

Daptomycin, elevated creatinine phosphokinase [CPK] and rhabdomyolysis – is there a co-relation?: Clinical experience from the UK EU-CORESM registry, 2006–2011 (RP1–4)

A. Guleri*¹, N. Waddington¹, R. Sharma¹, M. Purohit¹, V. Srivastava¹, A. Ibrahim¹, A. Jones²

*Presenting author 1. Blackpool Teaching Hospital, Whinney Heys Road, Blackpool.FY3 8NR 2. MSC Ltd, Brook Farm, Old Malton, YO17 7HD.

*Dr.Guleri@bflwh.nhs.uk Tel: +44 1253 300000

ABSTRACT (Amended)

BACKGROUND: Baseline and regular monitoring of creatine phosphokinase[CPK] is standard requirement during Daptomycin [DAP] therapy because early studies with DAP suggested an association with rhabdomyolysis. Literature suggests CPK elevation in patients may be related to several other causes including surgical procedures, diabetes mellitus, statin use, etc. We present a review of 5-year data on elevations in CPK levels during DAP use from the UK EU-CORESM database.

METHODS: Data were collected retrospectively from Jan 2006–Jun 2011. The analysis included patients treated with DAP with elevations in CPK recorded either at baseline or during DAP therapy.

RESULTS: 592 patients from 15 participating institutions in the UK are in the database.

Baseline CPK measurements were recorded for 193 patients (32.7%); of which 166 [86%] were <1xupper limit of normal (ULN); 15 [8%] >1 to 2xULN. 12 [6%] patients had CPK levels >2xULN prior to commencing DAP: 7 patients >2 to 5xULN; 2 patients >5 to 10xULN; 3 patients >10xULN.

During DAP therapy CPK measurements were recorded for 218 patients. CPK: <1xULN for 179 patients. >1 to 2xULN for 22. CPK >2 to 5xULN during therapy was reported for 5 patients, >5xULN, 12 (Table). Of the 17 patients with elevated CPK, 10 had levels in excess of >2xULN at the start of DAP therapy. Day of highest CPK ranged from 1 to 23 days. CPK elevations or high CPK levels were reported as an adverse event (AE) for 9 patients and asymptomatic CPK elevation for 1 patient. An AE of myalgia was reported in 1 patient where CPK was recorded as >10xULN at start of DAP therapy. Rhabdomyolysis was reported as an AE for 2 patients: CPK was not recorded for 1 and the other CPK was <1xULM during DAP therapy.

Conclusion: Of the patients reported with elevations in CPK in the registry, 10 had elevated CPK prior to DAP, suggesting that these elevations were related to other causes. BNF suggests discontinuing DAP only if both unexplained muscular symptoms and markedly elevated CPK co-occur.

INTRODUCTION

> The European Cubicin[®] Outcomes Registry and Experience (EU-CORESM) is a sister programme to the Cubicin[®] Outcomes Registry and Experience (CORE[®]), which has been conducted by Cubist Pharmaceuticals since 2004

> EU-CORESM is an ongoing, multicentre, retrospective, non-interventional registry that was designed to collect data on the characteristics (patient population, infections, pathogens and adverse events [AEs]) and clinical outcomes for patients receiving DAP

> Daptomycin (DAP), the first in class of cyclic lipopeptide antibiotics, was approved in Europe for the treatment of complicated skin and soft tissue infections (cSSTIs) in 2006, and for the treatment of right-sided infective endocarditis (RIE) due to *Staphylococcus aureus* and *S. aureus* bacteraemia when associated with RIE or with cSSTI in 2007¹

> EU-CORESM offers an insight into real life clinical experience with DAP in the treatment of Gram-positive infections

> Baseline and regular monitoring of creatine phosphokinase [CPK] is standard requirement during Daptomycin [DAP] therapy¹ because early studies with DAP suggested an association with rhabdomyolysis.

