Thiopurine Metabolites in Red Blood Cells

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Thiopurine drugs, including azathioprine, mercaptopurine, and thioguanine, are used to treat autoimmune diseases, inflammatory bowel disease, acute lymphoblastic leukemia, and to prevent rejection after solid organ transplant.[1] In some individuals, the accumulation of cytotoxic metabolites of these drugs leads to an increased risk of drug-related toxicity at standard doses. Concentrations of thiopurines and metabolites can be measured after the initiation of therapy to aid in dose optimization. This assay measures 6-thioguanine nucleotides (6-TGN) to determine whether dosing is in the optimal range and assesses the risk for leukopenia and myelotoxicity. 6-methylmercaptopurine nucleotides (6-MMPN) are also measured to assess the potential risk for hepatotoxicity.

Featured ARUP Testing

Thiopurine Metabolites in Red Blood Cells
3016503

Method: Quantitative Liquid Chromatography-Tandem Mass Spectrometry

Use this phenotypic test to optimize dosing of thiopurine drugs. This test can identify thiopurine metabolite concentrations (6-TGN and 6-MMPN) that may contribute to risk of toxicity.

Thiopurine Drug Therapy Overview

The inactivation of thiopurine drugs is catalyzed in part by thiopurine methyltransferase (TPMT) and nudix hydrolase 15 (NUDT15).[1,2,3] Variants in the *TPMT* and/or *NUDT15* genes are associated with impaired thiopurine inactivation and toxic effects including myelosuppression and/or hepatotoxicity. Enzyme phenotype testing for TPMT may be performed prior to treatment to assess risk for these effects; refer to the Thiopurine Methyltransferase, RBC Test Fact Sheet. Genetic testing may also be performed prior to or during thiopurine treatment to assess risk or investigate a toxic reaction to thiopurine drugs; refer to the *TPMT* and *NUDT15* Test Fact Sheet for more information.

Testing for thiopurine metabolites can be performed after the initiation of therapy to aid in dose optimization. This test should not be used as the sole basis for dose determination. Therapeutic drug management should be based on the complete clinical picture, including the clinical indication for thiopurine treatment, the degree of myelosuppression as measured by CBCs, comedications, and the results of other tests. Refer to the Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for thiopurine dosing based on TPMT and NUDT15 genotypes for more information.

Test Interpretation

This assay uses quantitative liquid chromatography-tandem mass spectrometry to detect 6-TGN and 6-MMPN. Results may vary between laboratories based on factors such as sample preparation methods and laboratory instrumentation. Therefore, concentrations reported by different laboratories should not be used for longitudinal comparison.

Limit of Quantification (LOQ)

- 6-TGN LOQ: 20 pmol/8 x 10^8 RBC
- 6-MMPN LOQ: 400 pmol/8 x 10^8 RBC

Results

Thiopurine Metabolites in Red Blood Cells: Results Interpretation[a]	
6-TGN Concentration (pmol/8x10^8 RBCs)	Interpretation
<235	Possible reduced response to therapy
235-450	Within therapeutic range
>450	Possible increased risk for leukopenia and myelotoxicity

[a]Results for both metabolites should be interpreted simultaneously in the context of dosing (eg, the time of dosing relative to specimen collection) and other clinical factors.

6-TGN Concentration (pmol/8x10^8 RBCs)	Interpretation
6-MMPN Concentration (pmol/8x10^8 RBCs)	**Interpretation**
≤5,700	Within therapeutic range
>5,700	Possible increased risk for hepatotoxicity

[a]Results for both metabolites should be interpreted simultaneously in the context of dosing (eg, the time of dosing relative to specimen collection) and other clinical factors.

References

1. Bayoumy AB, Crouwel F, Chanda N, et al. Advances in thiopurine drug delivery: the current state-of-the-art. *Eur J Drug Metab Pharmacokinet*. 2021;46(6):743-758.

2. Relling MV, Schwab M, Whirl-Carrillo M, et al. Clinical Pharmacogenetics Implementation Consortium guideline for thiopurine dosing based on TPMT and NUDT15 genotypes: 2018 update. *Clin Pharmacol Ther*. 2019;105(5):1095-1105.

3. Pratt VM, Cavallari LH, Fulmer ML, et al. TPMT and NUDT15 genotyping recommendations: a joint consensus recommendation of the Association for Molecular Pathology, Clinical Pharmacogenetics Implementation Consortium, College of American Pathologists, Dutch Pharmacogenetics Working Group of the Royal Dutch Pharmacists Association, European Society for Pharmacogenomics and Personalized Therapy, and Pharmacogenomics Knowledgebase. *J Mol Diagn*. 2022;24(10):1051-1063.

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