Early View Article: Online published version of an accepted article before publication in the final form.

Journal Name: International Journal of Case Reports and Images (IJCRI)

Type of Article: Case Report

Title: Monotherapy with erythromycin results in severe rhabdomyolysis

Authors: Lukas Birkner, Dimitri Zolotov, Mario Iasevoli

doi: To be assigned

Early view version published: May 26, 2016

How to cite the article: Birkner L, Zolotov D, Iasevoli M. Monotherapy with erythromycin results in severe rhabdomyolysis. International Journal of Case Reports and Images (IJCRI). Forthcoming 2016.

Disclaimer: This manuscript has been accepted for publication. This is a pdf file of the Early View Article. The Early View Article is an online published version of an accepted article before publication in the final form. The proof of this manuscript will be sent to the authors for corrections after which this manuscript will undergo content check, copyediting/proofreading and content formatting to conform to journal's requirements. Please note that during the above publication processes errors in content or presentation may be discovered which will be rectified during manuscript processing. These errors may affect the contents of this manuscript and final published version of this manuscript may be extensively different in content and layout than this Early View Article.
TYPE OF ARTICLE: Case Report

TITLE: Monotherapy with erythromycin results in severe rhabdomyolysis

AUTHORS:
Lukas Birkner\textsuperscript{1}, Dimitri Zolotov\textsuperscript{1,2}, Mario Iasevoli\textsuperscript{1}

AFFILIATIONS:
\textsuperscript{1}MD, Department of Internal Medicine, Ev Krankenhaus Witten gGmbH, University of Witten/Herdecke, Pferdebachstr, 27, 58455 Witten, Germany
\textsuperscript{2}MD, Dialysis Practice of Internal and nephrology Medicine, Pferdebachstr. 11, 58455 Witten, Germany

CORRESPONDING AUTHOR DETAILS
Dr. Lukas Birkner,
Department of Internal Medicine, Ev Krankenhaus Witten gGmbH, University of Witten/Herdecke, Pferdebachstr 27, 58455 Witten, Germany
Phone number: +49-177-3392330,
Email: lukasbirkner@freenet.de

Short Running Title: Erythromycin-induced rhabdomyolysis

Guarantor of Submission: The corresponding author is the guarantor of submission.
TITLE: Monotherapy with Erythromycin Results in Severe Rhabdomyolysis

ABSTRACT
Rhabdomyolysis is a potentially life-threatening condition caused by muscle necrosis and extravasation of intracellular muscle contents into the blood circulation. An elevation in serum creatine kinease is most confirmatory laboratory test. Erythromycin is an inhibitor of the CYP3A4 enzyme system which is responsible for the metabolism of several drugs, particularly some statins. Although rhabdomyolysis associated with macrolid-statin interaction has been previously described, we report the first case of erythromycin-induced rhabdomyolysis. In our case a 38 year-old man admitted with pneumonia developed rhabdomyolysis associated with erythromycin administration. Clinicians need to be aware of the risks this potential adverse drug reaction poses.

Keywords: rhabdomyolysis, pneumonia, erythromycin, penicillin intolerance
INTRODUCTION

Rhabdomyolysis is a potentially life-threatening condition characterized by the leaking of creatine kinease and other intracellular proteins and electrolytes into the blood circulation [1]. The most common symptoms of rhabdomyolysis include muscle weakness, brown urine, electrolyte imbalances, acute renal failure and disseminated intravascular coagulation. An elevation in serum creatine kinase (CK) and myoglobin is the most confirmatory laboratory test for rhabdomyolysis since all cases are associated with it [2,3]. Although there are multiple physical and nonphysical causes of rhabdomyolysis the most common cause is medication [4]. Especially rhabdomyolysis related to macrolide-statin interaction, such as clarithromycin or ketoconazole interacting with simvastatin, has been previously described in the literature [5].

