SHORT COMMUNICATION

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Fluoroquinolone-Associated Myasthenia Gravis Exacerbation

Evaluation of Postmarketing Reports from the US FDA Adverse Event Reporting System and a Literature Review

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Abstract

Background: Exacerbations of myasthenia gravis have been reported in antibacterial-treated patients. In animal and *in vitro* models of experimentally-induced myasthenia gravis, fluoroquinolones exhibit neuromuscular blockade.

Objective: The aim of this retrospective study was to evaluate postmarketing adverse event reports submitted to the US FDA and case reports published in the scientific literature for a potential association between fluoroquinolone exposure and acute exacerbations of myasthenia gravis.

Methods: On 1 March 2011, we searched the FDA Adverse Event Reporting System (AERS) database to retrieve all reports of myasthenia gravis exacerbation as a serious adverse event in patients treated with fluoroquinolones. We also conducted an Internet-based search using EMBASE for additional English-language cases in the scientific literature.

Results: We identified a total of 37 unique cases describing myasthenia gravis exacerbation following fluoroquinolone systemic exposure. We retrieved AERS reports for 27 non-ventilated patients administered the following fluoroquinolones: levofloxacin (n = 9), moxifloxacin (n = 6), ciprofloxacin (n = 6), ofloxacin (n = 2), gatifloxacin (n = 2), norfloxacin (n = 1) and trovafloxacin (n = 1). Additionally, we retrieved ten case reports published in the literature involving non-ventilated patients administered ciprofloxacin (n = 4), levofloxacin (n = 2) and ofloxacin, norfloxacin, pefloxacin and prulifloxacin (1 patient each). Myasthenia gravis exacerbations developed a median of 1 day following fluoroquinolone exposure. The 37 cases describe dyspnoea (n = 19; 51%), myasthenic crisis requiring ventilatory support (n = 11; 30%) and death (n = 2; 5%). Additional exacerbation-related adverse events were generalized muscle weakness (n = 20; 54%), dysphagia (n = 9; 24%), diplopia (n = 6; 16%) and ptosis (n = 6; 16%). Six patients (16%) experienced a positive rechallenge, with recurrent myasthenia gravis exacerbation after fluoroquinolone reintroduction.

Conclusions: Fluoroquinolone exposure may result in potentially life-threatening myasthenia gravis exacerbations in patients with underlying disease. Healthcare professionals should be aware of this serious drug-disease association and carefully weigh the benefit-risks of fluoroquinolones when treating infections in non-ventilated myasthenic patients.

Background

Myasthenia gravis is an autoimmune disease affecting the neuromuscular junction in which normal transmission of the neuron to muscle impulse is impaired or prevented by acetylcholine receptor antibodies.[1] Antibodies are directed at or bind to acetylcholine receptors on the motor endplate, thereby decreasing the number of effective receptors and impeding neuromuscular impulse transmission. The thymus plays a key role in the pathogenesis of myasthenia gravis and is likely the source of antigen that drives the disease.[2]

Myasthenia gravis is a rare disorder with an estimated worldwide annual incidence of 3–30 cases/1 million persons,[3,4] and a prevalence of 61–126 cases/1 million persons.[4,5] In 2006, the Myasthenia Gravis Foundation of America, Inc. estimated the US prevalence to be 14–20 cases/100 000 persons, with 36 000–60 000 Americans having the disease.[6]

Specific therapies for myasthenia gravis include acetylcholinesterase inhibitors, thymectomy and immunosuppression. However, disease exacerbations with a varying range of severity may occur. Manifestations of mild to moderate exacerbation include ptosis, diplopia, dysphagia, generalized muscle weakness and fatigue. In severe exacerbations, myasthenic crisis, characterized by acute respiratory failure requiring mechanical ventilatory support, may occur.

Suspected triggers of acute myasthenia gravis exacerbation include medications, infection, physical or emotional stress, disorders of the thyroid, surgery, pregnancy, childbirth and reductions in immunosuppressive drug regimen. Anti-infective agents are the most frequently implicated drugs. Table I summarizes non-fluoroquinolone drugs or drug classes previously associated with myasthenia gravis exacerbation.