> Here we report the data on elevations in CPK from the first 5.5 years of the database

Acknowledgements

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References

1.Novartis Europharm Ltd. Cubicin[®] (daptomycin) Summary of Product Characteristics
2.Waddington et al. Poster 120. Federation of Infection Societies Meeting 2011

BACKGROUND

Rhabdomyolysis ranges from an asymptomatic illness with elevation in creatine kinase (CK) level to a life threatening condition (Figure 1). Clinically, CK is assayed in blood tests as a marker of myocardial infarction, rhabdomyolysis, muscular dystrophy, autoimmune myositides and acute renal failure.

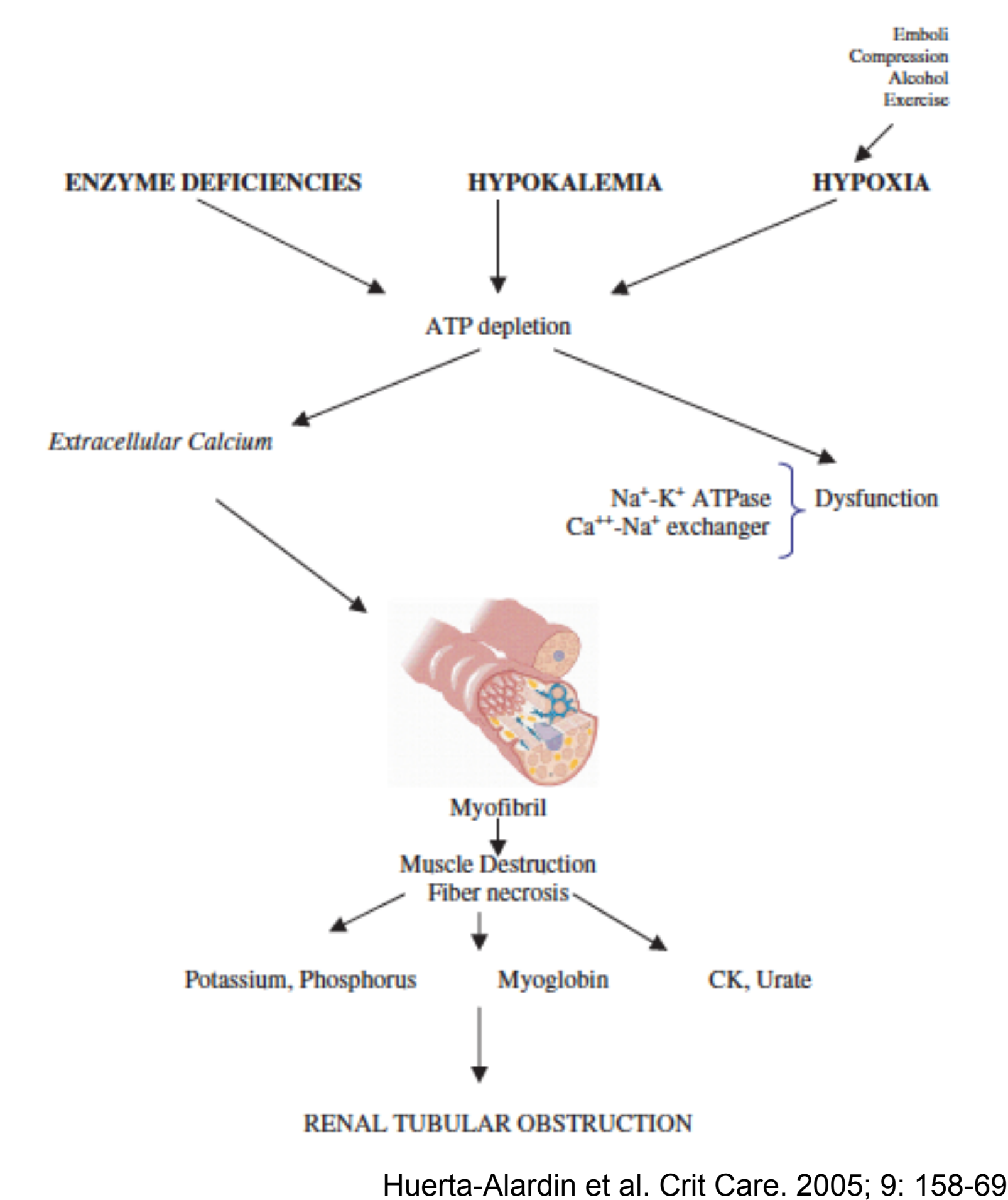
In the cells, the "cytosolic" CK enzymes consist of two subunits, which can be either *B* (brain type) or *M* (muscle type). Isoenzyme patterns differ in tissues. CK-BB is expressed in all tissues at low levels and has little clinical relevance. Skeletal muscle expresses CK-MM (98%) and low levels of CK-MB (1%). The myocardium (heart muscle), in contrast, expresses CK-MM at 70% and CK-MB at 25–30%.

