RELIAS MEDIA

Internal Medicine

Evidence-based summaries of the latest research in internal medicine [ALERT]

Vol. 41, Issue 19, October 15, 2019
ReliasMedia.com

ABSTRACT & COMMENTARY

NOACs vs. Warfarin: What Are the Data in Patients With Traumatic Brain Injury and Intracranial Hemorrhage?

By Kathryn Radigan, MD

Attending Physician, Division of Pulmonary and Critical Care, Stroger Hospital of Cook County, Chicago

Dr. Radigan reports no financial relationships relevant to this field of study.

SYNOPSIS: A three-year analysis of a prospectively maintained database with traumatic brain injury patients revealed that novel oral anticoagulant use is associated with increased risk of intracranial hemorrhage progression, neurosurgical intervention, and mortality.

SOURCE: Zeeshan M, Jehan F, O'Keeffe T, et al. The novel oral anticoagulants (NOACs) have worse outcomes compared with warfarin in patients with intracranial hemorrhage after TBI. *J Trauma Acute Care Surg* 2018;85:915-920.

Despite the increasing use of novel oral anticoagulants (NOACs), emergent reversal of these agents remains a management challenge. There are few data comparing the use of NOACs to warfarin in patients with intracranial hemorrhage (ICH) after traumatic brain injury (TBI). Zeeshan et al conducted a three-year analysis of their prospectively maintained database examining the outcomes after TBI in patients taking NOACs compared to those taking warfarin. Researchers analyzed all adult trauma patients admitted to a single level 1 trauma center with a diagnosis of TBI. Inclusion criteria were all adult TBI patients with ICH on initial head CT scans who received anticoagulation prior to injury. Anticoagulants included warfarin or NOACs, including direct thrombin inhibitors (dabigatran) and oral direct factor Xa inhibitors (rivaroxaban and apixaban). Patients with documented bleeding diathesis, chronic liver disease, penetrating mechanisms of injury, or those who died within 24 hours of trauma were excluded. The primary outcomes were ICH progression and the need for surgical intervention. Progression was defined as an increase in the size of an existing hemorrhage or development of a new hemorrhage not previously seen on CT scans. The need for surgical intervention was defined as intracranial pressure monitoring, craniotomy, or craniectomy that was performed

Financial Disclosure: *Internal Medicine Alert's* Physician Editor Stephen Brunton, MD, is a retained consultant for Abbott, Acadia, Allergan, AstraZeneca, Avadel, Boehringer Ingelheim, GlaxoSmithKline, Janssen, Mylan, and Salix; he serves on the speakers bureau of AstraZeneca, Boehringer Ingelheim, Janssen, Lilly, and Novo Nordisk. Peer Reviewer Gerald Roberts, MD; Editor Jonathan Springston; Editor Jason Schneider; Editorial Group Manager Leslie Coplin; and Accreditations Manager Amy M. Johnson, MSN, RN, CPN, report no financial relationships relevant to this field of study.

[INSIDE]

Neuropathy and Total Knee Arthroplasty page 147

Neuropathy and Fluoroquinolones page 148

When Did You Last Take an Antibiotic? page 149

Pharmacology Update: Wakix page 150

Internal Medicine
Evidence-based summaries of the latest research in internal medicine [ALERT]

Internal Medicine Alert (ISSN 0195-315X) is published semimonthly by Relias LLC, 1010 Sync St., Ste. 100, Morrisville, NC 27560-5468. Periodicals postage paid at Morrisville, NC, and additional mailing offices. POSTMASTER: Send address changes to *Internal Medicine Alert*, Relias LLC, 1010 Sync St., Ste. 100, Morrisville, NC 27560-5468.

GST Registration Number: R128870672.

SUBSCRIBER INFORMATION
(800) 688-2421
customerservice@reliasmedia.com
ReliasMedia.com

ACCREDITATION
Relias LLC is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

Relias LLC designates this enduring material for a maximum of 2 *AMA PRA Category 1 Credit(s)™*. Physicians should claim only credit commensurate with the extent of their participation in the activity.

This Enduring Material activity, *Internal Medicine Alert*, has been reviewed and is acceptable for credit by the American Academy of Family Physicians. Term of approval begins 1/15/2019. Term of approval is for one year from this date. Physicians should claim only the credit commensurate with the extent of their participation in the activity. Approved for 2 AAFP Prescribed credits.

The American Osteopathic Association has approved this continuing education activity for up to 2 AOA Category 2-B credits.

Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 2 MOC Medical Knowledge points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit.

