Managing Cough Without Codeine in the Urgent Care Setting

Urgent message: Opioid prescribing and opioid-related deaths have risen during the COVID-19 pandemic. Although supported in some scenarios by the CHEST Diagnosis and Management of Cough and NICE COVID-19 guidelines, it is time to reevaluate the appropriateness of using codeine in suppressing cough.

MEGAN PENNER, PHARMD and HOJUNG JANG, PHARMD CANDIDATE

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Clinical Scenario

A 54-year-old female with a past medical history of diabetes, hypertension, and depression presents to the urgent care center with congestion, nasal discharge, fatigue, and cough with symptoms starting 5 days prior to presentation. The patient is diagnosed with a viral respiratory tract infection and prescribed oral guaifenesin with codeine. The question is, are codeine-based antitussives really the safest and most efficacious agents for treating cough?

Introduction

Codeine is an opioid which exerts its antitussive effect by mediating mu and kappa opioid receptors in the medulla. Although considered a weak opioid, codeine is converted via cytochrome P450 (CYP) 2D6 to morphine and exerts its analgesic effects via this pathway. Codeine is often paired with anticholinergic and/or expectorant medications such as promethazine or guaifenesin to alleviate the symptoms of cough or related pain and congestion.

Therapies for cough are limited, with opioids and dextromethorphan being the two centrally acting antitussives, and benzonatate acting as a peripheral antitussive through local anesthetic effects. Patients often seek care after already trialing over the counter cough suppressants.

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The 2006 CHEST Diagnosis and Management of Cough guidelines recommend against centrally acting cough suppressants such as codeine and dextromethorphan for upper respiratory tract infections (URI) but endorse consideration of short-term therapy for chronic bronchitis, postinfectious cough, and other conditions if alternate agents have failed.[1] Since publication of the 2006 guidelines, CHEST has published

Author affiliations: Megan Penner, PharmD, Idaho State University College of Pharmacy. **Hojung Jang, PharmD** Candidate 2024, Idaho State University College of Pharmacy.

additional guidelines and expert panel reports regarding cough; however, these subsequent guidelines do not address priority of antitussive therapy utilization.

Management of cough has become critical in the COVID-19 pandemic. The NICE COVID-19 guidelines recommend starting with simple measures for cough management such as consuming honey, but also recommend consideration of a short trial of codeine or morphine.[2]

It is important to note that these recommendations are based on consensus rather than an evidence-based framework.

Therapeutics

Because of genetic variances in CYP2D6 metabolism, patient response to codeine can be unpredictable. This metabolism and subsequent risk for respiratory depression led to the boxed warning and contraindication for use in children.[3]

In addition to the variable response, codeine's CYP450 activity poses risk for many drug interactions. Although less potent than other opioids, codeine still carries the typical opioid risks such as constipation, hypotension, sedation, and respiratory depression. (This "low-potency" opioid isn't looking so harmless anymore, right?)

While codeine has shown some effect on time spent coughing compared with given baseline, studies have shown no significant difference when compared with placebo. Additionally, studies have shown no significant differences in cough challenge thresholds or subjective cough measured for codeine compared with guaifenesin and dextromethorphan.[4,5]

Although limited head-to-head comparisons have been published, the side effects of guaifenesin and benzonatate are minute compared with codeine.

Also, the formulation of codeine combined with promethazine is frequently utilized for cough suppression. This formulation is high risk for respiratory and central nervous system depression and has the associated common name of "purple drank" when being misused for recreational purposes. In addition to the additive central nervous system depression, promethazine carries the risk of anticholinergic side effects such as dry mucous membranes and sedation.

Dextromethorphan, which is structurally related to codeine, is also metabolized by CYP2D6, but exerts its antitussive effects through blockade of sigma opioid receptors rather than the mu and kappa opioid receptors which are associated with analgesia and euphoria. Dextromethorphan also acts as an antagonist at N-methyl-D-aspartate (NMDA) receptors, which can lead to dissociation effects and hallucinations if misused. This risk escalates when paired with codeine.

Dextromethorphan also has serotonergic properties which should be considered before using for a patient with multiple serotonergic medications at baseline because of the risk of serotonin syndrome. Dextromethorphan cannot be used with a concomitant monoamine oxidase inhibitor (MAOI) or within 2 weeks of its discontinuation.

Benzonatate, a local anesthetic, is FDA-approved for cough management in adults. Side effects are rare, given its local action. Benzonatate requires a prescription.

