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Rhabdomyolysis requiring emergency dialysis as a consequence of simultaneous administration of simvastatin and clarithromycin

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ABSTRACT

Iatrogenic complications from polypharmacy have significantly increased over the past decade and clinicians and pharmacists must remain aware of potentially dangerous drug interactions [1–3]. Our case is a reminder of the potential for significant patient harm from drug interactions when additional medication that is seemingly innocuous is prescribed in addition to a patient's regular long-term medications. Our case also highlights the diagnosis and management of rhabdomyolysis and acute kidney injury.

A 75-year-old Caucasian male presented to the emergency department with nausea, bilateral calf tenderness and a reduced urine output. Creatinine Kinase (CK) levels demonstrated severe rhabdomyolysis and the patient's creatinine was significantly elevated with a concurrent metabolic acidosis requiring urgent renal replacement therapy in the intensive care unit (ICU). He was recently prescribed clarithromycin 500mg twice daily as part of Helicobacter pylori eradication therapy in addition to his regular combination therapy of simvastatin 80mg and ezetimibe 10mg daily dose.

Statins may cause dose dependent Statin Associated Myopathies (SAMs) such as myositis and rhabdomyolysis and are metabolised by the hepatic cytochrome P450 (CYP450) 3A4 enzyme[4,5]. Clarithromycin is a potent CYP450 3A4 hepatic enzyme inhibitor that leads to significantly elevated plasma levels of statin medications, increasing the risk of SAMs[4,6–8]. Our patient responded to the cessation of the offending medications and initiation of continuous renal replacement therapy. This case demonstrates the dangerous side effects and interactions of commonly prescribed medications.

Keywords: Drug interaction, statins, macrolides, clarithromycin, simvastatin, rhabdomyolysis, acute kidney injury, dialysis

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Case Presentation

A 75-year-old Caucasian male presented to the emergency department with a four-week history of worsening nausea, lower limb weakness and bilateral calf pain. He also described a significantly reduced urine output and reduced oral intake. This occurred one week after completion of Helicobacter pylori eradication therapy that included clarithromycin 500mg twice daily, amoxicillin 1g twice daily and omeprazole 20mg twice daily. Prior to presentation, he was reviewed by his general practitioner who requested an abdominal and pelvic computed-tomography scan with intravenous contrast and this revealed no cause for his symptoms.

The patient's past medical history included ischemic heart disease managed with five coronary stents, hypertension, hypercholesterolaemia and Type II diabetes mellitus. His regular medications were aspirin 100mg daily, clopidogrel 75mg daily, combination of simvastatin 80mg and ezetimibe 10mg daily, perindopril 5mg daily and metformin 2g daily. Prior to admission he lived independently in a retirement village, was an ex-smoker, consumed alcohol occasionally and had a modest exercise regime. He denied any recent strenuous physical exertion, trauma or additional symptoms. He had no significant family medical history.

Examination revealed normal vital signs and a relatively comfortable patient. Jugular venous pressure was normal and he was euvolaemic. Examination of the chest and abdominal examination was normal and no jaundice or pallor was present. There were no rashes, lymphadenopathy or evidence of arthritis. He was able to stand but described feeling weak in his lower limbs. Reflexes were normal in all limbs with no evidence of upper or lower motor neuron pathology.

Investigations

Initial and subsequent investigations are presented in Table 1. The serum creatinine was 343micromol/L (normal range: 60-110micromol/L), Urea 5.9mmol/L (normal range: 3-10mmol/L) and CK 52646 units/L (normal range: 0-240units/L) on presentation with a baseline creatinine of 84micromol/L and Urea of 5.9mmol/L six weeks prior to hospital presentation. Initial arterial blood gas on room air demonstrated a significant metabolic acidosis (pH 7.28 [normal range: 7.35-7.45], PaO2 101mmHg [normal range: 83-108mmHg], PaCO2 24mmHg [normal range: 35-45mmHg], HCO3- 11mmol/L [normal range: 22-28mmol/L], Base Excess -13.9 mmol/L [normal range: -3.0 - 3.0mmol/L]) with incomplete respiratory compensation. A transaminitis was detected. Renal ultrasound and additional abdominal computed-tomography imaging without contrast was unable to identify the cause of the patient's symptoms and biochemical abnormalities. Chest x-ray was normal and electrocardiogram revealed sinus rhythm with no significant abnormalities. Autoimmune screening was within normal limits.