This CME activity is intended for the internist/family physician. It is in effect for 36 months from the date of the publication.

because of ICH progression. Secondary outcomes included complications in the hospital, discharge to rehabilitation hospital or skilled nursing facility (SNF), hospital and ICU length of stay, and in-hospital mortality.

From the 1,459 eligible patients, 210 matched TBI patients were identified (70 patients on NOACs and 140 patients on warfarin). The matched groups were similar in age ($P = 0.21$), the Glasgow Coma Scale (GCS) score ($P = 0.54$), the mechanism of injury ($P = 0.61$), the Injury Severity Score ($P = 0.62$), and type and size of ICH ($P = 0.09$). Compared to patients on warfarin, patients who had been treated with NOACs prior to injury exhibited a higher rate of progression ($P = 0.03$), neurosurgical intervention ($P = 0.04$), mortality ($P = 0.04$), and longer ICU length of stay ($P = 0.04$). There was no difference in hospital length of stay ($P = 0.22$) or SNF disposition ($P = 0.14$). A subanalysis for severe TBI patients (defined as GCS score ≤ 8) revealed no difference in rate of progression ($P = 0.59$), neurosurgical intervention ($P = 0.62$), or mortality ($P = 0.81$). NOAC use was associated with an increased risk of ICH progression, neurosurgical intervention, and mortality after mild and moderate TBI. It is important to carefully keep these risks in mind when deciding on the optimal form of anticoagulation for each patient.

■ COMMENTARY

Patients on oral antithrombotics are at increased risk of ICH after trauma.[1] Although vitamin K antagonists have been the only class of oral anticoagulants available for decades, clinicians may substitute NOACs for warfarin because of the ease of use. NOACs onset rapidly; there are fewer drug interactions, no dietary limitations, and no laboratory monitoring requirements; and the pharmacokinetics are predictable.[2] The difficulty in NOAC reversal in cases of serious, life-threatening hemorrhage (especially from ICH after TBI) remains an important clinical concern in the setting of growing use of these agents.

The findings of Zeeshan et al underscore this problem, revealing that prior NOAC use was associated with a higher risk of ICH progression, neurosurgical intervention, and mortality after a mild and moderate TBI when compared to similar patients receiving warfarin. Previous data regarding the outcomes of TBI patients on NOACs were published by Kobayashi et al and conducted by the American Association for the Surgery of Trauma.[3] Although in this study, Kobayashi et al found that TBI patients on NOACs were not at higher risk of ICH, ICH progression, or death, the study population was substantially different. These investigators included all trauma patients admitted to the hospital on prior dabigatran, rivaroxaban, apixaban, warfarin, aspirin, or clopidogrel. In the study by Kobayashi et al, only 30% of the patients showed ICH on presentation, while ICH was an inclusion criterion in the Zeeshan et al study. The Kobayashi et al study also included lower rates of subdural hematoma (SDH; 19% vs. 30%) and older patients with a lower Injury Severity Score. An additional limitation to the study was that only 10% of the study population was taking a NOAC.

Although NOACs often are favored for their attractive pharmacokinetic qualities previously discussed, the reversal tactics for these novel agents are evolving.[4] Ideally, most forms of anticoagulation include a specific reversal agent or antidote for episodes of serious or life-threatening bleeding. Dabigatran's reversal agent is idarucizumab, but this anti-dabigatran monoclonal antibody fragment often is unavailable to many because of its cost.[5] Andexanet alfa recently was approved as a reversal agent for the oral direct factor Xa inhibitors (apixaban, betrixaban, edoxaban, and rivaroxaban), but again, it is costly with limited availability. There are other promising antidotes under development, including a small molecule antidote, PER977, and a mutant form of factor Xa, FXa(I16L), but they are not available. Thus, clinicians often are left with less targeted interventions, such as four-factor prothrombin complex concentrate and fresh frozen plasma in this setting.

The use of NOACs will continue to rise. Critical care providers should ensure that their hospitals maintain a systematic protocol to treat patients receiving these agents who present with life-threatening or uncontrolled bleeding. Although the Zeeshan et al study appears to have been more deliberate in addressing the question of NOAC vs. warfarin in TBI, there were limitations. The study was a single-center, observational study without a true control

group. Because it was an observational study, there was an association between NOAC use and increased risk of progression of ICH, neurosurgical intervention, and mortality after mild and moderate TBI, but causation cannot be assigned. There also is concern for sampling bias, since the institution was a level 1 trauma center serving as a quaternary referral hospital. Although the authors reported the details of the reversal agents (fresh frozen plasma, prothrombin complex concentrate, vitamin K), the results of these data points were not mentioned again throughout the manuscript. Not knowing the frequency, timing, or type of reversal agent for each case is a major limitation. Despite these limitations, this study challenges a provider to balance risks and benefits of a particular anticoagulant carefully and to be ready to intervene with rapid recognition and reversal in patients with ICH. These findings also highlight the need for future larger, multicenter studies to further explore the outcomes of patients on NOACs after TBI. ■