Neuromuscular blockade, based primarily on preclinical data, is a putative pathophysiological mechanism for drug-induced exacerbations of myasthenia gravis. Deng et al.[9] investigated the neuromuscular blocking potential of several antibacterials using mice with experimentally-induced autoimmune myasthenia gravis, and concluded that aminoglycosides and fluoroquinolones may aggravate neural transmission at the neuromuscular junction. Additionally, an *in vitro* model demonstrated that some fluoroquinolones (norfloxacin, ofloxacin and pefloxacin) could effectively block neurotransmission across the endplate in a dose-dependent manner and at concentrations similar to those used in clinical practice.[10]

The ability of fluoroquinolones to induce exacerbations of myasthenia gravis may be related, in part, to structural similarities with other drugs shown to impair neuromuscular transmission.[11] All fluoroquinolones, by virtue of their quinolone ring, are structurally similar to quinoline compounds, such as quinine. Sieb et al.[12] evaluated the neuromuscular transmission blocking potential of quinoline derivatives (quinine, quinidine and chloroquine) and concluded that these drugs impede neurotransmission;[12] quinine is directly toxic to the acetylcholine receptor ion channel.[12] Myasthenic syndromes and unmasking of pre-existing myasthenia gravis have been described in patients administered chloroquine and quinidine.[13,14]

The purpose of our investigation is to determine if there is clinical evidence supporting a possible drug-adverse event association for fluoroquinolone exposure and acute myasthenia gravis exacerbation. Patient demographics and clinical outcomes cited in postmarketing adverse event reports found in the US FDA Adverse Event Reporting System (AERS) and published literature reports are described.

Table I. Non-fluoroquinolone drugs or drug classes associated with myasthenia gravis[1,7,8]

Anti-infectives	Cardiovascular drugs	Neurological drugs	Immune modulators	Anticholinergic drugs	Other drugs
Aminoglycosides[a]	β-adrenergic receptor antagonists[a]	Phenytoin[b]	D-penicillamine[c]	Trihexyphenidyl[b]	Magnesium[b]
Ampicillin[b]	Procainamide[a]	Lithium[b]	Corticosteroids[b]		D,L-carnitine[b]
Amoxicillin[b]	Propafenone[b]	Trimethadione[b]			Interferon-α[c]
Imipenem/cilastatin[b]	Verapamil[a]	Paralytics[a]			Levonorgestrel[b]
Macrolides[a]	Quinidine[a]	Gabapentin[b]			Methocarbamol[b]
Telithromycin[d]	HMG-CoA reductase inhibitors (statins)[a]	Chlorpromazine[b]			Nicotine[b]
Pyrantel[b]	Disopyramide[b]				Iodinated contrast media[a]
Chloroquine[b]	Reserpine[b]				Risedronate[b]
Colistin[b]					Imiquimod[b]
Tetracyclines[a]					Sevoflurane[b]
Quinine[a]					Halothane[b]
					Ephedrine[b]
					Botulinum toxin[c]

a Multiple case reports have been published reporting worsened myasthenia gravis symptoms following use of these drugs.

b Drugs may be problematic for use in patients with myasthenia gravis based on one or more published case reports.

c Myasthenia Gravis Foundation of America, Inc. recommends complete avoidance of these drugs in myasthenic patients.

d US FDA labelling indicates this drug is contraindicated for use in patients with myasthenia gravis.

