Drug induced rhabdomyolysis
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Rhabdomyolysis is a clinical condition of potential life threatening destruction of skeletal muscle caused by diverse mechanisms including drugs and toxins. Given the fact that structurally not related compounds cause an identical phenotype pinpoints to common targets or pathways, responsible for executing rhabdomyolysis. A drop in myoplasmic ATP paralleled with sustained elevations in cytosolic Ca²⁺ concentration represents a common signature of rhabdomyolysis. Interestingly, cardiac tissue is hardly affected or only secondary, as a consequence of imbalance in electrolytes or acid–base equilibrium. This dogma is now impaired by compounds, which show up with combined toxicity in heart and skeletal muscle. In this review, cases of rhabdomyolysis with novel recently approved drugs will be explored for new target mechanisms in the light of previously described pathomechanisms.

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Introduction

 Luckily, rhabdomyolysis is a rare event of rapid destruction of skeletal muscle cells. The range of trigger mechanisms is wide and span from mechanical injury, ischemia, infections, genetic alterations to drugs and toxins. Excellent reviews exist on the various aspects of rhabdomyolysis [1,2**,3,4***]. Here, I will concentrate on recently approved drugs that have been associated with clinical cases of rhabdomyolysis.

Currently, no algorithm exists that would predict a patients risk to develop rhabdomyolysis. The only manoeuvre to prevent skeletal muscle destruction represents avoidance of a drug in individuals that already suffered from rhabdomyolysis by this particular drug.

Statins are the only class of drugs that commonly lead to skeletal muscle injury, in particular when combined with drugs interacting on the level of pharmacokinetics. However, an excellent review on the mechanisms behind statins myotoxicity already exists in this journal [5*].

Generally, symptoms of myalgia and muscle weakness precede rhabdomyolysis. However, no laboratory parameters are available that might help to estimate a patients risk for the development of further muscle injury. Slight cases of rhabdomyolysis might exist that are subclinical, but still show up elevations of serum creatine kinase (CK). The ill defined conditions of myalgia and myopathy are often seen by clinicians, but only a very small number of these patients exacerbate rhabdomyolysis. Once skeletal muscle injury exceeds 100 g, myoglobin is massively released and detectable before CK raises [2**]. Consequently, myoglobinuria, elevated CK and serum potassium levels, hyperuricosuria and acidosis come along with the progression of tissue destruction. Conversely, the decline of these parameters may also serve as control of recovery and therapeutic success [1,2**,3,4***]. Leakage of the muscle protein myoglobin into the urine plugs the kidney in particular under acidic conditions. Thus, extensive and early fluid resuscitation is crucial to stabilize circulation, buffer acidosis and control serum potassium. Moreover, suggested volumes of 12 litres a day should flush the tubular system to keep it protected from damage by hyperuricosuria and/or myoglobin [1]. Thus, rapid and aggressive therapeutic intervention helps to prevent fatal complications like arrhythmias, renal failure and disseminated vascular coagulation [1,2**,3,4***].

O rganelles and rhabdomyolysis

Central to all forms of rhabdomyolysis are decline in intracellular ATP levels and elevation in myoplasmic Ca²⁺ concentration (Figure 1) [6**]. Thus, sufficient ATP supply by mitochondrial respiratory chain fails and as a consequence replenishing Ca²⁺ stores and extrusion of Ca²⁺ to the extracellular space is reduced. It is assumed that these long-lasting Ca²⁺ elevations activate calpain proteases, which further degrade proteins that participate in Ca²⁺ homeostasis and thereby aggravate myoplasmic Ca²⁺ overload, as has been shown for statins [5*,7]. This scenario is also corroborated by the finding that the dihydropyridine nifedipine and the ryanodine receptor blocker dantrolen are capable to attenuate exercise and hyperthermia induced skeletal muscle damage [6**,8–10]. Additionally, the skeletal muscle specific calpain 3 protease may contribute a further pathomechanism helping to explain the destruction of the myofibrils.
Calpain 3 is tethered to the giant protein titin, in particular to the N2A line and contributes to sarcomeric remodelling under physiological exercise [11].

Thus, mitochondria, sarcomplasmic reticulum and Ca\(^{2+}\) influx mechanisms, also besides excitation-contraction-coupling contribute and take over in the development of rhabdomyolysis.