REFERENCES

1. Siracuse JJ, Robich MP, Gautam S, et al. Antiplatelet agents, warfarin, and epidemic intracranial hemorrhage. *Surgery* 2010;148:724-729; discussion 729-730.
2. Verdecchia P, Angeli F, Aita A, et al. Why switch from warfarin to NOACs? *Intern Emerg Med* 2016;11:289-293.
3. Kobayashi L, Barmparas G, Bosarge P, et al. Novel oral anticoagulants and trauma: The results of a prospective American Association for the Surgery of Trauma Multi-Institutional Trial. *J Trauma Acute Care Surg* 2017;82:827-835.
4. Dzeshka MS, Pastori D, Lip GYH. Direct oral anticoagulant reversal: How, when and issues faced. *Expert Rev Hematol* 2017;10:1005-1022.
5. Levy JH, Douketis J, Weitz JI. Reversal agents for non-vitamin K antagonist oral anticoagulants. *Nat Rev Cardiol* 2018;15:273-281.

ABSTRACT & COMMENTARY

Neuropathy After Total Knee Arthroplasty

By Michael Rubin, MD

Professor of Clinical Neurology, Weill Cornell Medical College

Dr. Rubin reports he is a consultant for Merck Sharp & Dohme Corp.

SYNOPSIS: In a large series of cases from the Mayo Clinic, 54 cases of new neuropathy occurred in 14,450 total knee arthroplasties. Most were isolated peroneal neuropathies. No specific risk factors were identified.

SOURCE: Speelziek SJA, Staff NP, Johnson RL, et al. Clinical spectrum of neuropathy after primary total knee arthroplasty: A series of 54 cases. *Muscle Nerve* 2019;59:679-682.

Total knee arthroplasty (TKA) is expected to reach 2,854 procedures per 100,000 population by 2050. Although it is considered safe and effective for end-stage arthritis of the knee, complications occur during and after TKA, including myocardial infarction, thromboembolism, tourniquet-related ischemic injury, arterial injury, and neuropathy, most commonly peroneal nerve palsy. What is the spectrum and frequency of neuropathy following TKA, what are their clinical and electrophysiological features, and what is their mechanism of injury (mechanical, inflammatory, or both)?

In a retrospective review, Speelziek et al identified all patients ≥ 18 years of age who underwent TKA at Mayo Clinic Rochester between Jan. 1, 1996, and Sept. 30, 2016, and developed neuropathy within eight weeks of surgery. Exclusionary criteria included patients with pre-existing neuropathy, active radiculopathy, or central nervous system issues, which precluded accurate examination and evaluation. The review encompassed anesthesia type; findings on clinical, electrophysiologic, and radiologic studies; tourniquet time; and time to motor recovery. Among 14,450 TKAs performed during the study period, 54 instances of new neuropathy were identified in 53 patients, for a neuropathy incidence of 0.37%. Mean age was 65.2 years; 41 patients were female; postoperative day 2 was the mean time of neuropathy symptom onset (with a range of 0-28 days); and almost all were mononeuropathies of the ipsilateral limb (with one patient exhibiting both peroneal and tibial mononeuropathies). Over a mean of 10.1 months, but ranging from two to 136 months, complete or almost complete recovery occurred in all but one patient who appreciated no recovery. Four patients were lost to follow-up.

Peroneal neuropathy, presenting as foot drop, nonfocal in eight of 10 patients studied electrodiagnostically, was the most common form of post-TKA neuropathy, seen in 37 patients, followed by sciatic neuropathy in 11, tibial or ulnar neuropathy in two patients each, and sural or lumbosacral plexopathy in one patient each. Sciatic neuropathy was localized proximal to the short head of biceps femoris in four studies and distally in three studies, with two studies limited to nerve conduction studies only, precluding localization, and one additional study that was normal. Tibial neuropathy presented with tingling or hyperesthesia of the sole or toes, with impaired Achilles reflex and ankle inversion weakness. Diffuse progressive neuropathic pain and weakness of the ipsilateral leg were the features of the single instance

of post-TKA lumbosacral plexopathy. A 67-year-old woman responded to IV methylprednisolone after she was refractory to opiates, with significant improvement over the treatment period. Overall, for tourniquet time longer than 100 minutes (a time generally associated with an increased risk of complications), mean motor recovery time was 11.8 months, ranging from 7.9-15.7 months. For tourniquet time less than 100 minutes, mean motor recovery time was 8.1 months, ranging from 5.1-11.0 months, a nonsignificant difference due to a large standard deviation in each group. No correlation with type of anesthesia was evident. Inflammatory origin of post-TKA neuropathy, as evidenced by the single instance of lumbosacral plexopathy, was extremely rare.