Methods

US FDA Adverse Event Reporting System (AERS)

We searched the FDA AERS for all foreign and domestic postmarketing reports of myasthenia gravis exacerbation as a serious adverse event in patients treated with a fluoroquinolone between 1 January 1970 and 1 March 2011 using the Medical Dictionary for Regulatory Activities (MedDRA®) higher level terms (HLT) 'myasthenias' and 'neuromuscular junction dysfunction'. The FDA's regulatory definition of a serious adverse drug event is one that results in death, is life-threatening, requires initial or prolonged hospitalization, causes disability or congenital anomaly, or requires a medical intervention to prevent outcomes such as death, a life-threatening condition or hospitalization.[15]

The AERS is a voluntary FDA postmarketing adverse event database comprised of reports submitted by manufacturers (who have variable reporting requirements to the FDA) and the public (most often by patients, pharmacists, physicians and other healthcare professionals). Voluntary reporting databases such as the AERS are subject to inherent limitations for causality assessments, including underreporting of events, variable reporting quality, reporting biases (which potentially include misattribution of causality) and substantial missing data. Additionally, there is insufficient numerator and denominator data to provide incidence and risk estimates. The AERS houses spontaneous reports from both US and non-US sources. We retrieved relevant AERS reports for all fluoroquinolones previously or currently marketed in the US, including levofloxacin, ciprofloxacin, moxifloxacin, gemifloxacin, gatifloxacin, sparfloxacin, trovafloxacin, norfloxacin and ofloxacin. Where available in an AERS report, the following information was collected: demographic data (age, sex, country and received date), suspect drug information (indication, dose and duration), medical and medication history, reported clinical manifestations, hospitalization required or prolonged, cases of dechallenge and rechallenge, medical interventions, ventilatory status and outcome.

For the purposes of this investigation, we defined an acute exacerbation of myasthenia gravis

as the new onset or abrupt clinical worsening of one or more of the following symptoms in a patient who had been clinically stable prior to fluoroquinolone exposure: diplopia, ptosis, dysphagia, generalized muscle weakness, dyspnoea or respiratory failure. Additionally, using reporter attribution to identify the primary suspect drug, we used the following case definition for fluoroquinolone-associated myasthenia gravis exacerbation in which cases had to fulfill either criteria 1 or 2 below.

1. Newly diagnosed myasthenia gravis, or myasthenia gravis exacerbation in a previously diagnosed patient, requiring acute hospitalization within 10 days of fluoroquinolone initiation where the fluoroquinolone was the primary suspect drug, OR acute myasthenia gravis exacerbation that was attributed to a fluoroquinolone by the reporter AND clinical improvement following fluoroquinolone withdrawal, or initiation of an acetylcholinesterase inhibitor or corticosteroids.
2. Patients who died in the setting of a suspected acute myasthenia gravis exacerbation where the fluoroquinolone was a suspect drug.

Additionally, we defined a positive dechallenge as resolution of the acute myasthenia gravis exacerbation following fluoroquinolone discontinuation. We defined a positive rechallenge as re-exacerbation of myasthenic symptoms following reintroduction of a fluoroquinolone in patients whose initial symptomatic episode abated after fluoroquinolone withdrawal.

Literature Search

On 1 March 2011, we conducted an Internet-based search for published case reports of myasthenia gravis exacerbation in patients treated with a fluoroquinolone using EMBASE. We selected EMBASE as a search tool because it is a large international database holding more than 24 million indexed records from over 7500 active, mostly peer-reviewed journals (www.embase.com). This literature search tool retrieves articles indexed in MEDLINE® and other medical and pharmacological sources. EMBASE was searched using the following indexed Emtree terms (in combination):

- myasthenia gravis and quinolone-derived antiinfective agent;
- myasthenia gravis + each individual fluoroquinolone drug (ciprofloxacin, levofloxacin, moxifloxacin, gemifloxacin, norfloxacin, ofloxacin, gatifloxacin, sparfloxacin, trovafloxacin, pefloxacin, prulifloxacin)

Emtree terms, similar to medical subject headings (MeSH), are hierarchical terms used to index EMBASE content.