Physical causes include: trauma and compression, vessel occlusion, shock status, vigorous muscle exercise/excessive muscle activity, tetanus, hyperthermia and sepsis.

Non-physiological causes include: metabolic syndromes, toxins, drugs, infections, electrolyte imbalances, endocrine disorders and autoimmune disease.

Following a case where a patient entered into the UK EU-CORESM database with CK levels of 19744 IU/L (>113 times ULN) at the start of therapy who clinically improved and whose CK levels declined to 1608 IU/L whilst on DAP therapy², the UK EU-CORESM (Jan 2006–June 2011) was reviewed for other reports of elevations in CK either at baseline or during DAP therapy.

Figure 1: The pathophysiology of rhabdomyolysis



RESULTS

> 592 pts from the 15 participating institutions in the UK were added to the EU-CORESM database between Jan 2006 and June 2011 (Table 1)

> The majority of pts (89%) had significant underlying disease (Table 1)

> 17% of pts were recorded as receiving statins

> Baseline CPK measurements were recorded for 193 pts (32.7%)

> Of which 166 [86%] were <1xupper limit of normal (ULN); 15 [8%] >1 to 2xULN. 12 [6%] patients had CPK levels >2xULN prior to commencing DAP (Figure 2)

> During DAP therapy CPK measurements were recorded for 218 pts (36.9%).

> Of which CPK: 179 [82.2%] <1xUL; 22 [10.1%] >1 to 2xULN. CPK >2 ULN was reported 17 [7.8%] pts (Table 2)

Table 1. Patient demographics and characteristics of UK EU-CORESM registered patients (N=592)

Parameter	Patients, n (%)
Gender	
Female	278 (47.0)
Male	314 (53.0)
Weight (kg) [mean ± SD]*	77.9 ± 22.4
Age (Mean ± SD)	62.5 ± 18.5
Race	
Caucasian	532 (89.9)
Asian/Oriental	11 (1.9)
Black or African American	6 (1.0)
Unknown/Other	42 (7.1)
Any significant underlying disease	525 (89.0)
HMG-CoA reductase inhibitor	101 (17.1)

* Data missing for 2 pts

Figure 2. Patients with CPK >1 ULN at baseline (N=27)