Guaifenesin does not suppress cough, but acts as an expectorant by reducing viscosity of mucus and increasing hydration of the respiratory tract. Adverse effects with guaifenesin are also rare and usually limited to gastrointestinal irritation.

Many over-the- counter cold medications will contain multiple agents, so it is important to get a detailed history on the ingredients that have been trialed before moving on to opioid therapy. Additionally, nonpharmacologic treatments for cough such as increasing hydration, air humidification, eating 1-2 teaspoons of honey, utilizing cough drops, and breathing techniques should be used along with pharmacologic therapies.

Conclusion

Returning to the reference case: If the patient takes metformin, liraglutide, losartan, atorvastatin, escitalopram, and buspirone at home, how will this impact our medication choice? Both codeine and dextromethorphan will increase the serotonergic effect of escitalopram. Thus, guaifenesin should be trialed first to also assist with the congestion. Benzonatate could also be used. If these fail, dextromethorphan should be trialed before moving on to codeine. Although data regarding efficacy of cough suppressants are sparse, the available literature highlights the risks—and lack of benefits—of opioids. ■

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INSIGHTS IN IMAGES

CLINICAL CHALLENGE: CASE 1

In each issue, *JUCM* will challenge your diagnostic acumen with a glimpse of x-rays, electrocardiograms, and photographs of conditions that real urgent care patients have presented with.

If you would like to submit a case for consideration, please e-mail the relevant materials and presenting information to *editor@jucm.com*.

A 42-Year-Old with Swelling After a Kick to the Face

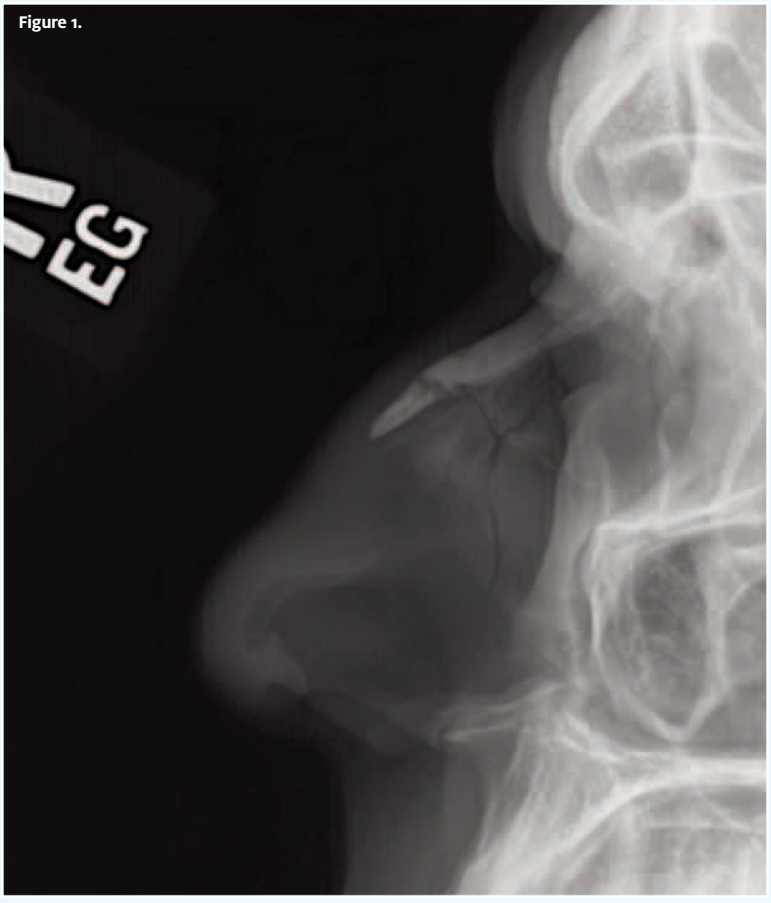
Figure 1.

Case

The patient is a 42-year-old male who presents with nose and facial swelling after being kicked in the face while wrestling with his teenage son.

View the images taken and consider what your diagnosis and next steps would be. Resolution of the case is described on the next page.