We retrieved and reviewed in detail all relevant English-language case reports. Articles published in non-English-language journals were retained in our analysis if the abstract was available in English. Abstracts translated into English were included in the literature review if sufficient data were provided to evaluate its relevance. Any article containing a case report of fluoroquinolone-associated myasthenia gravis exacerbation, regardless of FDA approval status (i.e. pefloxacin, prulifloxacin), was retained for inclusion as a literature case. We did not limit our case search to FDA-approved drugs because we suspected myasthenia gravis exacerbation was a drug class effect and sought to collect data on any globally available fluoroquinolone.

Our analysis differentiates literature derived from AERS cases as we found the published cases generally provided clinical and laboratory details often missing from AERS reports. Additionally, as some literature cases were also reported to the AERS, this approach avoided double counting of cases. We analysed published case reports submitted to the AERS as literature cases.

Results

Using our case definition, we retrieved AERS reports for 27 patients and 9 published case reports describing 10 patients, including one abstract translated into English. Table II summarizes selected demographic and clinical characteristics for these 37 patients. Exacerbations of myasthenia gravis generally developed within 1 day of systemic fluoroquinolone exposure in all patients. No cases were associated with non-systemic (e.g. ophthalmic) fluoroquinolone exposure, pregnancy or parturition.

All of our cases were temporally associated with fluoroquinolone administration. Positive

Table II. Selected demographic and clinical characteristics for fluoroquinolone-treated patients who developed acute exacerbations of myasthenia gravis

Parameter	Patients identified from US FDA AERS search [n = 27]	Patients identified from published case reports [n = 10]
Age (y)		
Mean ± standard deviation	61.7 ± 19.1	54.7 ± 19.6
Median (range)	63.5 (26–88)	47 (25–79)
Sex [n (%)]		
Male/female	10 (37.0)/17 (63.0)	3 (30)/7 (70)
Country of origin [n (%)]		
US/non-US	17 (63)/10 (37)	1 (10)/9 (90)
History of myasthenia gravis [n (%)]		
Myasthenia gravis	19 (70.4)	7 (70)
None or not reported	8 (29.6)	3 (30)
Myasthenia gravis exacerbating concomitant medications [n (%)]		
Anti-infectives	2 (7.4)	0 (0)
Corticosteroids	6 (22.2)	4 (40)
Unknown/missing data in report	12 (44.4)	3 (30)
None or no concomitant exacerbating medication	7 (25.9)	3 (30)
Myasthenia gravis exacerbating medical disorders [n (%)]		
Thymic disease (thymoma or thymectomy)	3 (11.1)	2 (20)
Thyroid disorder (thyroiditis)	0 (0)	1 (10)
Autoimmune disorders (rheumatoid arthritis)	1 (3.7)	1 (10)
Recent surgery	1 (3.7)	0 (0)
Pregnancy or childbirth	0 (0)	0 (0)
Unknown/missing data in report	2 (7.4)	0 (0)
None or no concomitant exacerbating disorders	20 (74)	6 (60)
Primary suspect fluoroquinolone [n (%)]		
Ciprofloxacin	6 (22.2)	4 (40)
Gatifloxacin	2 (7.4)	0 (0)
Levofloxacin	9 (33.3)	2 (20)
Moxifloxacin	6 (22.2)	0 (0)
Norfloxacin	1 (3.7)	1 (10)
Ofloxacin	2 (7.4)	1 (10)
Pefloxacin	0 (0)	1 (10)
Prulifloxacin	0 (0)	1 (10)
Trovafloxacin	1 (3.7)	0 (0)
Onset latency		
Mean ± standard deviation (days)	1.5 ± 2.1	2.6 ± 2.4
Median [d (range)]	1 (0.5 h–10 days)	2 (1 h–8 days)