Differential Diagnosis

The temporal association with the patient's symptoms, after commencement of therapy for Helicobacter pylori that included Clarithromycin 500mg twice daily in addition to his regular simvastatin 80mg daily lead to a diagnosis of statin induced rhabdomyolysis. It was considered likely to have been precipitated by inhibition of the CYP450 3A4 enzyme by clarithromycin[8]. His acute kidney injury was thought to be a consequence of his rhabdomyolysis and recent exposure to intravenous contrast on the background of his pre-existing nephrotoxic medications that included metformin and perindopril. The absence of any evidence of significant recent physical exertion, seizures, fevers, malignant processes and screening for autoimmune diseases made an alternative diagnosis unlikely. Moreover, ultrasound and computed-tomography imaging did not reveal any significant findings. A muscle biopsy and electromyogram were not considered necessary for diagnosis confirmation. Another potential contributing factor for the rhabdomyolysis presentation was the use of ezetimibe by the patient. However, previous

clinical trials of ezetimibe with statin therapy have not identified additional increased risk of myopathy or rhabdomyolysis [9,10]. The differential diagnosis for rhabdomyolysis with acute kidney injury is summarized in Table 2 [11].

Treatment

Initial treatment in the emergency department included the administration of intravenous normal saline and insertion of an indwelling urinary catheter. He remained oliguric, producing only 200mls of urine in the first 24 hours of his admission. Regular medications were reviewed and his simvastatin, ezetimibe, metformin and perindopril were withheld. After noting a significant metabolic acidosis on arterial blood gas analysis in the setting of oliguria, he was transferred to the ICU for placement of a radial artery catheter and insertion of a femoral vein dialysis catheter. Continuous- Veno- Venous- Haemodiafiltration was instituted for four days until renal recovery. Prednisolone 50mg daily was empirically prescribed for three days as therapy for an autoimmune myopathy and was ceased after further consultation deemed this unlikely. He was managed in the ICU for seven days and spent a total of ten days in hospital prior to discharge. He required a mobility aid and ongoing physiotherapy upon discharge, but had made a full recovery two weeks after discharge to home.

Discussion

Clinicians and pharmacists must remain aware of potentially dangerous drug interactions in an era of increased medication prescribing [1–3]. Our case is a reminder of the potential for significant patient harm from drug side effects and interactions when prescribing a short course of a seemingly innocuous medication in addition to a patient's regular long-term medications.

HMG-Co-Reductase inhibitors, also known as statins, are commonly used for the primary and secondary prevention of ischaemic heart disease, cerebrovascular disease, peripheral vascular disease and hypercholesterolemia [12–15]. Despite widespread use, they may occasionally cause SAMs, which can manifest as self-limiting elevations in CK, symptomatic myositis and in rare cases, rhabdomyolysis [4,5]. The risk of statin induced myositis and rhabdomyolysis appears greatest with simvastatin and is dose-dependent [8,16]. The mechanism of statin Induced rhabdomyolysis has not been fully elucidated with various mechanisms postulated. These include reduced sarcolemmal cholesterol leading to reduced calcium release during muscle contractions, increased myocyte concentrations of campesterol causing myopathy, disruption of mitochondrial function, activating the phosphoinositide 3-kinase (PI3K)/Akt pathway leading to muscle atrophy and disruption of carbohydrate utilisation within myocytes [4,5].

