Interference of Drugs on Clinical Chemistry- Shall We Start Thinking?

Sharda Yadav [*] ***and Sanjaya KC***

Central Clinical Laboratory, College of Medical Sciences, Bharatpur, Nepal

Email: shardaneps@gmail.com

Abstract

Clinical chemistry is emerging area in the field of clinical medicine which deals with the estimation of different analytes from body fluids. Different drugs interfere with the estimation of these analyte. The interference can be either physiological or analytical. Out of many analytes the most commonly estimated analyte are glucose, urea, creatinine, sodium and potassium. Small changes in these analytes also might give misleading information to the clinician. Though the clinicians will be aware of the major side effects of the drug, minor physiological effect might be overlooked also the analytical procedure and the effect of drug in different analytes. Hence, it is necessary for laboratory to inform clinicians regarding the possible effects of drugs on analytes.

Keyword: *Drug interference, clinical chemistry, physiological interference, analytical interference*

Introduction

Clinical chemistry is the branch in clinical medicine dealing with body fluids. The basic principle depends on the fact that a disease causes changes in biochemistry of the body. It may cause either increase in concentration, or decrease in concentration of certain biochemical parameters or even may cause a different substance to appear. Hence, clinical biochemistry deals with the changes in the composition of blood and other body fluids which are associated with the diagnosis of disease or monitoring the therapy.

Biochemical tests play an important part in clinical medicine for diagnosis of disease or to monitor therapy. So, it become challenging for a chemistry lab to provide accurate and reliable results. Many factors affect the accuracy of results in a clinical chemistry laboratory. Diurnal variation, circadian variation, seasonal variation, hydration state, eating habits and use of concurrent drugs affect the accuracy of test results. Drugs are one of the major interfering substances in biochemical tests.

Drugs interferes biochemical tests either

1. Physiologically (*In vivo* effects) and/or
2. Analytically (*in vitro effects*)

The In vivo effects are due to the intended (therapeutic) effects or side effects. The In vitro effects are caused due to

1. Alterations of chemical reactions (enhancement or inhibition)
2. Cause of turbidity in the reaction system
3. Interference with enzyme reactions
4. Cross-reaction with antibodies

[*] ***Corresponding author***

Almost all the biochemical tests face the interference. Our experience in a tertiary care centre at Central Nepal shows that Random Blood Glucose, Urea, Creatinine and Electrolytes are routinely ordered by the physicians at every visit of the patient at the casualty department. At the referral centre, much effort is given to diagnose iatrogenic diseases and these biochemical parameters play a crucial role. There are evidences that the drug interference in the laboratory causes misinterpretations. With the advancement of analytical techniques more precise results are obtained in the clinical laboratory. But, physicians are generally uncertain how to interpret the small changes. Physicians are generally aware of the major effects of drugs administered, but may be unaware of the side effects or other biological effects. Only few are likely to know about the analytical techniques and the possibility of the administered drug effecting the concentration of the analyte.

To facilitate the physicians in the interpretation of the possible interference it is necessary to enlist the interferences of the drugs in specific tests.

S.N.	Drug	Effect	Mode of Interference	Abnormality Reported
Drug effecting Glucose				
1	Ascorbic acid	Decrease	Analytical	At concentration above 150 mg/l it lowers glucose concentration measured by GOD method
2	Cefuroxime	Decrease	Analytical	False negative test may be observed when ferric cyanide methods are used to measure glucose
3	Metronidazole	Decrease	Analytical	With hexokinase reaction involving enzymatic coupling with oxidation-reduction of NAD. Interference may occur due to the similar absorbance peaks of NAD and metronidazole (322 nm) at PH 7.
4	Ciprofloxacin	Decrease	Physiological	Concurrent administration of ciprofloxacin with glyburide has on rare occasions been associated with severe hypoglycemia.
5	Propranol	Decreases	Physiological	Has slightly effect like that of prolong insulin. Rare cases due to inhibition of glycogenolysis in nondiabetics.
6	Ramipril	Decrease	Physiological	Slight but significant reduction from mean baseline of conc. of 8.5 mmol/L to 8.0 mmol/L in 21 hypertensive patients with noninsulin dependent diabetes mellitus treated with 5 mg/day for 12 weeks. Incidence of 1.6%