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Table II. Contd

Parameter	Patients identified from US FDA AERS search [n = 27]	Patients identified from published case reports [n = 10]
Indication for fluoroquinolone [n (%)]		
Respiratory tract infection[a]	15 (55.6)	4 (40)
Urinary tract infection or procedure[b]	4 (14.8)	4 (40)
Other/not reported	8 (29.6)	2 (20)
Impairment of spontaneous respiratory effort [n (%)]		
Dyspnoea or shortness of breath	14 (52)	5 (50)
Mechanical ventilation required	8 (30)	3 (30)
Treatment interventions[c] [n (%)]		
Discontinue or reduce dose of fluoroquinolone	12 (44.4)	4 (28.6)
Acetylcholinesterase inhibitor	5 (18.5)	6 (42.9)
Corticosteroids	4 (14.8)	4 (28.6)
Other	5 (18.5)	0 (0)
Mortality and rechallenge cases [n (%)]		
Deaths (all-cause mortality)	1 (3.7)	1 (10)
Positive rechallenge cases[d]	4 (14.8)	2 (20)

a Respiratory tract infections include bronchitis, cold-like symptoms, pneumonia, sinusitis and otitis media.

b Urinary tract infections include cystitis, prostatitis, urosepsis and urinary tract infections.

c Treatment interventions are not mutually exclusive; many were combined.

d Re-exacerbation of myasthenic symptoms following reintroduction of a fluoroquinolone in patients whose initial symptomatic episode abated after fluoroquinolone withdrawal.

AERS = Adverse Event Reporting System.

rechallenge was reported in 4 of the 27 AERS cases (15%) and 2 (20%) of the 10 published cases. The rechallenge cases involved multiple fluoroquinolones (moxifloxacin, ciprofloxacin, ofloxacin and norfloxacin). The six positive rechallenge patients rapidly improved when additional doses were withheld following reintroduction of the fluoroquinolone. Three of the six cases were rechallenged more than once and experienced acute symptomatic myasthenia gravis exacerbations following each rechallenge. One of these three patients required intubation for myasthenic crisis.

FDA AERS Cases

The 27 AERS cases occurred predominantly in female patients, with a median age in the overall cohort of 63.5 years (range 26–88 years; approximately 70% of patients had pre-existing myasthenia gravis) [table II]. The majority of the reports (17 patients; 63%) were from the US. In many cases, proximal or concomitant medications included acetylcholinestaerase inhibitors and corticosteroids. Five (18.5%) patients had a history of thymic disorders, recent surgery or other autoimmune disease that could precipitate or worsen myasthenia gravis. Acetylcholine receptor antibody status was reported in only one case. Respiratory or urinary tract infections (19 patients; 70%) were the most common indications for fluoroquinolone treatment (table II). The dosages prescribed for the fluoroquinolones were consistent with the dosing guidelines contained in the package insert for each product. Myasthenia gravis exacerbations tended to occur within a median of 1 day (range 0.5 hours–10 days). None of the patients received aminoglycosides or other non-fluoroquinolone antimicrobials that have the potential to affect transmission at the neuromuscular junction.

Dyspnoea, the most frequently reported exacerbation complaint, was observed in 14 patients (52%). Eight patients progressed to respiratory failure requiring mechanical ventilation and one patient died (cause undetermined). Other less frequently reported adverse events were muscle weakness or fatigue (13/27; 48%), dysphagia (5/27;

19%), diplopia (3/27; 11%) and ptosis (1/27; 4%). Seventeen (63%) of the cases documented an adverse event that resulted in or prolonged hospitalization.

For reports citing an outcome after fluoroquinolone cessation, nearly all (17/18; 94%) patients improved when the fluoroquinolone dose was reduced or withdrawn in conjunction with other interventions, including acetylcholinesterase inhibitors, corticosteroids or other treatments. Ten of these cases reported an improvement in exacerbation-related symptoms, with a reduction in, or elimination of, fluoroquinolone exposure alone. For patients where time to symptom resolution was reported, most (9/10; 90%) showed a rapid improvement (within 24 hours). Seventeen cases did not report a specific recovery time; one case cited a recovery lasting several weeks after medical intervention. Overall, however, the rate at which these patients improved was inconsistently reported, making a quantitative estimate of recovery time problematic.