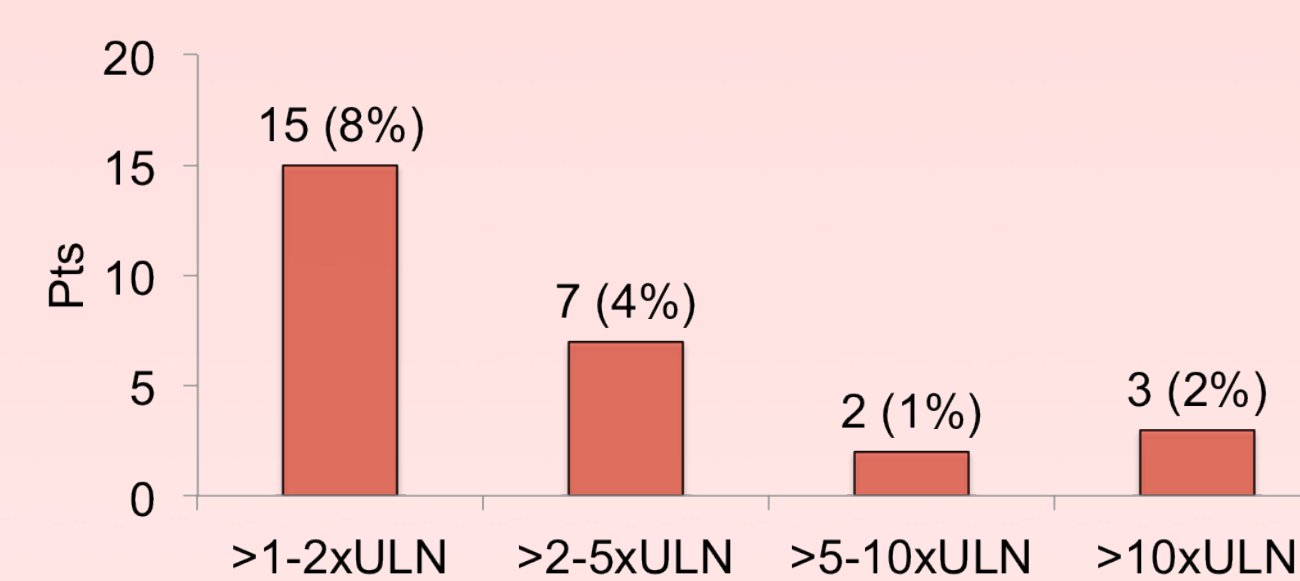


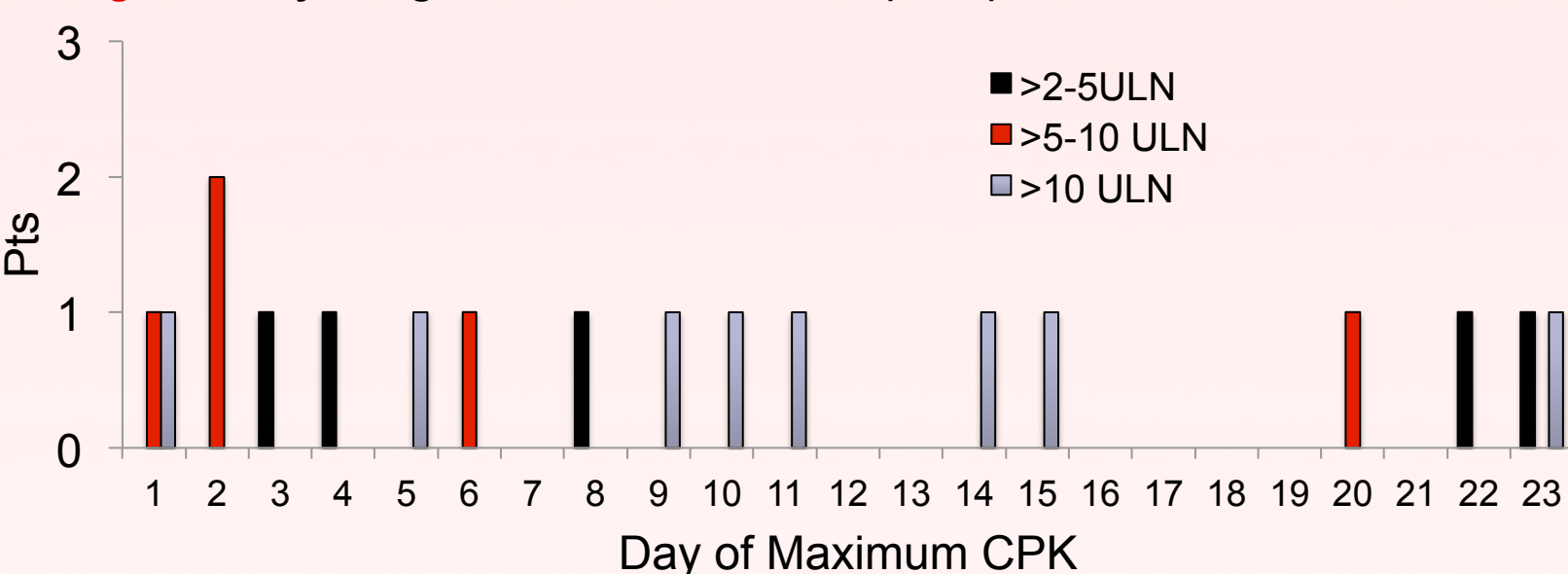
Table 2. Patients with CPK recorded at >2xULN during DAP therapy (n=17)