THE RESOLUTION

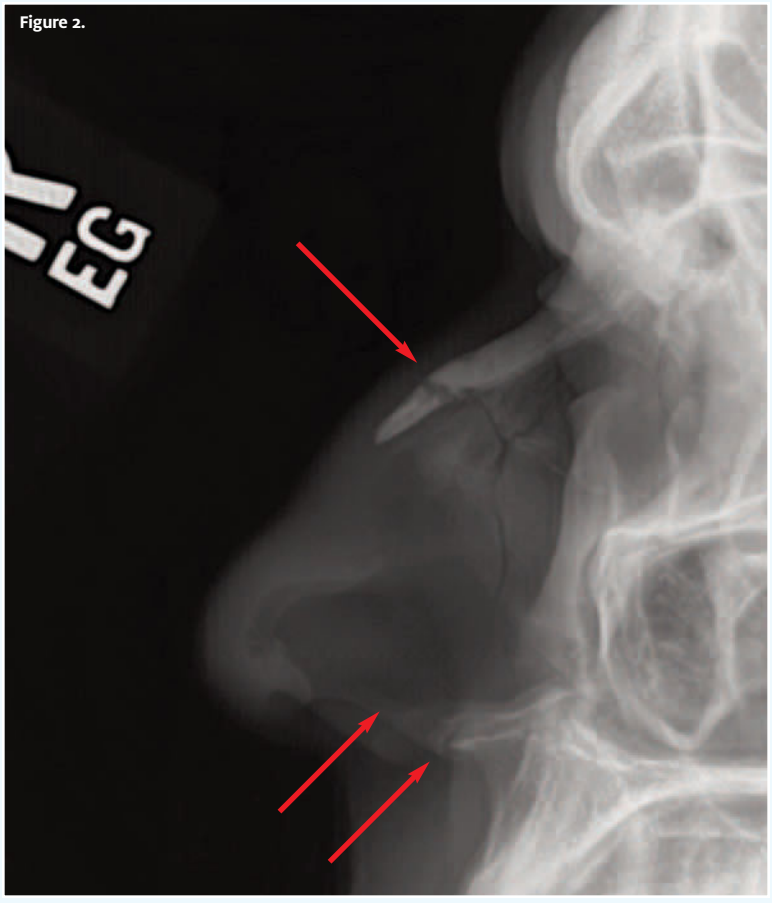
Figure 2.

Differential Diagnosis

- Fracture, anterior nasal spine
- Fracture, frontal nasal spine
- Fracture, nasal bone
- Fracture, nasal septum

Diagnosis

This patient sustained fractures of the anterior nasal spine and nasal bone.

Learnings/What to Look for

- The anterior nasal spine is a bony prominence at the intermaxillary suture located on the inferior edge of the nose at the level of the nostrils
- The anterior nasal spine is a major anatomic landmark for surgery involving the maxillofacial region, dental procedures, and in clinical nasal endoscopic sinus surgery
- Fractures of the anterior nasal spine in maxillofacial trauma are not uncommon (22%). However, the missed diagnosis rate of anterior nasal spine fractures is very high (95.4%) because this structure is often overlooked

Pearls for Urgent Care Management

- Conservative treatment is often sufficient, but open reduction and internal fixation via intraoral incision can be performed for displaced fractures

Acknowledgment: *Images and case presented by Experity Teleradiology (www.experityhealth.com/teleradiology).*