**Gene defects and rhabdomyolysis**

Genetic polymorphisms and defects accounting for skeletal muscle diseases potentiate the risk for episodes of rhabdomyolysis (Figure 1). These defects include enzymes from the glycolysis and glycogenolysis pathway and pentose phosphate pathway. Impaired mitochondrial pathways involve fatty acid oxidation, the citric acid cycle and the mitochondrial respiratory chain [4**]. And finally, defects in the Ca\(^{2+}\) homeostasis are seen in patients with mutations in proteins involved in excitation-contraction coupling, myotonias and skeletal muscle dystrophies [4**,12].

This is exemplified by a case of a two year old patient with recurrent hemolytic uremic syndrome and rhabdomyolysis. The child is diagnosed for succinate dehydrogenase Q reductase (complex II) deficiency, which is directly linked to the Krebs cycle via succinate dehydrogenase [13]. Hence, ATP depletion by a defect of oxidative phosphorylation is likely to be causative in this individual to trigger myotoxicity repetitively.

**Newly authorised drugs with risk of rhabdomyolysis**

The list of drugs that are reported to exert elevated risk for rhabdomyolysis is very long and has been extensively reviewed by others [3,4**,12,14]. In particular, HMG-CoA reductase inhibitors have a higher risk to generate skeletal muscle side effects alone or in combination with other drugs owing to interference on the level of uptake/transport and metabolism [5*]. Therefore, I will focus on novel compounds with recently described episodes of rhabdomyolysis and their possible molecular targets.

**Multitargeted tyrosine kinase inhibitors**

The novel multitargeted tyrosine kinase inhibitor sunitinib is beneficial in overall survival of renal and colon cancer patients and shows remarkable activity in a variety of other tumor types even when given as a single agent anti-cancer drug [15,16]. However, sunitinib is associated with hypertension, left ventricular dysfunction and congestive heart failure in up to 15% [16,17]. Human heart biopsies and off-target screening has identified disruption of the mitochondrial architecture and an IC\(_{50}\) for AMP-kinase inhibition as low as 0.2 \(\mu\)M [18*]. Thereby sunitinib interferes with fatty acid \(\beta\)-oxidation and glycogenolysis. The ATP concentration in sunitinib treated cardiomyocytes is significantly reduced, which corroborates abnormalities in energy generation. Under these conditions AMP-kinase activity acts as a rescue pathway (Figure 2). Hence, inhibition by sunitinib is therefore deleterious. Surprisingly, rhabdomyolysis has been
recently reported for sunitinib in two patients with metastatic renal cell cancer receiving 37.5–50 mg sunitinib per day for multiple cycles [19]. The two patients showed a more than 50% reduction in left ventricular ejection fraction and massive elevation of CK, myoglobinuria leading to renal failure. Myocardial infarction could be excluded and the diagnosis rhabdomyolysis was concluded, although using a cut off limit for CK of 5 fold above upper limit of normal.

Cardiac toxicity of tyrosine kinase inhibitors is described for imatinib, dasatinib, nilotinib, sorafenib and lapatinib [18*,20,21]. Sorafenib enhances the prevalence for myositis, but rhabdomyolysis is not found [22]. Interestingly, severe myotoxicity has not been reported for the above mentioned kinase inhibitors, except imatinib. In patients with chronic myelogenous leukemia or gastrointestinal stromal tumors rhabdomyolysis has been confirmed for imatinib to be more often then in other cohorts of patients [23]. However, a molecular target for imatinib triggered myotoxicity has not been identified [23,24].

The epidermal growth factor (EGF) receptor tyrosine kinase inhibitor, erlotinib, has been shown to cause rhabdomyolysis when combined with simvastatin. This is obviously true to a CYP3A4 interaction of the two drugs [25]. Importantly, one case of rhabdomyolysis is reported from a non-small cell lung cancer patient receiving second line erlotinib treatment (150 mg/day) [26]. In this patient myotoxicity is attributable to erlotinib, however, a molecular target is unknown at the moment.

Taken together, tyrosine kinase inhibitors exert cardio-toxicity and myotoxicity, most probably by a common target interaction.

**Trabectedin**

Approved in 2010, trabectedin represents a novel DNA-binding anti-cancer drug effective in soft tissue sarcoma. Severe cases of rhabdomyolysis have been reported already throughout phase II studies [27–29]. The mechanism by which trabectedin elicits rhabdomyolysis is unknown. Nevertheless, a positive correlation could be established between rhabdomyolysis with the area under the curve of trabectedin and elevated bilirubin levels [29]. Furthermore, elevated liver parameters precede rhabdomyolysis and reduced hepatic blood flow as it is seen under beta adrenergic receptor blockade, which should be avoided when trabectedin is applied. In fact, carvedilol was concomitantly administrated with trabectedin in two cases of rhabdomyolysis [27,29].