■ COMMENTARY

Combined general and spinal epidural anesthesia is used commonly for bilateral TKA, with accidental dural puncture occurring in 0.19-3.6%. Cranial nerve palsy is a rare complication of dural puncture, but both abducens nerve palsy and oculomotor nerve palsy have been reported following accidental dural puncture during bilateral total knee replacement. In either instance, reassurance of the patient is important as most cranial nerve palsies following dural puncture resolve within one to four weeks. Following total hip arthroplasty, foot drop also is the most common neurologic complication, but due to sciatic nerve injury, with the peroneal division more commonly and severely affected than the tibial. ■

ABSTRACT & COMMENTARY

Risk of Neuropathy With Fluoroquinolones

By Michael Rubin, MD

Professor of Clinical Neurology, Weill Cornell Medical College

Dr. Rubin reports he is a consultant for Merck Sharp & Dohme Corp.

SYNOPSIS: As a class, fluoroquinolones are some of the most commonly used antibiotics worldwide. Their use carries a significant risk of neurotoxicity, for both the peripheral and central nervous system.

SOURCE: Morales D, Pacurariu A, Slattery J, et al. Association between peripheral neuropathy and exposure to oral fluoroquinolone or amoxicillin-clavulanate therapy. *JAMA Neurol* 2019;76:827-833.

Fluoroquinolones, commonly used to treat respiratory, gastrointestinal, and urinary tract infections, include (among others) ciprofloxacin (Cipro), levofloxacin (Levaquin), and moxifloxacin (Avelox). Side effects include gastritis, hepatotoxicity, QT interval prolongation, and (among its most common adverse effects) altered mental status and neuropathy, including mononeuropathy, multiple mononeuropathy, and polyneuropathy. What are the risk estimates for polyneuropathy with fluoroquinolone exposure? What factors are associated with this risk?

Using The Health Improvement Network (THIN) database, covering approximately 6% of the United Kingdom population from more than 500 general medical practices, a nested case-control study design was used to evaluate the risk of incident peripheral neuropathy. Investigators included adults who were in the THIN database between Jan. 1, 1999, and Dec. 31, 2015. These adults were ≥ 18 years of age and were issued at least one prescription of oral amoxicillin-clavulanate (controls) or oral fluoroquinolone antibiotic therapy. The authors chose amoxicillin-clavulanate so that controls were sampled from a more representative population prescribed antibiotics. Patients with a history of neuropathy or diabetes were excluded. At least one year of observation prior to cohort entry was required of all participants. Cohort exit was defined as outcome occurrence, death, deregistration from the practice, end of study period, or date of last data collection from the general practice. Cumulative antibiotic exposure was measured as the total number of days of oral fluoroquinolone or oral amoxicillin-clavulanate exposure within each risk window. Cumulative days of exposure was calculated by dividing the prescription quantity information by the standard administration schedules for each antibiotic. Adults with incident peripheral neuropathy were matched with up to four controls using incidence density sampling, selected from a cohort prescribed oral fluoroquinolone or amoxicillin-clavulanate antibiotics. Statistical analysis included conditional logistic regression, sensitivity analyses, and multiple imputation, with a two-sided $P < 0.05$ considered statistically significant.

Among 1,338,900 adults issued one or more prescriptions of fluoroquinolone (34.3%) or amoxicillin-clavulanate (65.7%) (mean age, 52.8 years; 57% female) without a diagnosis of peripheral neuropathy at cohort entry, 11,224 incident peripheral neuropathy cases were identified and matched to 42,316 controls. Those with diabetes were identified and excluded, leaving 5,357 incident peripheral neuropathy cases (mean age, 65.6 years; 2,809 women) matched to 17,285 controls (mean age, 64.4 years; 9,485 women). Median duration of exposure was 10 days for fluoroquinolone and seven days

for amoxicillin-clavulanate, with risk of neuropathy calculated as increased by 3% for each additional day of current fluoroquinolone exposure, the risk persisting for up to 180 days following exposure. No significant increased risk was observed with exposure to oral amoxicillin-clavulanate. Absolute risk with oral fluoroquinolone exposure was 2.4 per 10,000 patients per year of use, with number needed to harm for a 10-day course being 152,083 patients, greatest among men and those > age 60 years.