Literature Cases

Characteristics of the ten patients described in the published case reports[16-24] were similar to those of the AERS cases: the majority of patients were female, patients were of a similar age and most had a history of myasthenia gravis (table II). Eight (80%) were treated with fluoroquinolones for a respiratory or urinary tract infection. Myasthenia gravis exacerbations generally developed 2 days following fluoroquinolone exposure, 1 day later than the latency period reported for the AERS cases. Five patients (50%) experienced dyspnoea, three (30%) developed ventilator-dependent respiratory failure and one died. Generalized muscle weakness was the most frequently observed event (7/10; 70%) followed by ptosis (5/10; 50%), dysphagia (4/10; 40%) and diplopia (3/10; 30%). The patients responded to similar treatment interventions as those cited in the AERS cases. Seven (70%) of the literature cases documented an adverse event resulting in or prolonging hospitalization. Acetylcholine receptor antibody status was provided as present in two cases.

Nearly all (9/10; 90%) patients improved when the fluoroquinolone dose was reduced or withdrawn in conjunction with additional treatment options such as acetylcholinesterase inhibitors or corticosteroids. One (10%) patient improved after discontinuing the fluoroquinolone independent of other treatment modalities. Five cases did not provide recovery time, two described rapid improvement as immediate or within 8 hours, another two reported symptom improvement or resolution within 48 hours and one additional case characterized recovery within days.

Discussion

We report cases of acute myasthenia gravis exacerbation in fluoroquinolone-exposed patients supporting a causal association based on biological plausibility, temporal association, and positive dechallenge and rechallenge data. Our combined AERS and literature-based case series shows that myasthenic symptoms frequently developed soon after systemic fluoroquinolone exposure. Many patients exhibited a positive dechallenge with fluoroquinolone cessation, although this was usually in the context of additional treatment measures (e.g. acetylcholineserase inhibitors or corticosteroids). Additionally, we identified six positive rechallenge cases in which symptoms of myasthenia gravis recurred promptly following reintroduction of the fluoroquinolone. Although underlying medical illnesses (such as infections) may predispose to development of myasthenia gravis exacerbation and confound causality assessments, clinical recovery following fluoroquinolone withdrawal in the presence of ongoing infections suggests that the acute exacerbation was likely related to fluoroquinolone exposure. We believe that myasthenia gravis exacerbation with systemic fluoroquinolone exposure is a class effect supported by our review findings citing nine different fluoroquinolones.

Biological plausibility of the drug-disease interaction is supported by the work of Deng et al.[9] and Sieb et al.;[10,12] however, the exact causal pathway has not been fully elucidated. Deng et al.[9] propose that fluoroquinolones can chelate ionized calcium and inhibit acetylcholine release pre-synaptically to attenuate neuromuscular transmission. In contrast, Sieb[10] postulated that fluoroquinolones can promote neuromuscular blockade

via a pre- or postsynaptic mechanism, and that quinolones can have a direct toxic effect on the acetylcholine ion channel. Taken together, their work demonstrates the neuromuscular blocking potential of five different fluoroquinolones; Sieb[10] also showed that this effect is dose dependent. Our case series generally shows a short latency period following initial fluoroquinolone exposure and rapid improvement after drug withdrawal, which is mechanistically consistent with rapid CNS accumulation and clearance of the drug. Swift onset and improvement after withdrawal better support a blockade of or direct toxic effect to the acetylcholine receptor rather than an autoimmune process such as that associated with some drugs (e.g. penicillamine).

The potential toxic effect of a fluoroquinolone on the neuromuscular junction has been described in a neuromuscular disorder other than myasthenia gravis. A report by Schottland[25] describes neuromuscular blockade attributed to ofloxacin in a patient with Lambert-Eaton syndrome, a rare, pre-synaptic, myasthenic syndrome associated with lung malignancy.

