Interference by piperacillin/tazobactam in the measurement of creatinine with the Jaffe method and of total protein with the biuret method

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ABSTRACT

Serum creatinine and total protein are routinely measured biochemical parameters used in clinical medicine. An abnormal result caused by interference with the assay does not accurately reflect a patient's clinical state and therefore risks misleading clinicians.

We report the case of a patient who had unexplainable high creatinine and total protein results. The blood collection was contaminated with intravenous fluid and the patient was receiving piperacillin/tazobactam. Additional laboratory studies demonstrated piperacillin/tazobactam was the cause of the false positive results and the elevation in both serum creatinine and protein level was dependent on the concentration of antibiotic present.

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A 79-year old man was treated for an obstructed left kidney and an infection associated with *Klebsiella oxytoca*. At the time of blood sample collection, the patient was being administered 5% dextrose and a bolus dose of piperacillin/tazobactam intravenously. The pathology results suggested a dilution effect typical of an intravenous contaminated sample with low analyte concentrations. The only elevated analytes were glucose level (57.3 mmol/L; reference interval [RI], 3.0–7.8 mmol/L), likely due to the dextrose infusion, serum creatinine level (179 μmol/L; RI, 64–108 μmol/L) and total protein (83 g/L; RI, 60–80 g/L), for which there was no obvious explanation. Clinical and laboratory review revealed that the patient had a mild acidosis, but there was no other clinical suspicion of a decline in renal function. The patient was not receiving any immunoglobulin infusions, dextran or contrast media, which may explain the elevated protein level. Blood tests were repeated and the results before and after the suspected intravenous contaminated sample were 154 μmol/L and 158 μmol/L for serum creatinine and 48 g/L and 50 g/L for total protein respectively.

Serum creatinine was measured using the Jaffe method and the total protein level was measured using the biuret method on the Beckman DxC 800 general chemistry analyser (Beckman Coulter, Brea, CA, USA). The sample was re-analysed with an enzymatic creatinine method on an i-Stat analyser (Abbott East Windsor, NJ, USA). The results on the intravenous fluid contaminated sample and the sample after contamination were 94 μmol/L and 153 μmol/L respectively, strongly suggesting that interference was the cause of the elevated serum creatinine level with the Jaffe method.

To determine if piperacillin/tazobactam was the causative agent, we added 40 mL of de-ionised water to dissolve the antibiotic and created a stock solution with a piperacillin concentration of 100 g/L and tazobactam 12.5 g/L. We added increasing concentrations of the piperacillin/tazobactam stock solution and saline in pooled serum as a control. The results confirm the interference was from the antibiotic solution (Table 1). When presented graphically (Figure 1), the results demonstrate the linear relationship with increasing piperacillin/tazobactam concentrations resulting in falsely increased concentrations of serum creatinine.

Discussion

Identifying potentially misleading laboratory results is an important aspect for both clinicians and laboratory staff. As pathology results are increasingly part of the integrated electronic medical record, how best to flag such misleading results becomes more important. Various algorithms can help identify anomalies with either critical, delta (prior result) differences or abnormal flags. Being aware of agents that can interfere with laboratory assays provides another opportunity to help interpret abnormal or unexpected results.

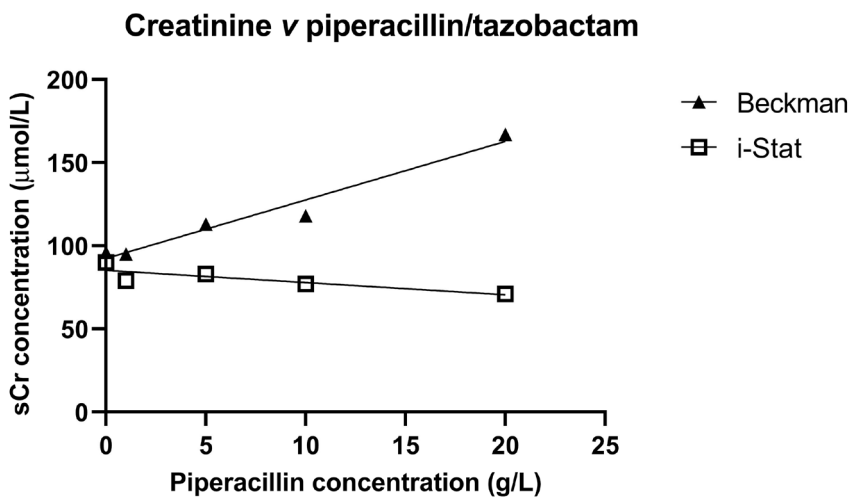
Creatinine is measured by both Jaffe and enzymatic methods. It is well known that all variations of the Jaffe