■ COMMENTARY

In use for more than 30 years, and currently among the most widely prescribed antibiotics worldwide (representing 10% of prescriptions per 1,000 population in 2015 in the United States alone), fluoroquinolones have been associated with significant side effects in susceptible individuals. Historically, these have included peripheral neuropathy, photosensitivity, prolonged QT interval, hypoglycemia, and tendon rupture. More recently, the FDA has extended these warnings to include a risk of aortic dissection, thus recommending avoidance of these drugs in patients with peripheral vascular disease, uncontrolled hypertension, vasculitides, and connective tissue disorders (e.g., Ehlers-Danlos syndrome). In addition to tendon rupture, there is an increased risk of tendonitis; myalgia; muscle weakness; arthralgia and joint swelling; neuropsychiatric issues, encompassing psychosis, anxiety, insomnia, depression, hallucinations, suicidal thoughts, confusion; and impairment of vision, hearing, smell, and taste. Transplant recipients, those with renal dysfunction, older patients, and those receiving concomitant corticosteroids, are at higher risk. Lastly, a fibromyalgia-like syndrome, termed fluoroquinolone-associated disability syndrome, has been associated with these antibiotics. However, the risk of fibromyalgia with fluoroquinolone is similar to that with amoxicillin and azithromycin; thus, the antibiotic is not likely causative.[1,2] ■

REFERENCES

1. Richards GA, Brink AJ, Feldman C. Rational use of the fluoroquinolones. *S Afr Med J* 2019;109:378-381.
2. Ganjizadeh-Azvareh S, Sodhi M, Spangehl T, et al. Oral fluoroquinolones and risk of fibromyalgia. *Br J Clin Pharmacol* 2019;85:236-239.

ABSTRACT & COMMENTARY

When Did You Last Take an Antibiotic?

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University

Dr. Deresinski reports no financial relationships relevant to this field of study.

SYNOPSIS: Approximately half of U.S. residents with health insurance filled an antibiotic prescription over a two-year period.

SOURCE: Olesen SW, MacFadden D, Grad YH. Cumulative probability of receiving an antibiotic prescription over time. *N Engl J Med* 2019;380:1872-1873.

Using the Truven Health MarketScan Research databases, Olesen et al assessed the probability that enrollees comprising approximately one-fifth of the U.S. population received an antibiotic prescription filled at an outpatient pharmacy during 2011 through 2014. During those years, 100 million claims for outpatient antibiotic prescriptions were made for the 62 million enrollees in health insurance plans. Consistent with their previous work, researchers found that 33% of the cohort filled an antibiotic prescription at an outpatient pharmacy during a single year. This increased to 47% over two years, 55% over three years, and 62% over four years. Women were more likely to fill an antibiotic prescription than men, as were residents of South Central region states vs. other regions (the North Central region was second, followed by the Northeast and the West.) The highest users were infants ages 0 to 2 years. Not only was the probability of patients filling an antibiotic prescription remarkably high, reaching 47% at two years and 62% at four years, it was not homogenous throughout the enrollees. Thus, while approximately one-third filled prescriptions during any one year, another one-third never did.

■ COMMENTARY

The number of prescriptions for antibiotics in the United States is remarkable, especially in the South. This undoubted overuse, and especially the heterogeneity of use, reminds me of something mentioned in the 2005 report of a clonal outbreak of methicillin-resistant *Staphylococcus aureus* infections among NFL players.[1]

Examination of the 2002 pharmacy log for a team revealed that players received an average of 2.6 antibiotic prescriptions per year — a rate 10 times higher than age- and sex-matched individuals in the general population. Concurrently, while approximately 60% of players reported receiving antibiotics during their 2003 season, 40% received no antibiotic. Previously, several groups have demonstrated the heterogeneity of antibiotic use in the United States based on, for example, geography.[2]

Olesen et al found that extensive use, defined as many people receiving few prescriptions, and intense use, defined as a small number of individuals receiving many prescriptions, had different relationships to the prevalence of antibiotic resistance. Thus, they found that extensive use was associated more strongly with resistance than was intensive use, suggesting the former could be a more effective focus of interventions. ■

REFERENCES

1. Kazakova SV, Hageman JC, Matava M, et al. A clone of methicillin-resistant *Staphylococcus aureus* among professional football players. *N Engl J Med* 2005;352:468-475.
2. Olesen SW, Barnett ML, MacFadden DR, et al. The distribution of antibiotic use and its association with antibiotic resistance. *Elife* 2019; May 3;8. pii: e47124. doi: 10.7554/eLife.47124.

