Drug Information Request and Response Form

		Date/time required: **June 14, 2017 2:00PM**	
Date **July 6, 2017**	Time **1:00 PM**	Contacted by **In person**	Patient specific? **Yes**
Requestor **Pharmacist**			
Nature of Request: **ADR/Safety**			**By Pharmacy Student**

Question

In a patient with myasthenia gravis and a new diagnosis of atrial fibrillation, which agent(s) would be most safe for rate control? Options include: diltiazem, beta-blocker, digoxin, and amiodarone.

Background Information`

RC is a 71 year old male patient (weight=130kg) admitted to the hospital on May 19th for respiratory distress induced by a myasthenia gravis crisis. RC has been diagnosed with myasthenia gravis since 2013. Myasthenia gravis is an autoimmune disease where antibodies against acetylcholine receptors cause muscle fatigue and weakness.

His past medical history includes: cataracts, chronic obstructive pulmonary disease, obstructive sleep apnea, osteoarthritis, obesity, and hypertension. During a hospitalization in early May, a new diagnosis of permanent atrial fibrillation (AF) was made. He was temporarily treated with amiodarone for his atrial fibrillation. RC also received a single IV dose of digoxin in June while he had an acute kidney injury. Patient's CHADS2 score is 1 and he reports no chest pain. He has been given diltiazem for rate control for at least a month so far. His target resting heart rate is below 110 bpm.

Patient drank alcohol moderately before admission and he is an ex-smoker (20 py). In hospital RC is currently on the following::

- Diltiazem 30mg i tab ng QID (for atrial fibrillation rate control)
- Warfarin 5mg i tabs ng once daily (for stroke prevention)
- Ferrous gluconate 300mg i tab po/ng qhs (for iron deficiency)
- Azathioprine 100mg ng BID (for myasthenia gravis)
- Prednisone 5mg viii tabs po breakfast (for myasthenia gravis)
- Pyridostigmine 60mg i tab po QID (for myasthenia gravis)
- Esomeprazole 40mg i tab po/ng daily (for gastric acid reduction)
- Loperamide 2mg i tab po/ng PRN (for diarrhea)
- Acetaminophen 325mg iii tabs po q6h (for pain relief)
- Dalteparin 5000 units sc BID (for DVT prevention)
- Melatonin 3mg ii tabs sl qhs PRN (for insomnia)
- Amoxicillin-clavulanate 825/125mg i tab po BID x 5d (for infection)
- Calcium carbonate 1250mg i tab po BID (supplements)
- Vitamin D 1000unit i tab po daily (supplements)

Patient experienced Steven Johnsons Syndrome when using IVIG in May 2017.

Patient has normal renal and liver functions; Cr=96umol/L, GFR=68ml/min, ALT=21U/L, and AST= 12U/L. Patient's blood pressure on July 10th was 118/73mmHg, and pulse was consistently between 80-90 bpm the past couple days.

Response

Necessary:
Atrial fibrillation (AF) is the most common type of arrhythmia. It is caused by abnormal atrial electrical impulses, often leading to tachycardia.[1] AF could be caused by conditions such as hypertension, coronary artery disease, diabetes, or heart failure.[1] AF symptoms include dizziness, shortness of breath, and palpitations.[1] ECG of AF patients lack P waves and consists of irregularly irregular rhythm (the irregular rhythm has no pattern).[1] Rate control is important to relieve symptoms and prevent tachycardia-related complications. A target HR is selected for a patient and medications are used to achieve these goals. As RC is requiring dilitiazem 30 mg po QID currently to achieve his target HR, he is clear that a rate controller medication is necessary.

