A case-control study of rhabdomyolysis to screen for drug-drug interactions in statin users

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CHRU

Statins and Rhabdomyolysis

- Statins inhibit HMG-CoA reductase, cholesterol synthesis in the liver
- Reduce risk of cardiovascular events and death
- Can cause a spectrum of muscle injury
- Rhabdomyolysis: symptoms with elevation of serum creatine kinase > 10x ULN
- Incidence ~ 1 per 10,000 person-years of statin use

Cerivastatin

- First marketed March 1998, withdrawn from market in Aug 2001 because of reports of rhabdomyolysis
- In a population-based cohort study,[1] risk of rhabdo with cerivastatin increased 10-fold
  - In gemfibrozil users, risk increased 50-fold
- In a small RCT, gemfibrozil use increased the area under the plasma time concentration curve 559%[2]
- *In vitro* studies[3]: oxidative metabolism through CYP2C8, transport into hepatocytes by OATP1B1

1. Graham DJ. *JAMA.* 2004;292:2585.
2. Backman JT. *Clin Pharmacol Ther.* 2002;72:685.
3. Shitara Y. *J Pharmacol Exp Ther.* 2004;311:228.

Specific Aims

- Primary Aim: Evaluate concurrent medication use in a case-control study of statin-induced rhabdomyolysis to discover potential new DDIs
  - Discover unrecognized inhibitors of CYP2C8 and OATP1B1
- Secondary Aim: Replicate positive findings from case-control study in a case-only analysis using FDA Adverse Event Reporting System

Cases

- Recruited through attorneys who represented cerivastatin users with rhabdomyolysis
- Muscle pain or weakness, CK > 10x ULN
- Medication use and medical history at time of diagnosis ascertained through medical records and interviews

Controls

- Statin users from the Cardiovascular Health Study
- Medication use ascertained annually by phone or in person
- Restricted controls to users of atorvastatin
  - Atorvastatin marketed Feb 1997, cerivastatin Mar 1998

Analysis

- Compared prevalence of concomitant medication use, restricted to subjects with indication for use
- Medications with frequency > 4% in cases evaluated
- ORs estimated by logistic regression
  - Adjusted for age, gender, race, and index year
- Analysis repeated excluding gemfibrozil users

Patient Characteristics

	Cases	Controls
n	72	287
Age, mean (SD)	76 (5)	80 (3)
Male	32%	32%
White	93%	88%
Treated hypertension	69%	70%
Treated diabetes	19%	20%
Myocardial infarction	22%	22%
Stroke	17%	11%
Cardiovascular disease	67%	48%
Congestive heart failure	14%	16%
Atrial fibrillation	19%	11%
Asthma	19%	14%

RHABDO CASES:
39% renal failure
14% dialysis
3% died

Median peak CK
- 31,390 U/L

Medications Evaluated

Alendronate
Allopurinol
Amitriptyline
Amlodipine
Aspirin
Atenolol
Celecoxib
Clopidogrel
Digoxin
Diltiazem
Enalapril
Furosemide
Gemfibrozil
Glimepiride
Glipizide
Glyburide
Fluoxymesterone
HCTZ
Irbesartan
Lansoprazole
Levothyroxine
Lisinopril
Losartan
Metformin
Metoprolol
Montelukast
Omeprazole
Pioglitazone
Ramipril
Ranitidine
Rofecoxib
Rosiglitazone
Triamterene
Valsartan
Verapamil
Warfarin

Association with Rhabdomyolysis

		Cases	Controls	Gemfibrozil Users Included		
	Restriction	n=72†	n=287†	OR	95% CI	P
Gemfibrozil	-	32%	0%	inf	25.0-inf‡	1.3×10^{-15}

† Prevalence of medication use in restricted population

‡ Exact methods used to estimate CI

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Clopidogrel	CVD	50%	8%	29.6	6.1-143	2.4×10^{-5}

CVD = cardiovascular disease

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Fluoxymesterone	-	8%	0%	inf	4.4-inf‡	1.2×10^{-4}
Lansoprazole	-	11%	3%	5.7	1.3-24.0	0.018
Propoxyphene	-	8%	2%	4.8	1.7-13.9	0.003
Rofecoxib	-	13%	4%	4.9	1.1-20.8	0.033
Rosiglitazone	DM	29%	5%	19.8	1.0-402	0.052

CVD = cardiovascular disease, DM = diabetes mellitus

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Excluding Gemfibrozil Users

	Gemfibrozil Users Included			Gemfibrozil Users Excluded		
	OR	95% CI	P	OR	95% CI	P
Clopidogrel	29.6	6.1-143	2.4×10^{-5}	47.8	12.5-182	1.6×10^{-8}

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Fluoxymesterone	inf	4.4-inf‡	1.2×10^{-4}	inf	5.8-inf‡	2.9×10^{-5}
Lansoprazole	5.7	1.3-24.0	0.018	4.7	1.3-17.5	0.020
Propoxyphene	4.8	1.7-13.9	0.003	2.7	0.6-11.2	0.174
Rofecoxib	4.9	1.1-20.8	0.033	5.1	1.2-22.1	0.031
Rosiglitazone	19.8	1.0-402	0.052	26.2	0.7-989	0.078

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Confirmation: AERS

- FDA Adverse Event Reporting System
- Compared medication use in rhabdo cases using cerivastatin and atorvastatin
  - Cerivastatin: June 1997 to Aug 2001
  - Atorvastatin: Dec 1996 to Jan 2001
- ORs from logistic regression
  - Adjusted for age, gender, and time from FDA approval
- Analysis repeated excluding gemfibrozil users

1. Graham DJ. *Am J Med.* 2003;114:299.

AERS Results

	CER	ATOR	Gemfibrozil Included			Gemfibrozil Excluded		
	N = 594	N = 75	OR	95% CI	P	OR	95% CI	P
Gemfibrozil	48%	7%	24.6	8.1-74.5	$1.1x10^{-8}$	-	-	-

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Gemfibrozil	48%	7%	24.6	8.1-74.5	1.1×10^{-8}	-	-	-
Clopidogrel	17%	0%	inf	2.6-inf‡	0.002	inf	5.2-inf‡	1.1×10^{-5}
Clopidogrel†	29%	0%	Inf	1.2-inf‡	0.037	inf	2.1-inf‡	0.003

† Restricted to aspirin users only

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Clopidogrel

- Antiplatelet agent used to treat atherosclerotic cardiovascular disease, approved in 1997
- Genetic variants in CYP2C19 associated with decreased efficacy
- Screening study of *in vitro* inhibition of CYP2C8 showed modest inhibition[1]
- No prior studies have assessed whether clopidogrel increases risk of an adverse event through a DDI

1. Walsky RL. J *Clin Pharmacol*. 2005;45:68.

Summary of Findings

- Other than gemfibrozil, six medications that increased the risk of rhabdo in cerivastatin users
  - May results in DDIs with other medications cleared by similar pathways
- Strongest association was for clopidogrel
  - Supported by analysis of FDA AERS data
- Restricting to nonusers of gemfibrozil did not markedly alter most findings
  - Confounding by gemfibrozil use did not explain findings

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