PHARMACOLOGY UPDATE

Pitolisant Tablets (Wakix)

By William Elliott, MD, FACP, and James Chan, PharmD, PhD

Dr. Elliott is Assistant Clinical Professor of Medicine, University of California, San Francisco.
Dr. Chan is Associate Clinical Professor, School of Pharmacy, University of California, San Francisco.

Drs. Elliott and Chan report no financial relationships relevant to this field of study.

The FDA has approved a first-in-class selective histamine 3 receptor antagonist/inverse agonist to treat excessive daytime sleepiness (EDS) associated with narcolepsy. Pitolisant received priority review and will be distributed as Wakix.

INDICATIONS

Pitolisant should be prescribed to treat EDS in adult patients with narcolepsy.[1]

DOSAGE

The recommended dosage is 17.8 mg to 35.6 mg daily.[1] The dosage should be titrated as follows: 8.9 mg once daily (week 1); 17.8 mg once daily (week 2); may increase to a maximum dose of 35.6 mg once daily (week 3).

The maximum dose is 17.8 mg for patients with hepatic impairment, renal impairment, or poor CYP2D6 metabolizers.[1] Pitolisant is available as 4.45 mg and 17.8 mg tablets.

POTENTIAL ADVANTAGES

Pitolisant is the first-in-class treatment for this indication. It also is the first and only drug for this indication that is not scheduled as a controlled substance. Current FDA-approved drugs include modafinil (C-IV), armodafinil (C-IV), solriamfetol (C-IV), methylphenidate (C-II), sodium oxybate (C-III), and amphetamine (C-II).

POTENTIAL DISADVANTAGES

Pitolisant prolongs the QT interval and should be avoided in patients with known QT prolongation, history of cardiac arrhythmias, or in combination with other drugs known to prolong QT interval. Reduce or avoid the dose for patients who are likely to experience increased systemic exposure to pitolisant (e.g., hepatic or renal impairment, poor CYP2D6 metabolizers, CYP2D6 inhibition). The drug may reduce the effectiveness of hormonal contraceptives (i.e., sensitive CYP3A4 substrate as pitolisant is a weak CYP34A inducer).[1]

COMMENTS

The efficacy of pitolisant was evaluated in two randomized, double-blind, placebo-, and active-controlled studies that included adult subjects with narcolepsy who registered an Epworth Sleepiness Scale (ESS) score ≥ 14. ESS is based on an eight-item, self-administered questionnaire rating the subject's perceived likelihood of falling asleep during daily activities.[1] Each item was rated from 0 to 3 (maximum score, 24). Each study included an eight-week treatment period (three-week dose titration and five-week stable dose period). Subjects received pitolisant, modafinil, or placebo. In study 1 (n = 95), subjects were randomized to pitolisant (initiated at 8.9 mg daily and increased at weekly intervals to 17.8 mg or 35.6 mg based on response and tolerability), modafinil (100 mg, 200 mg, or 400 mg), or placebo.[1,2] In study 2 (n = 166), pitolisant dose was initiated at 4.45 mg and increased to 8.9 mg or 17.8 mg based on response and tolerability, modafinil (200 mg daily), or placebo.[1,3] The primary efficacy endpoint was the difference in mean change in ESS score between pitolisant and placebo after the eight-week treatment period. If pitolisant was statistically different to placebo, then change between pitolisant and modafinil was assessed. In both studies, pitolisant showed statistically significantly greater improvement in mean ESS score compared to placebo (17% and 12% reduction, respectively). This represented a placebo-subtracted difference of -3.1 and -2.2, with a -3 regarded as clinically relevant.[2] In study 1, the improvement vs. placebo between pitolisant and modafinil appeared to differ; however, non-inferiority was not established (likely due to inadequate sample size).[2] Similar comparisons were not reported for study 2. In study 1, the results of a posthoc analysis suggested that the cataplexy rate was lower for pitolisant vs.

placebo. Those results were supported by the results of a recent larger, placebo-controlled study (n = 106; 75% reduction in cataplexy rate vs. 38% for placebo; 49% reduction).[4] The most commonly reported adverse reactions included headache, insomnia, and nausea (6-18%).