CASE REPORT

We report the case of a 38 year-old male patient presented with a clinical diagnosis of common acquired pneumonia. He was treated with Erythromycin (500 mg two times a day) for one and a half days due to a known penicillin intolerance. The patient subsequently developed joint and muscle pain after the first day of administration and an anuria with growing nausea after the second day without a documented source of infection. Consequently the patient was admitted to our inpatient hospital complaining of an anuria. An extremely elevated creatine kinase concentration of 40205 U/L (normal <200) was discovered after the first day of hospitalization and reached 228456 U/L the following day. The estimated glomerular filtration rate (GFR) was reduced to <10 ml/min (normal 120 ml/min per 1.73 m2). Other parameters indicating rhabdomyolysis were serum aspartate aminotransferase (AST) 5789 U/l (normal 5-34), serum alanine aminotransferase (ALT) 1093 U/l (normal < 55) and serum lactate dehydrogenase (LDH) increased to a maximum of 10100 U/l (normal 125-243). Rhabdomyolysis associated with acute renal failure and hepatopathy was diagnosed. Erythromycin was immediately stopped and the patient received dialysis treatment as required over the course of two and a half weeks. The
serum CK gradually decreased. Two weeks later creatine kinase returned to 2927 U/L. During the course of the dialysis treatment the micturition gradually increased and muscle pain subdued. No further laboratory tests were ordered. Because the patient was neither taking other medication nor had a conspicuous anamnesis or relevant pre-existing conditions, erythromycin was thought to be the precipitating factor for rhabdomyolysis. Additionally using the Naranjo adverse drug reactions probability scale a score of 6 was determined. Thus erythromycin can be considered a probable cause of rhabdomyolysis [6].

DISCUSSION
Rhabdomyolysis associated with macrolid-statins interaction has been previously described, however, rhabdomyolysis related to erythromycin has not been reported until now [7]. Erythromycin is an inhibitor of the CYP3A4 enzyme system, which is responsible for the metabolism of several drugs, particularly some statins as simvastatin or atorvastatin. Any documented cases of erythromycin induced rhabdomyolysis involved drug interactions with statins through inhibition of CYP3A4 enzyme system. It has a similar spectrum of activity as clarithromycin [8]. Of interest, clarithromycin induced rhabdomyolysis has been previously reported in a few cases. A 5-year-old Asian-American girl was admitted with 102°F fever and a 5-day history of productive cough. The patient was prescribed clarithromycin 125 mg twice a day. After five days a creatine kinase concentration of 949 U/L (normal <177) was discovered. Clarithromycin was immediately stopped and the child recovered [9,10]. Undoubtedly both cases show parallels, such as the elevation of serum CK associated with the respective drug and the course of recovery, although differences in the severity must be noted. In our case there was a definite connection between erythromycin exposure-withdrawal and the gradual recovery of the patient. Considering the sequence of events we ruled out infection as the possible cause of rhabdomyolysis. As a matter of fact the patients symptoms were inconspicuous, while serum CK drastically increased one day after the start of treatment with Erythromycin. Thus the chronological relationship between the appearance of myalgia and the start of
erythromycin suggest the conclusion that erythromycin is the responsible agent in our case.

**CONCLUSION**

We reported a probable case of erythromycin-induced rhabdomyolysis. The mechanism behind this adverse drug reaction is not understood, although there have been a few cases of rhabdomyolysis associated with macrolides. Clinicians need to be aware of the risks this potential adverse drug reaction poses, especially concerning patients at risk for rhabdomyolysis.

**CONFLICT OF INTEREST**

The authors declare no conflicts of interest in this work.

**AUTHOR’S CONTRIBUTIONS**

Lukas Birkner

Group1 - Conception and design, Acquisition of data, Analysis and interpretation of data
Group 2 - Drafting the article, Critical revision of the article
Group 3 - Final approval of the version to be published

Dimitri Zolotov

Group1 - Conception and design, Acquisition of data, Analysis and interpretation of data
Group 2 - Drafting the article, Critical revision of the article
Group 3 - Final approval of the version to be published

Mario Iasevoli

Group1 - Conception and design, Acquisition of data, Analysis and interpretation of data
Group 2 - Drafting the article, Critical revision of the article
Group 3 - Final approval of the version to be published
REFERENCES

1. Miller ML. Clinical manifestations and diagnosis of Rhabdomyolysis. In: UpToDate, Targoff IN, Shefner JM (Ed), UpToDate, Waltham, MA, 2012.