Statin induced rhabdomyolysis occurred in our case due to potent CYPP450 3A4 enzyme inhibition caused by clarithromycin [2,6]. Clarithromycin is a macrolide antibiotic and was used as part of the standard first line eradication therapy for Helicobacter pylori [17,18]. Macrolides as a class, and clarithromycin in particular, are well known CYPP450 3A4 enzyme inhibitors [6,8]. Prior case reports involving the combination of clarithromycin and simvastatin for various indications including sinusitis and pneumonia have also demonstrated severe rhabdomyolysis [19–22]. Knowledge of the role of hepatic enzyme inhibitors and inducers is essential for clinicians and pharmacists and a table of commonly prescribed hepatic enzyme inhibitors and inducers is provided in Table 3. For patient's requiring Helicobacter pylori eradication who also require a statin, clinicians and pharmacists should consider an alternative regime with metronidazole or levofloxacin, discontinuing the statin medication or changing to a non-statin medication to manage hypercholesterolaemia [17,18,23].

Although our patient made a complete recovery following the cessation of the offending medications and initiation of supportive renal replacement therapy, this case provides an important reminder about the potentially dangerous drug interactions of commonly prescribed medications.

Table 1. Pathology Results

	On Admission	On commencement of Dialysis	On discharge	Normal Ranges
Hb	128	110	92	130 - 180 g/L
WCC	9.4	9.3	7.9	4 - 11 X 10^9 /L
Platelets	270	233	272	150 - 400 X 10^9 /L
INR	1.1		1	1.0
APTT	30		26	25 – 35 seconds
Na+	134	131	143	135 – 145mmol/L
K+	5.3	5.8	3.6	3.5 – 5.2 mmol/L
Cl-	98	103	108	95 – 110 mmol/L
HCO3-	23	12	26	22 – 32 mmol/L
Urea	19.7	23.4	16.3	3.0 – 8.0 mmol/L
Creatinine	343	499	236	110 µmol/L
eGFR	14	9	22	>90 mL/min/1.73m^2
Creatinine Kinase	52646	31855	818	Male (> 60 years) 40 – 200 U/L
Bilirubin	14	9	8	1 – 20 µmol/L
AST	688	510	375	Male 5 – 35 U/L
ALT	855	646	75	Male 5 – 40 U/L
ALP				30 – 110 U/L
Gamma-GGT				Male 5 – 50 U/L
Lipase	154			10 – 60 U/L
pH		7.28		7.35 – 7.45
PaO2		101		80 – 100 mmHg
PaCO2		24		35 – 45 mmHg
HCO3-		12		22 – 32 mmol/L
Base Excess		-13.9		-2 - +2 mmol/L
Glucose		4.4		4 – 7.8 mmol/L
Lactate		0.9		< 2.0 mmol/L
ANA			Normal	
ENA			Normal	
ANCA			Normal	
Rheumatoid Factor			Normal	
Myositis Abs			Normal	

Table 2. Differential Diagnosis (11)

Statin Induced Rhabdomyolysis
Other drug induced myositis (Eg Sympathomimetics, Neuroleptic Malignant Syndrome, Malignant Hyperthermia)
Seizures
Polymyositis
Autoimmune Myositis
Severe hypokalaemia
Severe hypophosphataemia
Hyperthermia
Significant exertion
Trauma
Ischaemia
Envenomation
Metabolic disorders

Table 3. Common CYP3A4 enzyme inhibitors and inducers (6)

CYP450 Enzyme Inhibitors	CYP450 Enzyme Inducers
Macrolides	Phenytoin
Amiodarone	Carbamazipine
Allopurinol	Barbituates
Azole-antifungals	Rifampicin
H2- Receptor Antagonists	St John's Wart
Protease inhibitors	
Grapefruit juice	
Non-dihydropiridine Calcium Channel Blockers	

Abbreviations

Creatinine Kinase (CK)

Intensive Care Unit (ICU)

Cytochrome P450 (CYP450)

Statin Associated Myopathies (SAM)

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