Limitations of our analysis include the following considerations. Our case series is based primarily on voluntary reports with insufficient information to quantify risk. Additionally, spontaneous adverse event reporting to the AERS is generally subject to underreporting, variable reporting quality, reporting biases (which potentially include misattribution of causality) and substantial missing data. A robust causality assessment is also confounded by other factors such as concomitant medications and concurrent diseases with the potential to induce myasthenia gravis exacerbation independent of fluoroquinolone exposure. We did not find a published standardized definition for acute myasthenia gravis exacerbation, but developed a case definition compatible with accepted clinical indicators of exacerbation, most notably progressive respiratory insufficiency and generalized weakness. Although our case definition did not include quantifiably objective measures of disease severity, a substantial proportion of the patients experienced respiratory failure requiring mechanical ventilation indicative of the potentially life-threatening nature of the acute exacerbation.

We believe that fluoroquinolone-associated myasthenia gravis exacerbation is a preventable drug-related adverse event. Our study shows that some patients with relatively uncomplicated infections were prescribed fluoroquinolones for which the use of an alternative antibacterial agent may have been a safer option. For example, in myasthenic patients who do not require concurrent immunosuppressive therapy for symptomatic control of their disease, it may be safer to use alternative antibacterial agents to treat uncomplicated respiratory tract infections (i.e. bronchitis) or lower urinary tract infections (i.e. cystitis). Recent evidence suggests that fluoroquinolones continue to be overprescribed in the primary care setting,[26] a practice that generally places patients at increased risk for serious adverse events. Avoidance of fluoroquinolones in patients with myasthenia gravis will likely reduce the occurrence of life-threatening respiratory failure and other complications associated with myasthenia gravis exacerbation.

As our case series observations are based on voluntary reports, we cannot comment on the incidence of, or risk for, myasthenia gravis exacerbation due to fluoroquinolone exposure. A well designed observational study is better suited to address the relative risk of exacerbation among different fluoroquinolones or enable a comparison of risk differences between fluoroquinolone versus non-fluoroquinolone antibacterial agents. Such a study could also be used to inform estimates of absolute risk of exacerbation among myasthenic patients exposed to a fluoroquinolone. The primary purpose of our study was to promote awareness of a drug-related safety event; more rigorous methods are needed to characterize the risks and inform fluoroquinolone prescribing in myasthenic patients.

Healthcare professionals can affect the safe use of fluoroquinolones in patients with myasthenia gravis. Prescribers and pharmacists should be aware of the potential risk of fluoroquinolone-associated myasthenia gravis exacerbation in susceptible patients. Prescribers should choose the most appropriate antibacterial treatment under the circumstances; prescribers and pharmacists should counsel at-risk patients accordingly. In some instances, prescribers may determine that the benefits of fluoroquinolone treatment

outweigh the risk of exacerbation. This recommendation should be informed by the seriousness of the infection, as well as by the possibility of myasthenia gravis exacerbation associated with other antibacterials such as macrolides, tetracyclines, ketolides and the aminopenicillins. Unfortunately, the risk of myasthenia gravis exacerbation with a fluoroquinolone compared with other implicated antibacterials is unknown.

Conclusions

To our knowledge this is the largest cases series in the published English-language scientific literature describing fluoroquinolone-associated myasthenia gravis exacerbation. The preponderance of the evidence from the AERS case series, published case reports and preclinical studies supports a causal association for this drug-adverse event combination. Additional studies are necessary to further characterize the association and to quantify the risk.