CLINICAL CHALLENGE: CASE 2

A 32-Year-Old with Fever, Cough, Arthralgia, and Photophobia

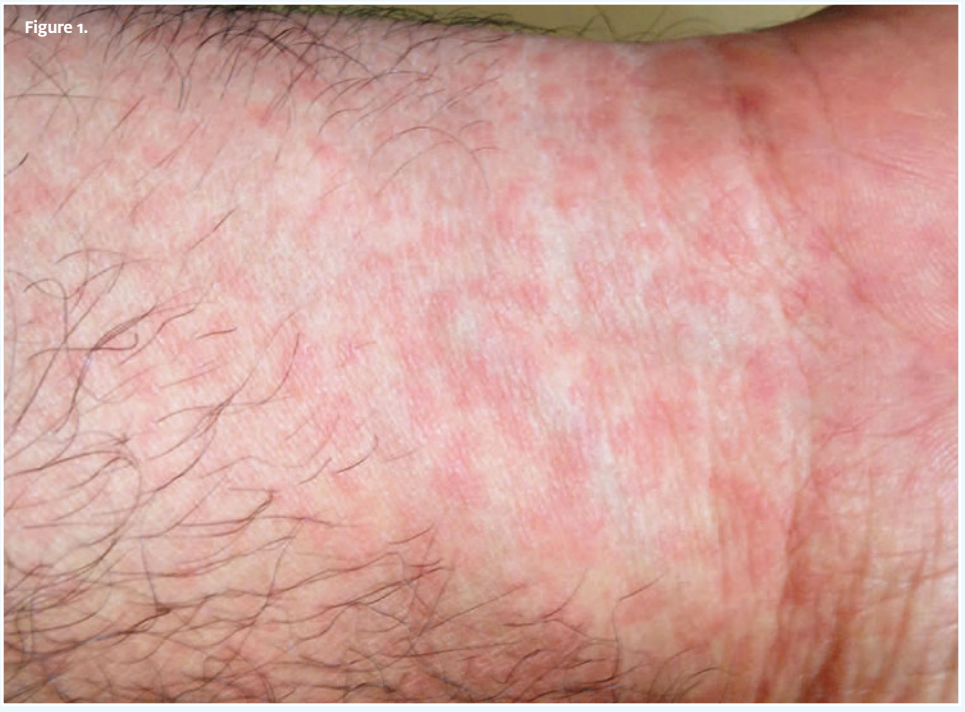

Figure 1.

Case

A 32-year-old immunocompetent male presents with fever, cough, arthralgia, and photophobia for a few days. On examination, he had a temperature of 100°F (37.8°C) and conjunctival injection. There was a widespread erythematous macular rash on his wrist.

When asked about travel, the patient mentioned that he recently visited his family in the Dominican Republic. During his travels, he drank local water and sustained a few mosquito bites. His symptoms began approximately 4 days after his return home.

View the photo taken and consider what your diagnosis and next steps would be. Resolution of the case is described on the next page.

THE RESOLUTION

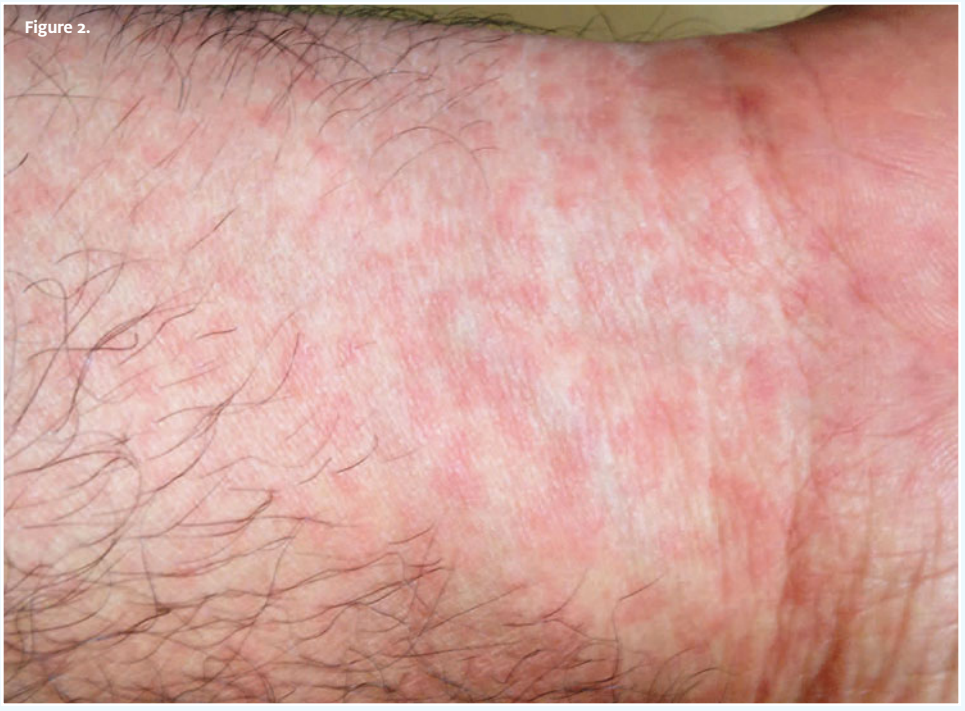
Figure 2.

Differential Diagnosis

- Dengue fever
- Influenza
- Chikungunya
- Leptospirosis

Diagnosis

This patient was diagnosed with chikungunya, an arthropod-borne alphavirus endemic in sub-Saharan Africa, Southeast Asia, Indonesia, the Philippines, and India. Additionally, since 2013 it has been reported in the Caribbean—especially the Dominican Republic. The typical clinical presentation is fever and joint pain. The incubation period is usually 3 to 7 days; however, it can be anywhere from 1 to 14 days.