	>2 to 5xULN n=5 (%)	>5 xULN n=12 (%)
Age (Mean)	54.8	57.4
Male	5 (100)	9 (75)
Weight kg (Mean)	99.1	88.0
HMG-CoA reductase inhibitor	1 (20)	3 (25)
Prior Antibiotics	4 (80)	11 (92)
Concomitant antibiotics	3 (60)	7 (58)
Days of therapy (Mean)	19.4	11.2
Baseline CPK		
<1xULN	-	4 (33)
>2 to 5xULN	1 (20)	1 (8)
>5xULN	-	4 (33)
Not measured	4 (80)	3 (25)

Table 3. CPK AE's (N=12)

AE Reported	Day of onset	Day of resolution	Action with DAP	Severity	Relationship to study DAP	Outcome
CPK RAISED	11	28	None	Mild	Susp	Resolved
CPK RAISED	8	21	None	Mild	Susp	Resolved
CPK RAISED	1	3	None	Mild	Susp	Resolved
CPK RAISED	1	9	None	Mod	Not susp	Resolved
CPK RAISED	8	12	None	Mild	Susp	Resolved
INCREASE IN CPK	1	11	Stopped permanently	Mild	Susp	Resolved
INCREASE IN CPK	15	15	Stopped permanently	Mod	Susp	Resolved
HIGH CPK	12	33	Stopped permanently	Mild	Susp	Resolved
HIGH CPK	15	29	Stopped permanently	Mod	Susp	Resolved
CPK ELEVATION-ASYMPTOMATIC	14	21	None	Mild	Susp	Resolved
MYALGIA	11	99	Stopped permanently	Mod	Susp	Resolved
RHABDOMYOLYSIS	28	28	Stopped permanently	Mod	Susp	Resolved
RHABDOMYOLYSIS	10	18	Stopped permanently	Mod	Susp	Resolved

Figure 3. Day of highest CPK measurement (N=17)



> Of the 17 pts with elevated CPK, 10 had levels >2xULN at the start of therapy

> Day of highest CPK ranged from 1 to 23 days (Figure 3)

> Overall, adverse events (AEs) were experienced by 14.9% (88/592) pts entered into the registry

> CPK elevations or high CPK levels were reported as an AE for 9 pts. Rhabdomyolysis was reported as an AE in 2 pts [CPK was not recorded for 1 pt, in 1 pt CPK was <1xULM during DAP therapy]. Myalgia was reported as an AE in 1 pt with CPK >10xULN at start of therapy (Table 3). 1 pt with elevated CPK was asymptomatic

CONCLUSION

> 10 pts had elevated CPK prior to DAP, suggesting that In complex cases, other factors may be associated with elevations in creatine kinase

> 1 pt with CPK >113 ULN clinically improved with a steady reduction in CPK during DAP treatment²

> BNF states that in the presence of elevated CPK and clinical symptoms DAP should be withdrawn. In this series CPK resolved even when DAP was continued

> Outcomes study and further research is needed to investigate if there is any relationship between DAP and rhabdomyolysis