INH ingestion and test performance was 23.4 h (IQR: 23.0–24.2 h). Table 1 shows test accuracy. Sensitivity was 10.3% greater at the fifth minute (94.7%) versus the first minute (84.4%; $p < 0.01$), and specificity was 98% at both readings. The difference between sensitivities at first and fifth minutes was due to nine specimens that became blue after the first minute. Table 2 shows demographic characteristics of individuals with false test results. Among smokers, the sensitivity and specificity decreased to 80% and 88.8% at fifth minute, respectively, though only 17% (24/144) were smokers.

Discussion

We evaluated a point-of-care test for measuring adherence to IPT, and our findings show high sensitivity and specificity (≥95%) with mean time from INH ingestion and test results of approximately 24 h. Based on these results, this test is being utilized in the THRio study in Rio de Janeiro, Brazil investigating the adherence of HIV-infected patients receiving IPT.[8]

Adherence to IPT has been reported to be enhanced by measures such as provision of incentives and treatment supervision.[2,9] However, due to the high number of patients who would be recommended to receive IPT, these measures are prohibitively expensive, especially in developing countries where the limited resources available are directed towards detection and treatment of active disease. The IsoScreen test might be a practical alternative for this purpose since it can be performed without strict laboratory conditions and provides an immediate confirmation of patient compliance. In a previous study, non-adherence to IPT was found in 28.5% of patients submitted to the Arkansas method. However, 83% of patients who were tested negative at the first visit became adherent in the second visit, suggesting that biological acknowledgement of their non-adherence may have changed their behavior.[6]

In our study, in five patients for whom INH ingestion was confirmed, the test was negative. Four of them were on regular treatment with other drugs, although none were receiving the same drugs. Although we did not assess acetylator status, the false-negative results could be due to faster drug metabolization, as previously reported, or it may actually reflect variability in INH metabolites detected in urine or inherent test inaccuracy.[10,11] Test accuracy may also have been compromised by tobacco smoke exposure similarly to another study evaluating the test spectrophotometrically. In that study, while the urine of non-smokers taking INH turned deep blue, the presence of nicotine and its metabolites in urine of smokers taking INH produced a green color after reaction, resulting in the blue-green color.[3]

Table 1 Isoscreen test accuracy at 1 and 5 min after test performance.

Color	1st Minute				5th Minute			
	INH group	Control group	Sensitivity (95% CI)	Specificity (95% CI)	INH group	Control group	Sensitivity (95% CI)	Specificity (95% CI)
Yellow	14	49			5	49		
Green	8	0			8	0		
Blue	68	1	84.4%[a]	98.0%	81	1	94.7[a]	98.0
Missing	4	0	(78.5–90.3)	(95.7–100)	0	0	(91.0–98.4)	(95.7–100)
Total	94	50			94	50		

Sensitivity/specificity calculated with blue and green reflecting a positive result.
[a] The difference between sensitivity at fifth and first minutes was 10.3% ($p < 0.01$).

Table 2 Demographic characteristics of patients with false test results at 1 and 5 min after test performance.

	Total	Age	Gender male	Race white	Smoker	Use of other medications[a]
		Mean (SD)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Urine color at 1st minute						
INH group						
Yellow (false-negative)	14	45 (10.3)	9 (64)	5 (36)	3 (21)	6 (43)
Control group						
Green (false-positive)	0	0	0	0	0	0
Blue (false-positive)	1	28	1 (100)	0	1 (100)	0
Urine color at 5th minute						
INH group						
Yellow (false-negative)	5	50 (5.3)	3 (60)	2 (40)	3 (60)	4 (80)
Control group						
Green (false-positive)	0	0	0	0	0	0
Blue (false-positive)	1	28	1 (100)	0	1 (100)	0

[a] Regular medication use other than TB drugs.

A limitation of our study is that it was unblinded. Since the study was conducted under routine operational conditions, the responsible nurse was aware of which subjects were under current INH treatment and which subjects were being investigated for TB (controls). Because a green color (also considered as positive in this study) may not definitively represent a positive result, we presented the results stratified by color (Table 1). If green was not considered to be a positive result, then sensitivity at 5 min would have been 86%, while specificity would have remained unchanged. We are confident that our technician was readily able to differentiate between yellow and green, and that the high sensitivity reported (95%) suggests strong utility for this test in operational settings. Another limitation is that the test accuracy was only measured within 24 h of drug intake, thus we cannot confidently extrapolate our results beyond this period of time. In programmatic settings, patients may miss a dose 24 h prior to providing a urine specimen, but may still be strongly adherent to their regimen or take IPT the day before the urine test simply to ''appear'' to be adherent. Thus, appropriate counseling for test objective and an oral history of adherence should always be included when using a biological assay for measuring adherence.

In conclusion, the IsoScreen test accurately detected INH metabolites 24 h following directly observed INH intake. As an objective test, it might be used repeatedly as a follow-up method to better characterize adherence and potentially increase adherence among patients receiving IPT or treatment for active TB.

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Authorship

Renata L. Guerra participated in data management, data analysis and interpretation, and drafted the manuscript. Marcus B. Conde, Anne Efron, Jonathan E. Golub and Richard E. Chaisson designed the study, participated in data interpretation, and reviewed the report. Carla Loredo e Gisele Bastos participated in data collection and data management. All authors approved the report final version.

Conflict of interest

The authors have no conflict of interest.

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