

Rhabdomyolysis due to Lamivudine administration in acute viral hepatitis B infection: a case report from Malaysia

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Abstract:

Rhabdomyolysis is a serious but rare side effect of Lamivudine treatment. Therefore, appropriate biochemical monitoring should be undertaken when it is used in the treatment of hepatitis B. This paper presents a case of Lamivudine-associated rhabdomyolysis in a 31-year-old man with congenital heart disease and hepatitis B. Three days after starting Lamivudine, the patient developed myalgia. Significant muscle tenderness and swelling of the upper and lower limbs was discovered during a physical examination. Creatine kinase was markedly raised. Lamivudine-induced rhabdomyolysis was suspected and the drug was discontinued. Symptoms and creatine kinase activity improved within four days of Lamivudine cessation and hydration. Early identification of Lamivudine-induced rhabdomyolysis is key in preventing this potentially fatal drug reaction; withdrawal of Lamivudine may contribute to complete remission of rhabdomyolysis.

Keywords: hepatitis B, Lamivudine, adverse effect, rhabdomyolysis

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1. Introduction

Rhabdomyolysis is a syndrome caused by the rapid breakdown of damaged skeletal muscle, which causes the release of potentially toxic intracellular content into plasma. It is characterized by a triad of muscle weakness, myalgia, and abnormal blood tests in the context of other underlying problems. Most adult cases of rhabdomyolysis are due to abuse of illicit drugs or alcohol, muscular trauma, crush injuries, prolonged immobilization, excessive muscular activity, electrolyte abnormalities, and myotoxic effects of prescribed drugs such as statins and cocaine (1–3). Lamivudine-induced rhabdomyolysis is a rare adverse drug reaction and can be fatal if not recognized early. Various complications are associated with rhabdomyolysis, including hypovolaemia, compartment syndrome, arrhythmias and cardiac arrest, disseminated intravascular coagulation, hepatic dysfunction, acidosis, and myoglobinuric acute renal injury (2). Fatality, which has been reported at rates as high as 59%, and myoglobinuric acute renal injury can be prevented by early fluid resuscitation (3, 4). Therefore, early identification of this syndrome is important. However, treatment may be complicated by the patient's underlying co-morbidities, such as

congestive cardiac failure or chronic kidney disease. Lamivudine-induced rhabdomyolysis has been reported previously in other literature, but it has not, to the best of our knowledge, been reported in Malaysia before (5, 6).

2. Case presentation

2.1. Clinical presentation

A 31-year-old Malay man, admitted to the cardiothoracic ward for an elective Bentall procedure, was referred to the medical team at day 4 of admission for worsening renal and hepatic profiles. Upon admission to the cardiothoracic ward, he appeared to be well within class II of the New York Heart Association (NYHA) Functional Classification. His vital signs were stable. Physical examination revealed a moderate pansystolic murmur and a palpable liver edge about 3 cm below the right costal margin. Other system examinations were unremarkable. Upon consultation with the hepatobiliary team, a provisional diagnosis of acute liver failure secondary to acute flare of hepatitis B infection was made and empirical antiviral treatment with 100 mg of oral Lamivudine daily was initiated. Three days after the initiation of Lamivudine, the patient developed myalgia. There was significant muscle tenderness and swelling of the upper and lower limbs, but he did not have tea-coloured urine or gross haematuria.

2.2. History

The patient had a history of congenital valvular heart disease, dissecting thoracic aortic aneurysm, and recently diagnosed hepatitis B viral infection. An echocardiogram showed a congenital bicuspid aortic valve with severe aortic regurgitation, complicated by dilated cardiomyopathy.

2.3. Laboratory and imaging findings

Baseline blood investigations conducted upon admission showed mild hepatic and renal impairments with alanine transaminase (ALT), aspartate transaminase (AST), total serum bilirubin, urea, and creatinine levels of 361 U/L, 181 U/L, 53 $\mu\text{mol/L}$, 8.9 mmol/L and 127 $\mu\text{mol/L}$, respectively (Table 1). On subsequent days of admission, his hepatic and renal function worsened, with ALT elevated tenfold from the baseline value, urea of 28 mmol/L, and creatinine of 152 $\mu\text{mol/L}$. A full blood count revealed thrombocytopenia with a platelet count of $71 \times 10^9/\text{L}$; also, the coagulation profile was deranged. Screenings for other common infectious diseases were negative, pending hepatitis B e-antigen and viral load. An ultrasound of the patient's hepatobiliary system revealed normal findings with no focal attributes. Worsening liver function tests led to a provisional diagnosis of acute liver failure secondary to acute flare up of hepatitis B viral infection.

Three days after the initiation of Lamivudine, creatine kinase increased from a baseline value of 353 U/L to 2249 U/L. An electrocardiogram showed T-wave inversion in leads II and III and aVF. Troponin T was within the normal range. Microscopic urine examination showed the presence of blood (3+), while urine myoglobin was not detected. Although the patient's liver function improved, his renal function showed continuous deterioration with persistent hyperkalaemia. This derangement in his biochemistry profile, coupled with myalgia and muscle tenderness, led to the suspicion of Lamivudine-induced rhabdomyolysis.

