Rhabdomyolysis in an Increasingly Common Heart Failure Patient for Internists

Ka Hong (Casey) Chan, PGY-3
University of Calgary Internal Medicine
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Disclosures

• There are no conflicts or disclosures

• The patient had provided consent to this case report
Meet Mr. Jones...

83M who presented with myalgias

**Past Medical History:**
1. Recent diagnosis of non ischemic dilated cardiomyopathy with EF of 18%, NYHA II baseline
2. Dyslipidemia
3. Hypertension
4. Type 2 Diabetes Mellitus
5. Chronic Thrombocytopenia

**Medications:**
1. ASA
2. Metoprolol
3. Irbesartan
4. Spironolactone
5. Atorvastatin
6. Metformin/Gliclazide
Meet Mr. Jones...

1. Irbesartan switched to sacubitril/valsartan

2. Progressive myalgias from walking to cane to almost bed bound due to lethargy and weakness

3. Presented to hospital due to fall

Calendar from https://www.pinterest.ca/pin/613263674234187255/
Physical Exam:

- Afebrile but tachycardic
- CNS: Normal CN. 4/5 strength in quadriceps/knees, otherwise normal including reflexes
- CVS: Elevated JVP, normal HS
- No rash, compartment syndrome or foci of infection
Investigations:

**CK**: 16500

**Bili**: 42

**Top HS**: 300 ➔ 382

**TSH**: Normal

**Troponin I**: -ve

**Urinalysis**: Hematuria on dipstick, negative RBC on microscopy. Granular casts
Why did this gentleman with CHF get Rhabdomyolysis?
Increasingly Common CHF Patient:

- Sacubitril/Valsartan has been approved by FDA and Health Canada since 2015
- 2017 CCS Guidelines recommend its use in patients who remain symptomatic despite appropriate goal-directed medical therapy

McMurray et al. (2014) PARADIGM-HF. NEJM
Adverse Effects:

- No mention of rhabdomyolysis as a side effect in PARADIGM-HF
- 60% of patients had ischemic cardiomyopathy and presumably, would have been on a statin

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>LCZ696 N=4203 n (%)</th>
<th>Enalapril N=4229 n (%)</th>
<th>Total N=8432 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients with at least one AE</td>
<td>3419 (81.35)</td>
<td>3503 (82.83)</td>
<td>6922 (82.09)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>740 (17.61)</td>
<td>506 (11.97)</td>
<td>1246 (14.78)</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>730 (17.37)</td>
<td>832 (19.67)</td>
<td>1562 (18.52)</td>
</tr>
<tr>
<td>Hyperkalaemia</td>
<td>488 (11.61)</td>
<td>592 (14.00)</td>
<td>1080 (12.81)</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>426 (10.14)</td>
<td>487 (11.52)</td>
<td>913 (10.83)</td>
</tr>
<tr>
<td>Cough</td>
<td>369 (8.78)</td>
<td>533 (12.60)</td>
<td>902 (10.70)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>266 (6.33)</td>
<td>206 (4.87)</td>
<td>472 (5.60)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>251 (5.97)</td>
<td>236 (5.58)</td>
<td>487 (5.78)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>227 (5.40)</td>
<td>237 (5.60)</td>
<td>464 (5.50)</td>
</tr>
<tr>
<td>Oedema peripheral</td>
<td>215 (5.12)</td>
<td>213 (5.04)</td>
<td>428 (5.08)</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>213 (5.07)</td>
<td>306 (7.24)</td>
<td>519 (6.16)</td>
</tr>
</tbody>
</table>

McMurray et al. (2014) PARADIGM-HF. NEJM
Mechanism of Adverse Effect:

- OATP1B1
- OATP1B3
- Atorvastatin
- CYP3A4
- Metabolites
- P-glycoprotein
- BRCP
- Blood
- Hepatocyte
- Bile
- Sacubitril/valsartan
- Cyclosporine
- Rifampin
Why Atorvastatin?

Clinical Implications:

- Other statins metabolized through OATP, but pharmacokinetics do not align with maximum concentration for possible adverse effects
- Alter the dosing timing, or consider other statins
- Importance for understanding this risk when co-prescribing this medication and counselling patients accordingly
Back to Mr. Jones
Objectives:

1. Recognize the increasing importance of evaluating for drug interactions in complex patients with new presentations
2. Identify rhabdomyolysis as a potential drug interaction when prescribing sacubitril/valsartan with statins, and the role that information technology played to find the mechanism
3. Apply the underlying pharmacokinetic mechanism to provide alternatives when co-administration is required
Questions?
References:


