Thiopurine drugs, therapeutic drug monitoring by quantification drug metabolites or measure incorporation into DNA as deoxythioguanosine. Carlsson B., Karlsson L., Ärlemalm A., Sund S., and Lindqvist Appell M. Department of Clinical Pharmacology and Department of Biomedical and Clinical Sciences, Linköping University, Linköping, Sweden.

Background. The thiopurine drugs azathioprine (AZA) and 6-mercaptopurine (6-MP) are used in the treatment of inflammatory bowel diseases (IBD) or leukaemia (ALL). AZA and 6-MP are the first-line drugs in the maintenance treatment of Crohn's disease and ulcerative colitis. Thiopurines are so-called "pro-drugs", transformed in several steps to the active metabolites so-called, 6-thioguanine nucleotides (6-TGNs). 6-thioguanine triphosphate (6-TGN) acts as an antimetabolite utilising its immunomodulatory effect by being incorporated into RNA and DNA. The expression of pro-inflammatory transcription factors and proliferation of cells is inhibited leading to increased apoptosis. To follow these patients' treatment today, the concentration of the metabolites is measured in whole blood. The aim is to measure the thiopurines closer to their pharmacological endpoint as incorporated deoxythioguanosine (dTG) and evaluate whether dTG is a better predictor for treatment effect and/or toxicity than the current routine method of measuring metabolite levels.

Methods. Samples from IBD-patients have been analysed for thiopurine drug metabolites with our standard TDM method and with a newly developed method for measuring incorporated dTG.

Results. Twenty IBD-patients, in clinical remission and on AZA therapy, have been analysed. The doses varied between 25 to 275 mg/day. dTG concentrations between 0.19-1.64 nmol/L and the complementary nucleotide deoxycytidine (dC) from 0.49 to 1.60 µmol/l were found. dTG/dC ratio was calculated with a variation between 0.18*10-3 to 1.57*10-3. Using the measured DNA concentrations, the quantity of dTG was expressed as fmol dTG/µg DNA, with a calculated range between 54.2 to 922.1 fmol dTG/µg DNA. Metabolite concentrations were for 6-TGN 133-554 pmol/g Hb and for MeTIMP 0-5.3 nmol/g Hb.

Conclusions. The results, from the patient samples analyzed, agrees with earlier studies measuring dTG. In our method the complementary natural nucleotide dC is also measured. The ratio dTG/dC is calculated and used as a tool for interpretation of results. The methods will be used in an ongoing study on IBD-patients to scrutinize if measuring the pharmacological markers, incorporated dTG or ratio dTG/dC, are better predictors or new components in the TDM toolkit to interpret clinical response for thiopurine treated patients.

Key words: thiopurine, TDM, IBD, ALL, deoxythioguanosine, DNA