Fasting Plasma 5-hydroxyindolacetic Acid (5-HIAA) Correlates with 24-hour Urinary 5-HIAA; Evaluation of a Simpler Assessment of 5-HIAA

INTRODUCTION/BACKGROUND

Research has shown that decreasing serotonin, as reflected by a decrease in 5-hydroxyindolacetic acid (5-HIAA) concentration, is associated with clinical improvement in carcinoid syndrome (CS) patients. Collection of 24-hour urine samples is standard practice to assess 5-HIAA excretion in patients with CS. However, this method is highly variable between patients, has missing time points due to compliance issues with sample collection, and is time-consuming, cumbersome, and inconvenient for patients. This analysis compared plasma 5-HIAA (p5-HIAA) and urinary 5-HIAA (u5-HIAA) to determine if a single blood plasma sample can be used to accurately assess 5-HIAA as a potential alternative to 24-hour u5-HIAA. For this assessment, plasma and urine samples were collected from fasted normal healthy individuals receiving LX1033.

LX1033 is an oral serotonin synthesis inhibitor (SSI) that inhibits tryptophan hydroxylase (TPH), the rate-limiting enzyme in the conversion of tryptophan to serotonin. LX1033 acts locally in the gastrointestinal tract and produces low systemic exposure. For TSQ software

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RESULTS

A total of 409 paired samples were analyzed. Correlations were statistically significant based on observed values for all treatment groups. Analysis of correlations based on change from baseline 5-HIAA paired values also showed statistically significant results, p<0.001.

CONCLUSIONS

5-HIAA, the primary metabolite of serotonin, is used as a biomarker for serotonin production. Since 5-HIAA is excreted in the urine, urine is most often analyzed to detect changes in 5-HIAA, which are reflective of changes in serotonin levels in the patients. More recently, plasma 5-HIAA has been reported as a simple alternative in the assessment of serotonin changes in carcinoid patients, thus u5-HIAA has become the standard measurement for the analysis. Additional determinations of serotonin in serum are used to provide complementary information.

There are several problems inherent with 24-hour urine collections, including large patient-to-patient and sample-to-sample variability, and difficulties with patient compliance in sample collection.

In this study we have compared the changes in p5-HIAA and u5-HIAA in individuals administered Lexicon Pharmaceutical’s SSI, LX1033. Inhibition of TPH decreases the level of serotonin’s metabolite 5-HIAA.

The objectives of this study were to investigate whether plasma 5-HIAA could serve as an acceptable surrogate for the commonly measured u5-HIAA, whilst providing easier convenience, precision and reproducibility in sample collection. Feeding whole p5-HIAA and u5-HIAA (24-hour) concentrations were measured by LC-MS/MS in normal healthy volunteers administered the TPH inhibitor LX1033.

Statistically significant correlations were seen across all dose groups. LX1033 is currently undergoing clinical evaluation in IBS patients.