

CASE SERIES

Suspected cardiotoxicity of clarithromycin in critically ill patients

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ABSTRACT

Clarithromycin, a macrolide antibiotic is known to have an arrhythmogenic potential in the presence of comparable QT prolongation. Indeed, the extent of QT prolongation has been used as a surrogate marker for cardiotoxicity and sudden cardiac death. We report a case series of three adult patients who were transferred to our intensive care unit (ICU) at Peradeniya Teaching Hospital, Peradeniya (Sri Lanka), and needed inotropic support and mechanical ventilation. All the three of them were treated with a standard dose regimen of intravenous clarithromycin for suspected atypical pneumonia, after which they dramatically deteriorated and unexpectedly died within 72 hours. In the absence of other known precipitating factors, cardiotoxicity of clarithromycin was suspected as the main causative factor for these deaths.

Key words: Clarithromycin; cardiotoxicity; Naranjo Causality Scale

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INTRODUCTION:

QT interval prolongation is a risk factor in a number of cardiovascular as well as non-cardiovascular diseases (e.g. microbial infections). Among non-cardiovascular drugs that prolong repolarization, macrolide antibiotics are widely prescribed and have been incriminated in prolonging action potential of the heart apart from their antibiotic effects. Clarithromycin is a relatively new macrolide broad spectrum antibiotic. It binds to 50 S ribosomal subunit of the susceptible microorganisms resulting in inhibition of protein synthesis. It is rapidly absorbed, widely distributed and metabolized to 14-hydroxyclearithromycin, a metabolite with considerable pharmacological activity.¹⁻²

The macrolides have been associated with the prolongation of cardiac repolarization and blockage of the HERG channel dependent potassium in myocyte membranes resulting in prolongation of the QTc interval which may give rise to potentially life-threatening polymorphic ventricular tachycardia of the torsade de pointes type or ventricular fibrillation. Thus, clarithromycin, which has a potential to cause cardiac toxicity, is best avoided in critically ill patients especially receiving inotropic support. The aim of this case series is to highlight the possibly aggravated cardiotoxicity of clarithromycin in the critically ill patient and establish link through Naranjo Causality Scale.^{3,4}

We report three patients, who rapidly deteriorated clinically following the administration of

clarithromycin in the ICU on a standard dose regimen of clarithromycin 500mg IV bid for atypical pneumonia. The brand 'Klarid®' which contained clarithromycin lactobionate (50mg/ml), batch No. 220624XVO3 marketed by Messers Abbott Laboratories Ltd., Landhi, Karachi (Pakistan), with license No. 000001 and registration No. 018142 was used.

CASE REPORT 1

A 55 year old male patient was admitted to ICU of our hospital with suspected dengue shock syndrome. On admission his pulse rate was 110/min and blood pressure was maintained at 80/56 mmHg on dopamine 10µg/kg/min and dobutamine 10µg/kg/min support and central venous pressure 13 cmH₂O. 2D echo revealed an ejection fraction of 60% with mild left ventricular hypertrophy. He was mechanically ventilated with FiO₂ of 100%, maintaining a peripheral saturation (SpO₂) of 98-100%. Blood gas analysis revealed a pH of 7.29, PCO₂ of 30.7 mmHg and Po₂ of 95mmHg. On the second day of his admission to ICU, intravenous clarithromycin was prescribed for signs of atypical pneumonia in the chest X-ray.

The next day, hemodialysis had to be started utilizing continuous venovenous haemodiafiltration (CVVHDF) due to acute renal failure. His CVP was maintained at 13 cmH₂O and the SpO₂ was 95% with 100% inspired oxygen. Despite optimization of metabolic environment and fluid balance by CVVHDF, his blood pressure continued to deteriorate. The arterial blood gas analysis revealed a pH of 7.15, PCO₂ 31.3 mmHg and a PO₂ of 56.9 mmHg. He also developed a bleeding tendency and a low platelet count (33 x 10⁹ /mm³). His hemoglobin was 8.8g/dl. On 4th day in ICU his blood pressure remained persistently low (68/35, 76/41, 69/27mmHg) and CVP rose to 20mmHg. An ECG trace taken before 24 hours of his death demonstrated a QTc of 0.55 sec (normal upper limit: males 0.44sec, females 0.46sec).The acidosis

gradually worsened (pH: 7.06) despite sodium bicarbonate therapy, CVVHDF and hyperventilation. He developed severe bradycardia and ultimately irreversible asystole.