Table 1. Patient's biochemistry trend in relation to initiation and cessation of lamivudine

Blood test	Admission Day	4 th Day (Lamivudine started)	7 th Day (Lamivudine stopped)	14 th Day	24 th Day
Hb	16.9	14.7	14.8	12.8	11.8
Platelets ($\times 10^9/\text{L}$)	147	71	102	223	168
TWC ($\times 10^9/\text{L}$)	9.7	9.0	12.7	12.2	7.6
ALT (U/L)	361	2906	635	142	48
AST (U/L)	181	1818	161	72	-
ALP (U/L)	86	80	72	62	62
Albumin (g/L)	38	32	32	20	23
T. Bilirubin ($\mu\text{mol/L}$)	53.7	41.2	51.6	31.2	14.7
Urea (mmol/L)	8.9	27.7	28.2	14.5	4.8
Creatinine ($\mu\text{mol/L}$)	127	152	188	72	61
PT (secs)	19.8	23.2	17.4	17.1	-
Creatinine Kinase (U/L)	-	353	2249	140	45

2.4. Treatment and follow-up

In view of possible Lamivudine-induced rhabdomyolysis, the drug was stopped and the patient was managed supportively with adequate and (due to his underlying cardiomyopathy) cautious intravenous hydration. Strict input/output charting was done, along with daily electrolytes, renal profile, and creatine kinase monitoring. Equal fluid balance was allowed. Any electrolyte abnormality was treated accordingly. Following the cessation of Lamivudine, the patient's symptoms improved slowly and his serum creatine kinase declined drastically to 645 U/L. Within four days, his creatine kinase reduced to within normal range. His renal, hepatic, and coagulation profiles returned to the normal range after two weeks off Lamivudine and subsequent supportive management with cautious intravenous fluid hydration.

2.5. Ethics of case report

Informed consent was obtained directly and in writing from the patient for publication of this manuscript. The Faculty of Medicine and Health Sciences (Universiti Putra Malaysia) approved this case report research.

3. Discussion

3.1. Clinical presentation

This case illustrates rhabdomyolysis as a rare adverse reaction of Lamivudine. In this case report, we can observe that rhabdomyolysis developed quite rapidly (within a few days after the initiation of Lamivudine). A few medical articles documenting occurrences of the same event in Lamivudine-treated patients have reported that the development of rhabdomyolysis can take place as early as a few hours and as late as up to six weeks after the initiation of treatment (5, 6).

3.2. History

The patient had been recently diagnosed with hepatitis B infection prior to admission to the cardiothoracic ward for an elective procedure and developed a worsening liver profile whilst in the ward. As other infective screening was negative, an acute flare of his hepatitis B viral infection was suspected and he was empirically started on oral Lamivudine. At that point in time, his hepatitis B e-antigen and viral load were not available yet. The underlying comorbidity that affected the management of this patient was his congenital valvular heart disease with cardiomyopathy, which made fluid management tricky. Therefore, it was essential to carefully monitor the urine output since a fluid infusion can lead to congestive heart failure and pulmonary oedema (7).

3.3. Laboratory findings

This adverse reaction is often characterized by a marked elevation of creatine kinase, urine myoglobin, and acute kidney injury. It is interesting to note that, despite an abrupt increase in creatinine kinase, the classical concurrent rise in urine myoglobin level was not observed in this patient. Although it is a common observation that myoglobinuria tends to occur following rhabdomyolysis, it does not necessarily mean that rhabdomyolysis will lead to detectable myoglobin in the urine. This is because myoglobin elimination by hepatic metabolism is often rapid and unpredictable, which makes it a non-sensitive diagnostic parameter (8). Myoglobinuria can be inferred if urinary dipstick testing shows a false positive result for blood and is unable to distinguish between myoglobin and hemoglobin. The test has a sensitivity of 80% for the detection of rhabdomyolysis (1).

Acute kidney injury is widely reported as one of the grave complications of rhabdomyolysis and is associated with high morbidity and mortality. It has been reported to occur in up to 17% of patients with rhabdomyolysis (9). In our patient, his pre-existing kidney impairment showed further deterioration, with greatest insult documented on the third day of treatment with Lamivudine, as shown in the table 1. The main pathophysiologic mechanisms are renal vasoconstriction, intraluminal cast formation, and direct heme protein-induced cytotoxicity (8, 10). Other serious complications that may arise from rhabdomyolysis include acute hepatic impairment and coagulopathy. Hepatic involvement was reported to occur in 25% of patients, through proteases released from injured muscle (11). In this case scenario, both liver impairment and coagulopathy were observed. However, it is difficult to relate it to rhabdomyolysis as the co-existence of hepatitis B viral infection confounded the end point complications.

3.4. Treatment and follow-up

In rhabdomyolysis, there is sequestration of water in injured muscles, leading to volume depletion. Therefore, the key in managing the condition is early, aggressive repletion of fluids. Patients often require about 10 liters of fluid per day, with the amount administered depending on the severity of the rhabdomyolysis (3, 4). However, administration of large volumes of intravenous fluid was not possible in view of his underlying cardiomyopathy. His

fluid balance was monitored closely by the nursing staff in our cardiovascular intensive care unit and he was allowed to have equal fluid balance. Electrolytes and renal profile were monitored daily and any abnormalities were treated accordingly. Complete remission of rhabdomyolysis, measured by normalized renal, hepatic, and coagulation parameters, was seen within two weeks of Lamivudine cessation. The recovery period for organ impairment in this patient is consistent with other similar Lamivudine-induced rhabdomyolysis cases reported in other literature (5).

4. Conclusion

This paper reported a rare adverse reaction to Lamivudine, in which management of the condition was complicated by the patient's underlying co-morbidities. This case report concludes that Lamivudine-induced rhabdomyolysis is a potential cause for serious metabolic derangement and multi-organ impairment. It is essential for clinicians to identify the condition early to institute appropriate fluid management and withdrawal of the causative agent.

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Conflict of Interest:

There is no conflict of interest to be declared.

Authors' contributions:

All of authors contributed to this project and article equally. All authors read and approved the final manuscript.

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