Learnings/What to Look for

- Symptoms include 7-10 days of fever, chills, arthralgias, rash, myalgias, headache, and photophobia
- Arthralgias are typically migratory, symmetrical, polyarthralgia of the small joints lasting weeks to months
- Macular/maculopapular rash may develop on the trunk and extremities and, occasionally, the palms, soles, and face. Flushing of the face and trunk may also be seen
- Rarely, mucosa and gastrointestinal hemorrhage may occur; this is more likely in children

Pearls for Urgent Care Management

- Rest, fluids, and anti-inflammatory and analgesic agents may provide symptom relief
- Instruct patients to avoid aspirin until dengue can be ruled out to reduce risk for bleeding

Acknowledgment: *Images and case presented by VisualDx (www.VisualDx.com/JUCM).*

CLINICAL CHALLENGE: CASE 3

A 79-Year-Old Male with Left Shoulder Pain and a History of Hypertension and CAD

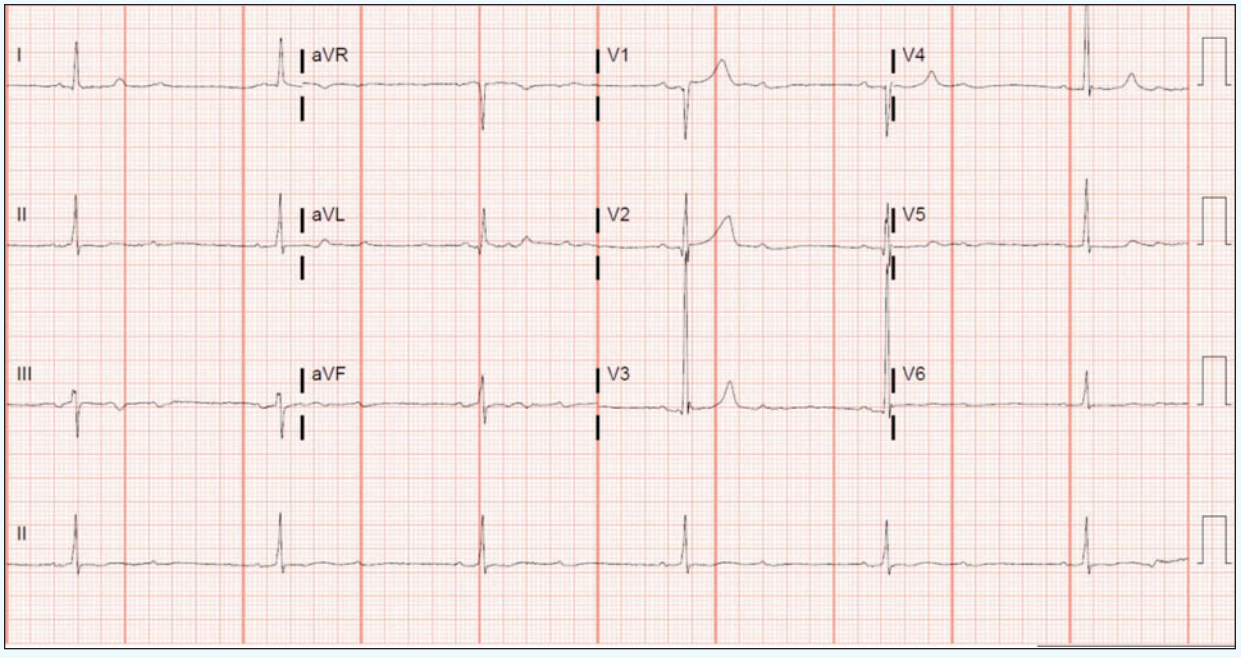

Figure 1. Initial ECG

A 79-year-old male with past medical history of hypertension and coronary artery disease presents to urgent care with left shoulder pain that is worse with movement. He reports intermittent nausea and vomiting, but denies dizziness, chest pain, shortness of breath, or history of trauma.

View the ECG taken and consider what your diagnosis and next steps would be. Resolution of the case is described on the next page.

(Case presented by Catherine Reynolds, MD, McGovern Medical School at UTHealth Houston Department of Emergency Medicine.)

THE RESOLUTION

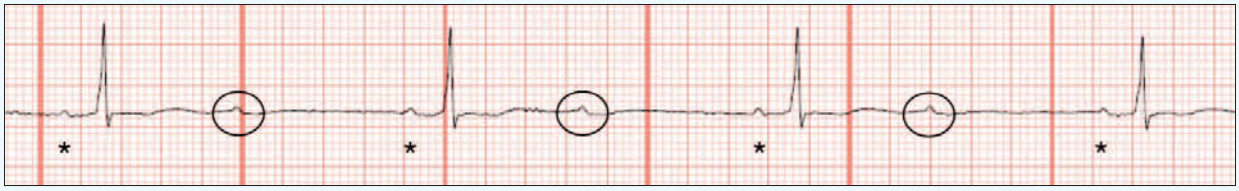

Figure 2. 2:1 AV block. Conducted P waves are designated with a circle while asterisks designate nonconducted P waves.

