Title: Creatine Kinase (CK) Serum Levels for the Diagnosis of Rhabdomyolysis in Patients Taking HMG-CoA Reductase Inhibitors (Statins)

Date: 23 Nov 2007

Context and policy issues:

Rhabdomyolysis is characterized by the destruction of striated muscle, and subsequent leakage of cellular muscle components, such as creatine kinase (CK) and myoglobin, into the circulation and extracellular fluid.\(^1,2\) It may produce an asymptomatic rise in CK levels or may be associated with muscle weakness, myalgia, dark coloured urine, and acute renal failure. The HMG-CoA reductase inhibitor class of medications (otherwise known as statins) are associated with an incidence of fatal rhabdomyolysis of 0.15 deaths per one million prescriptions.\(^1\) Prompt diagnosis and treatment may help preserve kidney function.\(^1,2\)

A number of different biochemical tests, such as myoglobin, CK, carbonic anhydrase, troponin and aldolase, have been evaluated for their diagnostic or prognostic value for rhabdomyolysis.\(^1-9\) CK is an enzyme that consists of several tissue specific subtypes: the MM form from skeletal and cardiac muscle; the BB form from brain and kidney tissue; and the MB form primarily from cardiac muscle.\(^8,10\) After muscle injury, CK levels rise within 12 hours and peak after one to three days. The elimination half life is 36 hours.\(^1,10\)

Research questions:

1. What is the comparative efficacy of CK testing versus CKMB testing to diagnose rhabdomyolysis in patients taking HMGCoA reductase inhibitors?

2. If CKMB testing is warranted, which type of CKMB testing should be employed?
Methods:

A limited literature search was conducted on key health technology assessment resources, including PubMed, The Cochrane Library (Issue 4, 2007), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international HTA agencies, and a focused Internet search. Results include articles published between 2002 and the present, and are limited to English language publications only. No filters were applied to limit the retrieval by study type. Internet links are provided, where available. Reference lists of relevant review articles and clinical practice guidelines were also searched.

Summary of findings:

The search identified no systematic reviews, health technology assessments, meta-analyses or randomized trials that compared testing CK levels to CKMB. Of the clinical practice guidelines or review articles identified, serum CK testing was advocated as the standard to establish the diagnosis of rhabdomyolysis.

Clinical practice guidelines related to the management of hyperlipidemias were identified from Canada, US, UK, Finland, Australia and New Zealand, and Singapore.

In patients treated with statins, the guidelines recommended the following:

- Routine monitoring of CK levels is not necessary in asymptomatic patients. Certain populations, such as those with advanced age, liver disease, chronic renal failure, or those treated with high doses of statins or concomitant medications that may increase the risk of myopathy, may require periodic monitoring of CK levels. A baseline CK level at the start of statin treatment was recommended in some guidelines.
- Patients who experience muscle symptoms (pain, tenderness or weakness) should have their serum CK levels measured.
- In patients with muscle symptoms, CK levels > 5 times, or >10 times the upper limit of normal were considered significant. Most guidelines recommended stopping statin treatment and monitoring CK levels.

One guideline on the management of rhabdomyolysis was identified. The guideline recommended measuring serum CK levels in patients with suspected rhabdomyolysis. In patients with rhabdomyolysis, CK activity is often 10,000 to 100,000 units/L. They also suggested that routine measurement of other muscle enzymes was not necessary.

The level of evidence to support the laboratory monitoring recommendations was either not stated or based on expert opinion. Measuring the CKMB fraction was not mentioned in any of the guidelines. Some of the information provided in this document was based on summaries available from the National Guideline Clearinghouse. One summary was based on an earlier version of the guideline. We were unable to obtain the updated guideline. One guideline was a draft for consultation.

In the review articles identified, serum CK levels were reported as the most sensitive test to detect rhabdomyolysis. One article mentioned measuring the CKMB fraction in patients with suspected rhabdomyolysis and a CK level five times the upper limit of normal. A CKMB fraction of < 5% could be used to rule out myocardial infarction as a potential cause of the elevated CK levels.
Conclusions and implications for decision or policy making:

There were no studies that compared the efficacy of CK testing versus CKMB testing to diagnose rhabdomyolysis in patients taking HMGCoA reductase inhibitors. Evidence was limited to clinical practice guidelines. According to the clinical practice guidelines identified in our search, serum CK level is the preferred biochemical test to assess for rhabdomyolysis in patients treated with statins who experience muscle symptoms. Furthermore, there was no evidence regarding the various CKMB tests available and which one should be employed.

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