the upper reference decision limits (URDL) specific for each category used in our laboratory (Table 1). Of the 49,824 creatinine results reported, 15,686 (or 31.5%) exceeded their respective URDLs. The range of analytical error attributable to miscompensation was greatest in the pediatric age categories 2 (0–1 month) and 3 (1 month to 5 years) (e.g., errors of −29% to +24% in group 2) for which the URDLs are lowest, and albumin concentrations are usually lower than adult values. This magnitude of error invalidates use of the single-value protein compensation method for these age groups. In patient categories 1 and 4, in which URDLs were higher, the range of error observed was still unacceptably high, as indicated by the large proportions of error >3.4% (namely 97% and 38%). In the adult categories 5, 6, 7, and 8 the proportion of error >3.4% were lowest, but the range of error encountered was still too high for ensuring reliable creatinine results for clinical practice.

The data presented here indicate unacceptable inaccuracy in creatinine results due to variations in albumin concentrations. Hence, the single-value compensated creatinine Jaffe assay cannot achieve the current desired performance goal of 3.4% bias as recommended by the Laboratory Working Group of the National Kidney Disease Program (1), nor the recommended optimum goal of 1.7%. Awareness of this limitation may be helpful in setting clinical guidelines for result interpretation and in making future choices on methodology.

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References


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Stability of Thiopurine Metabolites: A Potential Analytical Bias

To the Editor:

In a report recently published in this journal (1), Reinshagen et al., who investigated 6-thioguanine nucleotide (6-TGN) concentrations in patients with inflammatory bowel disease (IBD), concluded that standard and adapted dosage of azathioprine led to identical 6-TGN concentrations and remission rates and that thiapeu-
scribed by Shipkova et al. (2) was used to measure 6-TG and 6-MMP nucleotides. The assay had precision values of 5.7% and 4.9% (within day) and 6.9% and 7.2% (between day) for 6-TGN and 6-MMP, respectively. To report the measured metabolite concentrations, erythrocytes were isolated, washed, and counted in the final suspensions before analysis. Analysis was performed at baseline and on days 1, 4, 5, 6, and 7 after sampling.

We obtained samples from 10 patients. The (pseudo)median 6-TGN concentration at day 7 decreased significantly to 53% during storage at room temperature (V = 0, P = 0.002, 95% CI 40%–69%) and 86% (V = 2, P = 0.011, 95% CI 75%–96%) during storage at 22°C and 4°C, respectively (Table 1; Wilcoxon rank-sum test). In addition, decreases in (pseudo) medians were significantly less for both metabolites from day 4 to day 7 during refrigeration [paired Wilcoxon rank-sum test]. These data have been reported previously (5).

Pike et al. (3) reported less dramatic decreases in nucleotide concentrations (14%–28% decrease at day 7), but our findings are more or less equivalent to the results reported by Sauviat et al. (4). Differences may be largely attributable to the study designs (i.e., the exact storage conditions) and the various analytical methods used. Higher storage temperatures can result in more substantial decreases in 6-TG and 6-MMP concentrations in blood samples, as is clearly demonstrated by our work. Despite a high correlation shown between various analytical methods, nucleotide hydrolysis techniques vary considerably, mainly in the type of acids, D,L-dithiothreitol, and hydrolysis time used in the analytical procedure (2). These variations can ultimately lead to incomplete hydrolysis and subsequent lower measured 6-TGN concentrations.

Apart from these analytical issues, we have again demonstrated an essential and clinically relevant decrease in both 6-TGN and 6-MMP concentrations attributable to sample storage/shipping conditions, findings that are of pivotal importance for the

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Table 1. Median decreases (±95 CI) in 6-TGN and 6-MMP values (N = 10) during 7 days storage under controlled conditions.
use of therapeutic monitoring in (future) multicenter studies and for interpretation of pharmacological data in clinical practice in patients on thiopurine therapy. In addition, exact storage conditions are often not mentioned in published reports; their omission may partly explain the current controversy concerning thiopurine metabolite research.

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References

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Drug Monitoring and Toxicology (DMT)

To the Editor:

Tazocin is an injectable antibiotic preparation with broad-spectrum activity against aerobic and anaerobic gram-positive and gram-negative bacteria (1). Reported side effects that might prompt metabolic disease investigations include change in consciousness and encephalopathy (2, 3). We report 2 patients in whom interpretation of organic acid analysis was complicated by administration of tazocin.

Case 1 was a 56-year-old man admitted for routine aortobifemoral bypass graft surgery. Past medical history included peripheral vascular disease, hypercholesterolemia, and epilepsy. Postoperatively the patient developed an acute abdomen and at laparotomy required extensive small bowel resection to treat a mesenteric infarction. His subsequent course was complicated by hepatic-induced thrombocytopenia. The patient further deteriorated, with a reduced level of consciousness (Glasgow Coma Scale 12/15), and was noted to have metabolic acidosis, with an increased anion gap of 27 mmol/L (reference interval 14–18 mmol/L). To exclude pyroglutamic acidosis as a cause of the metabolic derangement, a urine sample was sent for organic acid analysis by GC-MS (4). The results showed the presence of 4-ethyl 2,3-dioxo-1-piperazine, which was identified from a standard library (Fig. 1). This GC-MS peak was attributed to drug consumption, but its exact nature was not immediately recognized by the analyzing laboratory or other specialist laboratories consulted.

The 2nd case was a 67-year-old man admitted with a myocardial infarction. This patient underwent angioplasty, and subsequently developed left ventricular failure, hypotension, and acute renal failure necessitating intensive care. This patient had known severe peripheral vascular disease and developed osteomyelitis of his right foot, requiring right below-knee amputation. He developed a high anion gap metabolic acidosis (32 mmol/L) and a urine sample was sent for organic acid analysis. The presence of 4-ethyl 2,3 dioxo-1-piperazine was detected.

Each patient had been prescribed a number of drugs, but only tazocin was being given to both individuals. Tazocin is a combination of piperacillin sodium and the lactamase inhibitor tazobactam sodium. The structure of piperacillin is sodium (2S,5R,6R)-(5R)-2-{[(R)-2-(4-ethyl-2,3-dioxo-1-piperazine-carboxamido)-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid, and it was this substance that was detected in the urine.

Tazocin has previously been reported to produce a peak in the β region in capillary zone electrophoresis, potentially simulating a small monoclonal protein (5). We observed that organic acid analysis by GC-MS of intravenously administered tazocin produced a peak. Although the presence of this tazocin peak is unlikely to result in