CLINICAL IMPLICATIONS

Narcolepsy is a rare, chronic, neurological disorder characterized by excessive daytime sleepiness with or without cataplexy.[5,6] The latter is defined as sudden, transient loss of muscle tone triggered by emotions and accompanied by a preserved state of consciousness.[6] The American Academy of Sleep Medicine and European Academy of Neurology/European Sleep Research Society/European Narcolepsy Network recommend modafinil/armodafinil as effective treatment of daytime sleepiness due to narcolepsy.[5,6] The FDA recently approved solriamfetol, a selective dual dopamine norepinephrine reuptake inhibitor, for narcolepsy. Generally, these are not effective in reducing cataplexy.[5,7,8] Sodium oxybate is the only drug approved in the United States and Europe for treating cataplexy and is available only through the restricted Xyrem REMS Program in the United States. Pitolisant is newly approved in the United States for narcolepsy but has been available in Europe since 2016. It is recommended as a first-line agent for narcolepsy with or without cataplexy but not currently approved in the United States for treating cataplexy. Pitolisant is an alternative to modafinil, especially since pitolisant is a nonscheduled product that may be effective in reducing cataplexy episodes and could prolong QT intervals. The cost of pitolisant has not been announced. The drug is expected to be available in the fourth quarter of 2019. ■

REFERENCES

1. Harmony Biosciences, LLC. Wakix Prescribing Information, August 2019. Available at: http://bit.ly/2ldo2wh. Accessed Sept. 24, 2019.
2. Dauvilliers Y, Bassetti C, Lammers GJ, et al. Pitolisant versus placebo or modafinil in patients with narcolepsy: A double-blind, randomised trial. *Lancet Neurol* 2013;12:1068-1075.
3. ClinicalTrials.gov. Effects of BF2.649 in the treatment of excessive daytime sleepiness in narcolepsy. Available at: http://bit.ly/2mnkdVn. Accessed Sept. 24, 2019.
4. Szakacs Z, Dauvilliers Y, Mikhaylov V, et al. Safety and efficacy of pitolisant on cataplexy in patients with narcolepsy: A randomised, double-blind, placebo-controlled trial. *Lancet Neurol* 2017;16:200-207.
5. Morgenthaler TI, Kapur VK, Brown T, et al. Practice parameters for the treatment of narcolepsy and other hypersomnias of central origin. *Sleep* 2007;30:1705-1711.
6. Kallweit U, Bassetti CL. Pharmacological management of narcolepsy with and without cataplexy. *Expert Opin Pharmacother* 2017;18:809-817.
7. Golicki D, Bala MM, Niewada M, Wierzbicka A. Modafinil for narcolepsy: Systematic review and meta-analysis. *Med Sci Monit* 2010;16: RA177-RA186.
8. Thorpy MJ, Shapiro C, Mayer G, et al. A randomized study of solriamfetol for excessive sleepiness in narcolepsy. *Ann Neurol* 2019;85:359-370.

CME QUESTIONS

1. **In the study by Zeeshan et al, after mild and moderate traumatic brain injury, novel oral anticoagulant use was associated with:**
   a. increased risk of progression of intracranial hemorrhage.
   b. an increase in antibiotic prescriptions.
   c. lower rates of mortality.
   d. no adverse effects.

2. **Which statement is true regarding total knee arthroplasty (TKA)?**
   a. Certain forms of anesthesia are more prone to be associated with post-TKA neuropathy.
   b. An inflammatory origin of post-TKA neuropathy is common.
   c. Peroneal neuropathy, presenting as foot drop, is the most common form of post-TKA neuropathy.
   d. Sciatic neuropathy is the most common form of post-TKA neuropathy.

3. **According to the results of the Morales et al study, which statement is true?**
   a. Fluoroquinolones are not associated with peripheral neuropathy, myalgia, and weakness.
   b. Fluoroquinolones are associated with tendon rupture.
   c. Fluoroquinolones are not associated with impairment of vision, hearing, smell, and taste.
   d. Fluoroquinolones are associated with cerebellar atrophy and ataxia.