**Leflunomide**

Leflunomide represents a novel disease modifying anti-rheumatic drug, which inhibits the mitochondrial dihydro-orotate dehydrogenase and thereby the de novo pyrimidine synthesis [30,31]. The exceptional long half-life of leflunomide, which is about 2–3 weeks, implicates long lasting adverse effects even when the drug has been discontinued. The spectrum of side effects involves hypertension, transient hepatotoxicity, alopecia, gastrointestinal symptoms and also cutaneous adverse reactions. Two cases of a more than 10 fold increase in CK are found in the literature [30,31]. A mechanistic explanation for the
development of rhabdomyolysis is pending, but from one case a histological examination of a skeletal muscle biopsy exists. Necrotic areas and infiltrations with inflammatory mononuclear cells are documented. Again a molecular target for this compound is not available and needs further investigation to identify the cause of these rare side effects of leflunomide [30].

**Daptomycin**

Daptomycin is the first approved cyclic lipopeptide with bactericidal activity against Gram-positive bacteria [32]. Dosages above 8 mg/kg and an application interval shorter than 24 h significantly enhance the risk for skeletal muscle side effects, including rhabdomyolysis [33]. Interestingly, cardiac muscle is not affected. *In vitro*, these observations are confirmed in spontaneous contracting rat myoblasts and myocytes. While undifferentiated myoblasts were resistant to daptomycin-induced injury up to concentrations of 6 mg/ml, differentiated myocytes were damaged with 2 mg/ml. Moreover, already 0.75 mg/ml daptomycin were sufficient to suppress spontaneous contractility [34]. Thus, a breakdown of the membrane potential is most likely and could be explained by the pore forming ability of daptomycin. However, this does not explain the resistance of myoblasts against the lipopeptide and the lack of effects in the heart. In humans, CK is the proven and recommended marker to monitor possible skeletal muscle side effects during daptomycin application, given by the fact that myopathies occur with a frequency of 0.2% [32,33]. Consequently, a once daily application has been recommended to reduce the risk for rhabdomyolysis [35–38]. Again, coadministration of HMG-CoA reductase inhibitors should be avoided, because of the enhanced risk to develop rhabdomyolysis and renal failure [39].

**Propofol**

For long propofol is widely used as a short acting anesthetic and for sedation of critical ill patients up to several days. Current recommendations suggest a dosage less than 8 mg/kg/h and application not longer than 2 days in adults. Vasile et al. have summarized 14 cases of propofol syndrome with an average application duration of 86.1 ± 42.9 h (mean ± S.D.) and a mean dosage of 8.7 ± 3.6 mg/kg/h [40]. Elevation of CK, myopathy and finally rhabdomyolysis are often observed in this syndrome [40–42]. On molecular level propofol is toxic for mitochondria and elevates malonyl-carnitine levels. It uncouples the oxidative phosphorylation, inhibits the respiratory chain at complex II and most probably also at complex IV on the level of cytochrome oxidase activity [43,44,45]. In particular, fatty acid transport is inhibited by elevated malonyl-carnitine levels that thereby hamper the energy production from catecholaminergic lipolysis [45]. However, a correlation of the symptoms with morphological alterations has not yet been determined. Unfortunately, the exact molecular mechanisms leading to this potentially life threatening condition are diverse and still a matter of debate especially for new drugs on the market. Report systems are maintained by world health organisations to facilitate registration of new adverse drug events. But then it is difficult and time consuming to award domain experts to detect further events in order to confirm a drug-induced rhabdomyolysis.

Interestingly, a recent concept for *in silico* detection and prediction of possible risk drugs for rhabdomyolysis was introduced by Vilar et al. [46]. Fingerprinting new compounds with drugs in a database with an already existing hazard risk for rhabdomyolysis have improved prediction and reduction of false positive hits for rhabdomyolysis. Accordingly, these results strengthen the conjecture that structural prerequisites are the crucial determinants for the risk of rhabdomyolysis. Moreover, one can also draw the conclusion that molecular switches have to exist that propagate and support the development of rhabdomyolysis, as shown for ATP production and Ca²⁺ homeostasis.

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**References and recommended reading**

Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
- of outstanding interest


3. Excellent overview on handling myoglobinuria.