				observed in French pharmacovigilance database
7	Sildenafil	Decrease	Physiological	Hypoglycemia reaction observed in some patients when administered with sildenafil.
8	Furosemide	Increase	Physiological	Hyperglycemia and alterations in glucose tolerance may occur with treatment. Diabetogenic like action of drug affects glucose tolerance tests.
Drug effecting Urea				
1	Atenolol	Increase	Physiological	Increase in urea levels (mean baseline 9.0 ± 3.0 mmol/l to 10.5 ± 4.4 mmol/l) have been seen in hypertensive patients with proteinuria
2	Enalapril	Increase	Physiological	Increase noted (8.2 ± 3.1 mmol/l to 11.4 ± 3.4 mmol/l) in hypertensive patients with proteinuria
3	Albendazole	Increase	Physiological	Acute renal failure observed in patients receiving albendazole leading to elevated urea
4	Methotrexate	Increase	Physiological	May cause severe nephropathy, azotemia.
5	Prednisone	Decrease	Physiological	Cases have been reported with low urea concentration following Prednisolone administration.
6	Streptomycin	Decrease	Analytical	It inhibits Berthelot * reaction.
7	Chloramphenicol	Decrease	Analytical	It inhibits Berthelot* reaction.
8	Guanethidine	Increase	Analytical	It has chemical similarity to urea.
Drug effecting Creatinine				
1	Cefixime	Serum Increase	Analytical	It shows up to 20% increases in Creatinine with Jaffe's method[#]
2	ACE inhibitors	Serum Increase	Physiological	Serum Creatinine was increased (120 ± 39 μmol/L) in patients using ACE inihibitors compared to controls (103 ± 25 μmol/L)

3.	Albendazole	Serum Increase	Physiological	Acute renal failure observed in patients
4.	Barbiturates	Serum Increase	Physiological	Shock and renal failure in intoxication
5.	Methyldopa	Urine Increase	Analytical	Acts as reducing agent with alkaline picrate[#]
6.	Nitrofurans	Urine Increase	Analytical	Reacts with reagents in Jaffe's method[#]
7.	Corticosteroids	Urine Increase	Physiological	Associated with negative nitrogen balance
8.	Nandrolone	Urine Increase	Physiological	Increase in Creatinine concentration due to increase in muscle mass
9.	Prednisone	Serum Increase	Physiological	Significant decrease (from 717± 103µmol/l to 262 ± 31 µmol/l) has been noted in patients with HIV associated nephropathy
Drug effecting Sodium				
1	Lactulose	Increase	Physiological	Hypernatremia has been reported infrequently during lactulose treatment of the portal-systemic encephalopathy. Due to its osmotic cathartic effects, the drug may cause fecal water loss in excess of sodium resulting in contraction of ECF volume and hypernatremia. Reducing dose to produce not more than 2 to 3 soft stools dialy in order toavoid severe water loss is suggested.
2	Lithium	Increase	Physiological	Diabetes Insipidus like syndrome with lithium had been reported after 2 weeks of therapy and is usually reversible on discontinuation of the drug. While affected, however, many patients are unresponsive to exogenous Antidiuretic hormone.
3	Demeclocycline	Increase	Physiological	Demeclocycline can also cause Diabetes Insipidus and has been used in the management of patients with the Syndrome of Inappropriate Antidiuretic

				Hormone (SIADH).
4	Phenytoin	Increase	Physiological	Phenytoin inhibits ADH secretion at the level of the central nervous system and is known to cause hypernatremia.
5	Amiloride	Decrease	Physiological	Amiloride combined with hydrochlorothiazide has been implicated. Amiloride may be the offending agent because patients have tolerated hydrochlorothiazide with a potassium supplement.
6	Captopril	Decrease	Physiological	In 5 men with CHF, serum sodium fell by 7 mmol/L on the 3rd to 4th days.
7	Diclofenac	Decrease	Physiological	It enhances the actions of ADH due to prostaglandin inhibition. Water intoxication and hyponatremia only occur with NSAIDs in clinical practice in patients in a state of endogenous or exogenous active antidiuretic hormone secretion, such as in elderly or neonatal patients, chronic renal failure, low salt diet, excessive oral water intake or heart failure, or concurrent analgesic use.
8	Glimeperide	Decrease	Physiological	Although specific cases are lacking, the drug is capable of inducing SIADH, similar to other sulfonylureas.
9	Oxytocin	Decrease	Physiological	Continuous intravenous infusion of oxytocin in electrolyte-free solutions has resulted in water intoxication. This usually occurs when administration rate for oxytocin is greater than 45 milliunits/minute.
Drug effecting Potassium				
1	Amphotericin B	Decrease	Physiological	In clinical trials, of the 556 patients treated with Amphotericin B, 5% had hypokalemia. This is potentially caused by the concurrent administration of