Efficacy:
Rate control interventions prevent some of the electrical impulses from reaching the atrioventricular (AV) node by prolonging the AV node refractory period.[1] The following drugs are indicated for and have demonstrated efficacy in ventricular rate control: beta-blockers, diltiazem, digoxin, amiodarone.[1] Beta-blockers and calcium channel blockers are more effective than digoxin when physical activity, including activities of daily life, is involved.[1] Beta blockers inhibit the beta-1 adrenergic receptors in the myocardium, inhibiting sympathetic innervation and resulting in slowed conduction of the SA and AV node.[2] Diltiazem is a non-dihydropyridine calcium channel blocker (non DHP CCB).[2] Diltiazem inhibits calcium transport across slow calcium channels in cells such as cardiac myocytes and vascular smooth muscle.[2] This binding also prolongs AV node refractoriness.[2] This prevents some of the abnormal atrial electrical impulses from stimulating the AV node, resulting in decreased frequency of ventricular contractions and achieving rate control.[2] Diltiazem binds more when there is an increase in frequency of depolarization and binds less when there are longer periods of repolarization.[2] Therefore, diltiazem exhibits selective activity during a tachycardic state (frequent depolarizations and short repolarizations) with minimal effect on normal heart rates.[2] Digoxin is useful in short-term purposes as it only has comparable effectiveness to CCB's and beta-blockers when patient is at rest.[1] Digoxin is a cardiac glycoside that decreases AV node conduction and increases AV refractory period either directly, through stimulation of vagal tone, or through inhibition of sympathetic activity in the heart.[2] Digoxin only produces a clinical effect on the AV node when supraventricular tachyarrhythmias (atrial fibrillation) are present.[2] Amiodarone is a class III antiarrhythmic that prolongs repolarization and refractory period throughout the heart including both SA node and AV node.[2] It also has electrophysiological effects on calcium and sodium channels and interferes with the adrenergic innervation of the heart.[2]

Safety:
Side effects of beta blockers include: bradycardia, hypotension, syncope, and fatigue.[2] There have been reports of beta-blockers worsening or causing myasthenia gravis.[3,4,5,6,7] It is theorized that beta-blockers could reduce the activity in the neuromuscular junction thereby further exacerbating the condition.[6] In one of the cases, a 74 year old patient developed myasthenia gravis within two weeks of acebutolol therapy.[7] Discontinuation of the medication did not reverse the condition.[7] Another patient, 66 year old female using propranolol, experienced weakness and diplopia which was confirmed as myasthenic symptoms by an electromyogram.[6] On the other hand, there are also some conflicting reports of beta blockers causing no significant effect in patients with myasthenia gravis.[8,9] Although the use of beta-blockers in this condition is controversial, it is better to be cautious and avoid the medication due to the majority of case reports, studies, and letters leaning towards a possible association.
The limitations are that most of the reports are very outdated and there is a lack of recent studies available. As well, all the studies revolved around the older types of beta blockers, such as propranolol, and the safety profile of the new selective beta-blockers, such as atenolol or metoprolol, in myasthenia gravis is unavailable.

Diltiazem's common adverse effects are headache, dizziness, bradycardia, hypotension, and nausea.[2] Research studying diltiazem use in myasthenia gravis is currently unavailable. Verapamil, also a non-DHP CCB class, is theorized to depress neuromuscular activity and reduce acetylcholine.[5,10] It is hypothesized

that the additional sodium channel inhibiting function of verapamil is somehow linked to affecting neuromuscular transmission, unlike diltiazem.[10] In a case report, a 71 year old male patient experienced severe worsening of myasthenia gravis symptoms within two hours of switching from diltiazem to verapamil.[10] It exemplifies a situation of diltiazem possibly being safe in such patients, recognizing that this in only a case report. There has also been an experimental mouse model which demonstrated that verapamil had a greater effect on inhibition of acetylcholine release through calcium channel blockage compared to diltiazem.[11] In the New England Journal of Medicine, a letter report, on the basis of the study mentioned, diltiazem was regarded as a safer drug of choice in atrial fibrillation for patients with myasthenia gravis.[5] Furthermore, it is important to consider that there has not been any reports advising against using diltiazem in myasthenia gravis. The limitation of this data must be noted – there are not controlled trials or clinical reviews of diltiazem. Critical appraisal is not applicable in this case as the information is very scant.

That said, RC has been using diltiazem with no adverse effects reported so far. The recommended diltiazem dosage is 120-480mg daily and the patient is receiving a lower dosage.[12] In geriatric patients, both renal and hepatic function should be monitored and diltiazem should be dosed cautiously as it undergoes both hepatic metabolism and renal excretion. [2] As mentioned earlier, RC has normal hepatic and renal functions. Plasma half life of oral diltiazem varies from 2-11 hours.[2] It is almost entirely metabolized by CYP 3A4 to active and inactive metabolites.[2] Only 2-4% is excreted in urine unchanged.[2] Diltiazem levels can be increased if taken with concomitant medications that are CYP 3A4 metabolized such as cimetidine, cyclosporine, carbamazepine, and atorvastatin.[2] There is no duplication of therapy.