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References

1. Wittbrodt ET. Drugs and myasthenia gravis: an update. Arch Intern Med 1997; 157: 399-408
2. UpToDate. Pathogenesis of myasthenia gravis [online]. Available from URL: http://www.uptodate.com/online/content/topic.do?topicKey=muscle/2054&selectedTitle=1%7E150&source=search_result [Accessed 2010 Sep 20]
3. McGrogan A, Sneddon S, de Vries CS. The incidence of myasthenia gravis: a systematic review of the literature. Neuroepidemiology 2010; 34: 171-83
4. Meyer A, Levy Y. Geoepidemiology of myasthenia gravis. J Autoimmun Rev 2010; 9: A383-6
5. Heldal AT, Owe JF, Gilhus NE, et al. Seropositive myasthenia gravis: a nationwide epidemiology study. Neurology 2009; 73 (2): 150-1
6. Myasthenia Gravis Foundation of America, Inc. Clinical overview of MG. Myasthenia gravis: a summary [online]. Available from URL: http://www.myasthenia.org/hp_clinicaloverview.cfm [Accessed 2011 Apr 6]
7. Myasthenia Gravis Foundation of America, Inc. Medications and myasthenia gravis (a reference for health care professionals) [online]. Available from URL: http://www.myasthenia.org/LinkClick.aspx?fileticket=JuFvZPPq2vg%3d [Accessed 2011 Mar 18]
8. Barrons RW. Drug-induced neuromuscular blockade and myasthenia gravis. Pharmacotherapy 1997; 17 (6): 1220-32
9. Deng M, Wang YF, Hu F, et al. Effect of different kinds of antibiotics on transmission function at the neuromuscular junction in mice with myasthenia gravis. Chin J Clin Rehabil 2005; 9 (17): 233-5
10. Sieb JP. Fluoroquinolone antibiotics block neuromuscular transmission. Neurology 1998; 50: 804-7
11. Maddix DS, Stefani S. Myasthenia gravis and ciprofloxacin [letter]. Ann Pharmacother 1992; 26: 265
12. Sieb JP, Milone M, Engel AG. Effects of the quinolone derivatives quinine, quinidine and chloroquine on neuromuscular transmission. Brain Res 1996; 712: 179-89
13. Robberecht W, Bednarik J, Bourgeois P, et al. Myasthenic syndrome caused by direct effect of chloroquine on neuromuscular junction. Arch Neurol 1989; 46 (4): 464-8
14. Kornfield P, Horowitz SH, Genkins G, et al. Myasthenia gravis unmasked by antiarrhythmic agents. Mt Sinai J Med 1976; 43 (1): 10-4
15. US FDA. United States code of federal regulations title 21, section 314.80. Postmarketing reporting of adverse drug experiences [online]. Available from URL: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=314.80 [Accessed 2011 Apr 7]
16. Rossi M, Lusini G, Biasella A, et al. Prulifloxacin as a trigger of myasthenia gravis. J Neurol Sci 2009; 280: 109-10
17. Moore B, Safani M, Keesey J. Possible exacerbation of myasthenia gravis by ciprofloxacin [letter]. Lancet 1988; 1 (8590): 882
18. Rauser EH, Ariano RE, Anderson BA. Exacerbation of myasthenia gravis by norfloxacin. DICP 1990; 24: 207-8
19. Mumford CJ, Ginsberg L. Ciprofloxacin and myasthenia gravis [letter]. BMJ 1990; 301 (6755): 818
20. Azevedo E, Ribeiro JA, Polonia J, et al. Probable exacerbation of myasthenia gravis by ofloxacin [letter]. J Neurol 1993; 240 (8): 508
21. Vial T, Chauplannaz G, Brunel P, et al. Exacerbation of myasthenia gravis by pefloxacin. Rev Neurol 1995; 151 (4): 286-7
22. Roquer J, Cano A, Seoane JL, et al. Myasthenia gravis and ciprofloxacin. Acta Neurol Scand 1996; 94 (6): 419-20
23. Gunduz A, Turedi S, Kalkan A, et al. Levofloxacin induced myasthenia crisis [letter]. Emerg Med J 2006; 23 (8): 662
24. Nemoto K, Beppu H, Yagi K. Exacerbation of myasthenia gravis: possible adverse effect of levofloxacin [letter]. Neurol Med (Shinkei Naika) 1997; 46: 443
25. Schottland JR. Ofloxacin in the Lambert-Eaton syndrome [letter]. Neurology 1999; 52 (2): 435
26. Altiner A, Wilm S, Wegscheider K, et al. Fluoroquinolones to treat uncomplicated acute cough in primary care: predictors for unjustified prescribing of antibiotics. J Antimicrob Chemother 2010; 65: 1521-5

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