CASE REPORT 2

A 25 year old female university student was transferred to the ICU for mechanical ventilation following treatment for a febrile illness with features suggestive of myocarditis. Her platelet count was 91 x 10⁹ /mm³, whilst hemoglobin was 9.2g/dl. She had had a demand temporary pacemaker inserted as a prophylactic measure following an episode of severe bradycardia in the ward. On admission to ICU, she was in a state of shock with cold and clammy peripheries and a blood pressure of 60/40mmHg. She was maintaining a sinus rhythm of 80 to 110 beats/min. She was resuscitated with ionotropes, oxygen therapy and mechanical ventilation. Her cardiorespiratory parameters were then recorded as pulse rate 105/min, blood pressure 110/65mmHg with dopamine and dobutamine support at 10µg/kg/min each and SpO₂ at 99% with FiO₂ of 35%. Features of atypical pneumonia seen on her chest X-ray prompted the inclusion of intravenous clarithromycin in the management regimen. A single dose of clarithromycin was administered. Six hours later she developed a severe sinus tachycardia with pulse rates reaching 150/min to 190/min despite carotid sinus massaging, β-blockers, adequate sedation with morphine and hyperventilation. Her SpO₂ rapidly deteriorated and the FiO₂ had to be increased to 80% to maintain her SpO₂ above 95%. Her CVP was 17 cmH₂O. Later on, FiO₂ was raised to 100%, but the tachycardia continued. Her blood pressure progressively reduced. The next day she expired following a cardiac arrest.

CASE REPORT 3

A 44 year old female was transferred to the ICU due to falling blood pressure and a low SpO₂. She had a low platelet count (40x10⁹) and her hemoglobin was 10.9g/dl. On admission to ICU, she received the first

Table 1 : Naranjo Causality Scale and its application to the 3 cases

Drug reactions	Case 1	Case 2	Case 3
1. Are there previous conclusive reports on this reaction?	+1	+1	+1
2. Did the ADR appear after the suspected drug was given?	+2	+2	+2
3. Did the ADR improve when the drug was discontinued or a specific antagonist was given?	0	0	0
4. Did the ADR appear when drug was re-administered?	0	0	0
5. Are there alternative causes that could have caused the reaction?	0	0	0
6. Did the reaction appear when placebo was given?	0	0	0
7. Was the drug detected in any body fluid in toxic concentration?	0	0	0
8. Was reaction more severe when the dose was increased or less severe when the dose was decreased?	0	0	0
9. Did the patients have a similar drug in any previous exposure?	0	0	0
Total Score	+3	+3	+3

dose of clarithromycin intravenously for a chest infection, which was revealed by the chest radiograph. Before the commencement of clarithromycin, her blood pressure was 110/70mmHg, but had a tachycardia (120-150/min) and was breathing spontaneously. In the ICU, she went into respiratory failure, so was intubated and ventilated and a peripheral saturation of 92% was maintained with 80% oxygen. The arterial blood gas analysis revealed a pH: 7.24, PCO₂ 21.9 mmHg and PO₂ 75.1 mmHg. Her blood pressure fell to 95/65 mmHg and hence an infusion of dobutamine was started at 5µg/kg/min, increasing successively to 10.5µg/kg/min. Her tachycardia continued between 150-170/min and she expired following a cardiac arrest within 8 hours of admission to the ICU.

DISCUSSION

The ADR is considered severe (FDA definition) if the consequences resulted in (a) death (b) a life threatening situation (c) hospitalization (d) disability significant, persistent, or permanent change, impairment, damage or disruptions in the patient's body function/structure, physical activities or quality of life (e) congenital anomaly or (f) required

intervention to prevent permanent impairment or damage. In our cases, all the three patients deteriorated rapidly and succumbed to the disease condition before any positive change could be noticed with withdrawal of the suspected drug.

Thus, it appears to be prudent that clarithromycin is best avoided in critically ill patients who have already compromised cardiac function with associated cardiac instability and receiving ionotropes.

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