Table 1. Effects of piperacillin/tazobactam on serum creatinine and total protein levels with the Jaffe (Beckman) method and on serum creatinine levels using the enzyme (i-Stat) method compared with pooled serum samples with added saline

Sample	Jaffe creatinine (μmol/L)	Enzymatic creatinine (μmol/L)	Biuret total protein (g/L)
Pooled serum (PS)	96	90	61
1/5 (saline/PS)	65	61	48
1/5 (PipTaz/PS = 20 g/L)	167	71	92
1/10 (saline/PS)	85	76	54
1/10 (PipTaz/PS = 10 g/L)	118	77	89
1/20 (saline/PS)	92	85	58
1/20 (PipTaz/PS = 5 g/L)	113	83	80
1/100 (PipTaz/PS = 1 g/L)	95	79	59

* PipTaz = piperacillin/tazobactam

Figure 1. Effects of increasing piperacillin/tazobactam concentration on the Jaffe (Beckman) versus enzyme (i-Stat) creatinine methods



sCr = serum creatinine.

method lack specificity, but they are still widely used due to relatively low cost.[1] A review of the enrolled laboratories in the Royal College of Pathologists of Australasia Quality Assurance General Chemistry Program (RCPAQAP-GCP) showed that 59% of laboratories use the Jaffe method.

Interference resulting in a falsely elevated serum creatinine level with the Jaffe method has been reported from glucose, ascorbic acid, pyruvate, protein, acetoacetate, protein, fluorescein and various cephalosporin antibiotics.[1,2]

Interference with total protein measurement using the biuret method has been reported from carbenicillin, methicillin and rifampin.[3] Published data also show other compounds, such as dextran,[4] contrast media[5] and IgM-λ paraprotein,[6] can result in falsely elevated total protein results. RCPAQAP-GCP data showed that all laboratories used the biuret reagent for total protein.

Piperacillin/tazobactam is a very commonly used antibiotic; it was dispensed close to 74 000 times in the past 12 months in our tertiary level hospital. It is a combination of piperacillin (a broad-spectrum β-lactam) with tazobactam (a β-lactamase inhibitor) to enhance the antimicrobial spectrum and effectiveness. One limitation of our study is that we did not conduct studies of each component separately to identify the specific cause of the interference. Given the agents are provided and administered together, while this would be of academic interest, it does not alter clinical utility of the observation of interference.

The concentrations achieved in the intravenous infusion solutions are clearly higher than those that may be found with therapeutic plasma levels. When therapeutic drug monitoring is used in clinical practice, the target plasma concentration for piperacillin is usually greater than 22.5 mg/L, with plasma concentrations greater than 150 mg/L considered toxic.[7] While errors in sample collection are uncommon, it remains unknown if the inadvertent collection of blood for pathology testing at the same time as a bolus dose is administered could result in antibiotic concentrations that may cause interference in the laboratory assays.

The rate of grossly intravenous contaminated biochemical samples in our hospital is about 0.5%, most of which originated from critical care units. Intravenous contaminated samples are primarily due to a lack of knowledge on collection techniques from sites where an intravenous line is in place. The level of potential sample contamination can vary depending on the time of sample

collection after intravenous commencement and with the order of blood collection tubes used, with the first tube being the most contaminated. An additional common source of contamination is the use of a syringe to inject medication fluids, then drawing blood back into the same syringe, collecting the blood for pathology testing, and transferring it into the pathology blood collection tubes. Identification of intravenous contaminated samples becomes more challenging when it involves only mildly contaminated samples, leading to smaller but nonetheless clinically relevant misdirection from pathology results.

This case highlights that interferences can be method- or analyser-specific. Both laboratory and clinical staff should be aware that piperacillin/tazobactam can cause a false elevation when using the Jaffe serum creatinine method and the biuret method for total protein.

Competing interests

No relevant disclosures.

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