Internal Medicine [ALERT]

ECG Review

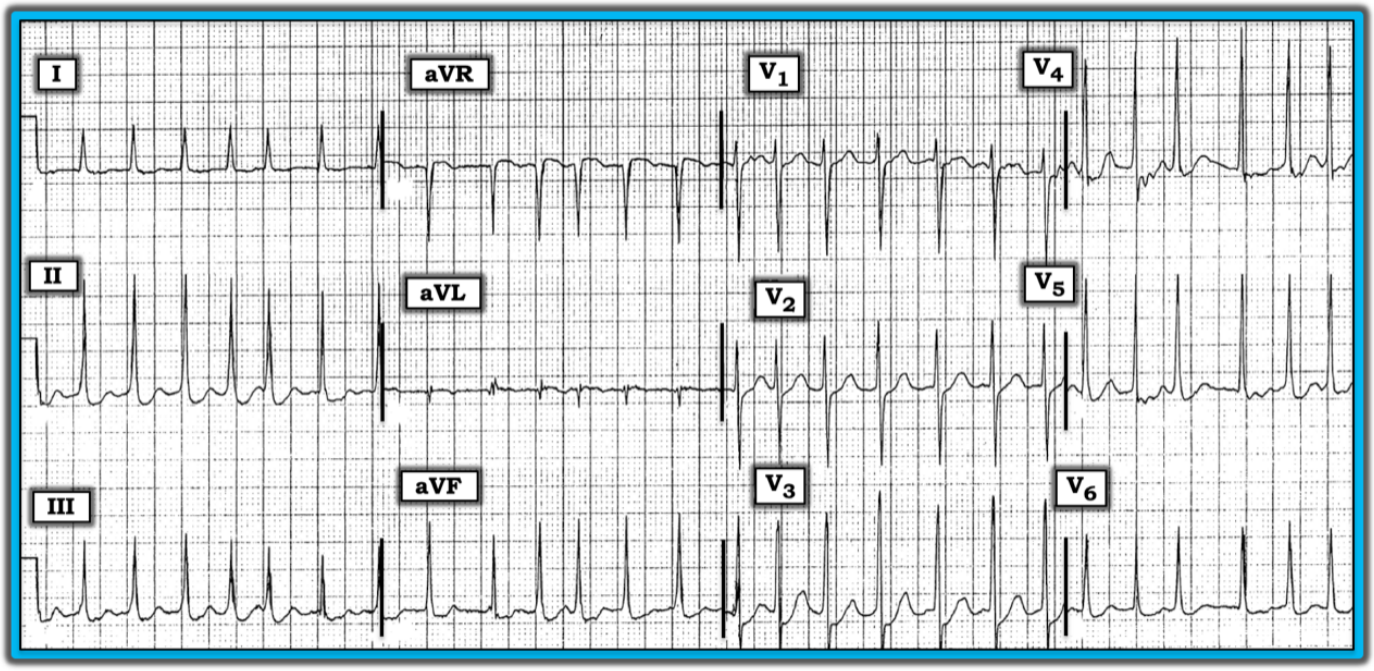
By Ken Grauer, MD

Professor Emeritus in Family Medicine, College of Medicine, University of Florida

Dr. Grauer reports no financial relationships relevant to this field of study.

What Might Account for the ST-T Changes?

The ECG in the figure below was obtained from a 65-year-old woman who presented with an exacerbation of heart failure. A medical history revealed she was taking multiple medications. The patient was dyspneic and complained about intermittent chest pain. How might one interpret this tracing? What causes of the ST-T wave should be considered?



The rhythm is atrial fibrillation with a rapid ventricular response (irregularly irregular, without any P waves). There is no PR interval because the rhythm is atrial fibrillation. The QRS complex is narrow. The QTc is without clinical significance at this rapid rate. There is left ventricular hypertrophy (LVH), satisfied by at least two voltage criteria (deepest S wave in V1, V2 + tallest R wave in V5, V6 ≥ 35 mm, and R wave in any inferior lead ≥ 20 mm).

There are no Q waves. R wave progression is appropriate, with transition occurring between lead V2 to V3. The most remarkable finding is the "scooped" ST segment depression seen in multiple leads. There are numerous potential causes of ST-T wave depression, many of which are not cardiac-related. Among noncardiac-related causes are hyperventilation, expression of strong emotions (i.e., anxiety or fear), heat or cold exposure, neurologic disease/fatigue, nonspecific medical illness, and many others.

All that said, remember six common causes of ST-T wave depression whenever encountering the ECG finding of generalized, nonspecific ST-T wave changes. The six causes are: ischemia, repolarization changes associated with LVH (i.e., left ventricular "strain"), digitalis effect, electrolyte disorders (e.g., hypomagnesemia or hypokalemia), tachycardia, and any combination of the other five causes.

In this case, this older patient went into heart failure, experienced intermittent chest pain, was taking multiple medications, and presented in rapid atrial fibrillation. Depending on which medications she was taking (e.g., a diuretic and/or digoxin for heart failure), it may be that each cause contributed to the ST-T wave changes on this ECG.

For more information about and further discussion on this case, please visit: http://bit.ly/2kGjC0J.