				corticosteroids and corticotrophin.
2	Glucose	Decrease	Physiological	Insulin, together with glucose to prevent hypoglycemia is given to stimulate cellular uptake of potassium in emergency treatment of moderate to severe hyperkalemia.
3	Enalapril	Increase	Physiological	May cause hyperkalemia in approximately 1% patients treated with Enalapril. In 427 patients with essential hypertension, treatment for 6 months caused significant increase in plasma potassium from a baseline of 4.2 ± 0.4 mmol/L to 4.3 mmol/L.
4	Cyclosporin	Increase	Physiological	Significant hyperkalemia sometimes associated with hyperchloremic metabolic acidosis and hyperurecemia has been seen in individual patients receiving cyclosporine. Of 266 treated patients, hyperkalemia was observed in 26 (10%) one year after liver transplant with cyclosporin used as immunosuppressant.
5	Amiloride	Increase	Physiological	It can cause hyperkalemia, particularly in elderly patients, and in patients with impaired renal function.
6	Digoxin	Increase	Physiological	In 10 healthy individuals who had received digoxin for 10 days, serum potassium concentration increases from mean baseline of 4.2 ± 0.3 mmol/L to 4.4 ± 0.3 mmol/L after 2 hour supine rest.
7	Succinylcholine	Increase	Physiological	Increased chemosensitivity of muscle membrane and development of receptor site in extrajunctional areas causes transient hyperkalemia in patients undergoing general anesthesia.

* Berthelot reaction is one of the common methods of urea estimation
# Jaffe's method is one of the common methods of Creatinine estimation in clinical chemistry laboratory using alkaline picrate as one of the reagents

Conclusion

Different drugs at different doses interfere with the estimation of different analytes in clinical laboratory. Sometimes the interference is physiological or sometime merely analytical. Most of the times this factor is overlooked but this might be an important factor for deviated laboratory values. In a situation, where a small change of the value in the analytes changes the diagnosis and overall treatment process it is necessary for not only the laboratory but also for the treating clinician.

Acknowledgements

The authors acknowledge Dr. P Subish and Dr. Kadir Alam for permission to use the facilities at the Drug Information Centre at, Manipal Teaching Hospital.

References

1. Young DS, *Effect of drugs in clinical laboratory tests*, Advancing clinical laboratory science. Vol I Worldwide Publishing Company, Washington DC, 1999.
2. Young DS, *Effect of drugs in clinical laboratory tests*, Advancing clinical laboratory science. Vol II Worldwide Publishing Company, Washington DC, 1999.
3. *Indian Drug Review.* Nov-Dec 2003, **IX.**
4. Satoskar RS, *Pharmacology and Pharmacotherapeutics*, Popular Prakashan, Mumbai. Revised Sixteenth Edition, 1999.
5. Wynne HA, Edwards C, Laboratory Data in Walker R, Edwards C, *In Clinical Pharmacy and therapeutics*, Churchill Livingstone edited by: Walker R & Edwards C, 3rd edition, 2003, 51-53.
6. Beers MH and Berkow R, *The Merck Manual*, Merck Research Laboratories, The Merck Manual, 17th Edition 1999; 134-41.
7. Kazmierczak SC, Catrou PG, *Am. J. Clin Pathol* 2000, **113**, 9.
8. Kailajarvi M, Takala T, Gronroos P, Tryding N, Viikari J, Irjala K, *Clin Chem, 2000*, **46(9)**, 1395.
9. Saibaba KSS, Bhaskar MV, Srinivasa Rao PVLN, Ramana GV, Dakshinamurty KV, *Ind. J. of Clin. Biochem.*, 1998, **13(2)**, 55.
10. Young DS, Thomas DW, Friedman RB, *J. Clin. Path*., 1972, **25**, 984.