There are no studies or case reports available regarding digoxin and myasthenia gravis. Medline, UptoDate, and myasthenia gravis official websites were searched.[13,14] In addition, according to the Beers Criteria, digoxin should not be used as a first-line in atrial fibrillation patients over 65 due to a possible increase in mortality risk.[15] Side effects of digoxin are dose dependent and usually occur when dose is too high.[2] These include ventricular arrhythmias, nausea, and gynecomastia.[2]

Likewise, amiodarone also lacks any evidence of safe usage in myasthenia gravis patients. Amiodarone exhibits highly toxic side effects and almost 75% of patients experience adverse events.[2] Common side effects include nausea, vomiting, constipation, and hypotension.[2] Many adverse reactions requiring discontinuation have been reported as well, such as congestive heart failure, liver damage, pulmonary toxicity, and thyroid effects.[2] These adverse effects are usually reversible upon drug discontinuation, but may persist for months before disappearing and thus amiodarone is generally reserved for extreme cases when other means of treatment are not feasible/ideal.[2] Moreover, specifically for RC, he is taking warfarin which interacts with amiodarone.[16] Amiodarone inhibits warfarin-metabolizing enzymes and causes warfarin's concentration to increase in the body.[16] However, warfarin dosing can be adjusted to account for this interaction.

Adherence:
Patient's adherence to his medication regimens is not reported. Dosing frequency needs to be considered as some formulations of drugs may require up to four times daily administration. All of the drugs have cheaper generic alternatives so cost concern interfering with compliance is not an issue.

Conclusion

Out of the four agents, diltiazem is possibly the safest in myasthenia gravis. It is the only drug that exhibits safe usage with no negative complications reported. However, there is a lack of recent high-quality evidence (randomized control trials, prospective trials) regarding rate controlling drugs in myasthenia gravis patients. As there is no strong evidence as to the level of safety of diltiazem is in this population, ongoing monitoring for worsening of myasthenia gravis is essential. Compared to diltiazem, there is no research regarding amiodarone and digoxin safety with myasthenia gravis, and both these drugs exhibit more serious side effects. Therefore, digoxin and amiodarone should only be used if

diltiazem is ineffective in RC. Beta blockers should be avoided due to multiple case reports of worsening myasthenia gravis.

Monitoring Plan and Follow Up

Positive Endpoints	**Monitored By**	**Expected Change**	**Follow Up**
Atrial fibrillation- prevention of symptom (palpitations, shortness of breath, dizziness)	Patient, physician	Asymptomatic status maintained	Daily by healthcare professionals.
Ventricular rate controlled	Physician	Controlled under 110 bpm	Daily by healthcare professionals.
Negative Endpoints	**Monitored By**	**Expected Change**	**Follow Up**
Side effects of diltiazem: (hypotension-90/60, bradycardia- HR > 50, headache)	Patient, pharmacist	Absence anytime	Daily by healthcare professionals.
Worsening myasthenia gravis: (facial paralysis, difficulty breathing, eyelid drooping)	Patient, pharmacist	Absence anytime	Daily by healthcare professionals.
Myasthenia gravis complication: Respiratory distress	Pharmacist, physician	Absence anytime	Daily by healthcare professionals.

References (Attach citations - Vancouver Style - for any primary literature used to answer the DIR)

· Medline – keyword searches “myasthenia gravis”, “diltiazem”, “calcium channel blockers”, “anti arrhythmia agents”, “beta blockers”, “digoxin”, and combinations of above.

· Myasthenia Gravis Foundation of America (www.myasthenia.org) - mentions beta-blockers should be used in caution.

· Up to Date – says beta-blockers should be avoided when possible (reference #11) and “calcium channel blocker (e.g. verapamil)” are well tolerated but may cause exacerbation (reference #10).

· Myasthenia Gravis Society of Canada – unable to obtain information about drugs to avoid.

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