Challenges in Isoniazid Therapeutic Drug Monitoring

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Background

In certain settings, therapeutic drug monitoring (TDM) during tuberculosis treatment can be a useful adjunctive tool to assist in management. TDM is indicated in patients with suspected treatment failure (persistent or worsening clinical symptoms, unchanged/worsening radiographic findings or delayed culture conversion) not explained by non-adherence or drug resistance (1). Settings where drug levels may be low include the presence of malabsorption, impaired renal clearance and HIV infection. Isoniazid (INH) levels, in particular, can be challenging to interpret. Because of instability at room temperature of INH in particular, meticulous attention to specimen collection, processing and maintaining the specimen at -20^{0}F during transport and shipping is required (2).

Objectives

To better understand how to interpret INH TDM, and to assess the effect of specimen packaging and shipping protocols on TDM results.

Methods

We reviewed all results from specimens sent for INH TDM in our clinic. Standard protocols for INH TDM recommend collection of 2 ml of blood two hours after directly observed therapy; specimens should be centrifuged, separated and frozen within one hour of collection (–70º C is preferable, but at a minimum –20ºC). At ZSFG, standard protocols included shipping specimens via overnight courier on dry ice to reference laboratory #1 outside of California, which in turn sent the sample by overnight shipping to reference laboratory #2 in a different state, where testing was ultimately performed.

Methods

In order to evaluate the impact of shipping times on TDM results, we collected paired specimens in four patients two hours after INH dosing. Both specimens were immediately placed on ice, processed and frozen at -70°C within 60 minutes of collection. The first specimen was sent for TDM using the standard protocol described above from ZSFG to reference laboratory #2 via reference laboratory #1 (indirect route) and the second specimen was shipped overnight from ZSFG to reference laboratory #2 (direct route).

Results

Between November 19, 2015 – March 5, 2018, 82 specimens were collected from 15 patients for INH TDM. Thirty-six specimens were collected at two hours after dosing; the desired therapeutic range for isoniazid two hours after a 300 mg dose is 3-8 mcg/ml. Of these, 34 (94.4%) showed levels below the lower limit of normal (<3 mcg/mL), and 9 (25%) were undetectable (<0.50 mcg/mL).

Parallel testing was conducted in four patients (Table). In three patients, INH levels in specimens shipped directly by overnight courier were higher, ranging from 1.35 to 7.7 fold, when compared to specimens shipped by the indirect route. In the fourth patient, levels were undetectable in both specimens. The average time for shipping (time from ZSFG to reference laboratory #2) by the indirect route was 27 hours 7 minutes and by the direct route was 82 hours 29 minutes [difference 55 hours 30 minutes (2.29 days)]. Two of the four patients with non-therapeutic INH levels identified by direct route testing were young and otherwise healthy.

Results

	Dose (2 hr)	INH Level (mcg/ml) Indirect	Duration of Shipping	INH Level (mcg/ml) Direct	Duration of Shipping	Difference in INH Level (fold)
Pt # 1 (68 yr old, poorly controlled DM)	600 mg	2.07	167 hr, 0 m	2.8	20 hr, 37 m	1.35
Pt # 2 (28 yr old, healthy)	300 mg	0.72	44 hr, 0 m	2.18	20 hr, 57 m	3.02
Pt # 3 (27 yr old, healthy)	600 mg	<0.5	72 hr, 0 m	3.86	81 hr, 22 m	7.72
Pt # 4 (37 yr old, healthy)	300 mg	<0.5	44 hr, 14 m	<0.5	39 hr, 39 m	0

Abbreviations: hr- hours, INH-isoniazid, mcg- micrograms, ml- milliliter, Pt- patient, yr-years, DM- diabetes mellitus, mg-milligrams, m-minutes,

Conclusions

We found higher INH levels in specimens shipped directly to the reference laboratory when compared to indirect courier transport. Even a two day difference in duration of shipping time resulted in a decrease in measurable levels; the difference is likely due to difficulty keeping specimens frozen consistently during transport by commercial carriers. Further research is needed into which populations are at risk for low INH levels. Additionally, rigorous attention to specimen collection, processing and transport is needed to ensure reliable INH TDM.

References

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