Differential Diagnosis

- Sinus bradycardia
- First-degree atrioventricular block
- Second-degree atrioventricular block, 2:1 conduction
- Second-degree atrioventricular block, Mobitz type I (Wenckebach)
- Second-degree atrioventricular block, Mobitz type II
- Complete heart block

Diagnosis

This patient was diagnosed with a second-degree atrioventricular block, 2:1 conduction. The initial ECG shows a ventricular rate of 36 BPM, with an atrial rate of 72 BPM. There are more P waves than QRS complexes, indicating the presence of an atrioventricular block.

In this case, there are always two P waves for each QRS complex (**Figure 1** and **Figure 2**).

Careful analysis of the rhythm reveals that P waves are conducted in a 2:1 ratio, with every other P wave "dropped," or failing to conduct through the atrioventricular (AV) node. When P waves are conducted but intermittently dropped, it is referred to as second-degree AV block, which comes in two varieties: Mobitz I (or Wenckebach) and Mobitz II.

"When AV block occurs in a 2:1 ratio, it is impossible to distinguish between Mobitz I and Mobitz II; therefore, 2:1 AV block is simply referred to as '2:1 AV block.'"

Mobitz I occurs when conduction is progressively delayed through the AV node and eventually fails. It is represented by progressively prolonging PR intervals followed by a dropped P wave. It does not always represent pathology, particularly when seen in younger or physically fit individuals with high vagal tone.

Mobitz II occurs when the infranodal conduction system intermittently fails, resulting in intermittently dropped P waves

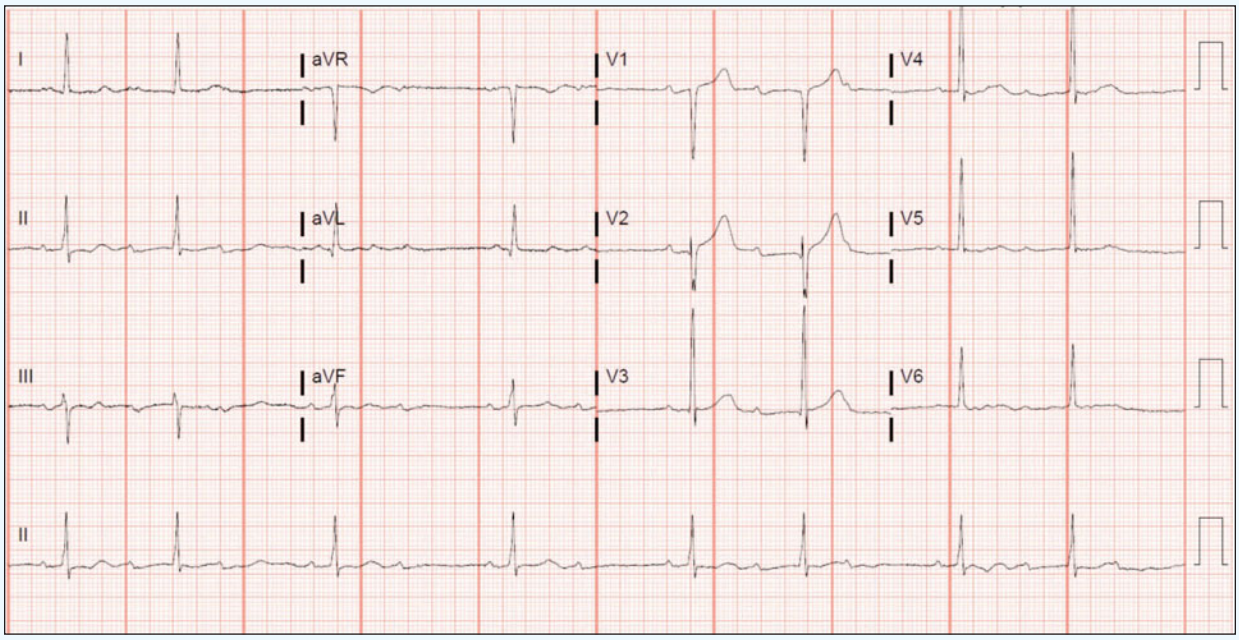

Figure 3. Repeat ECG

THE RESOLUTION

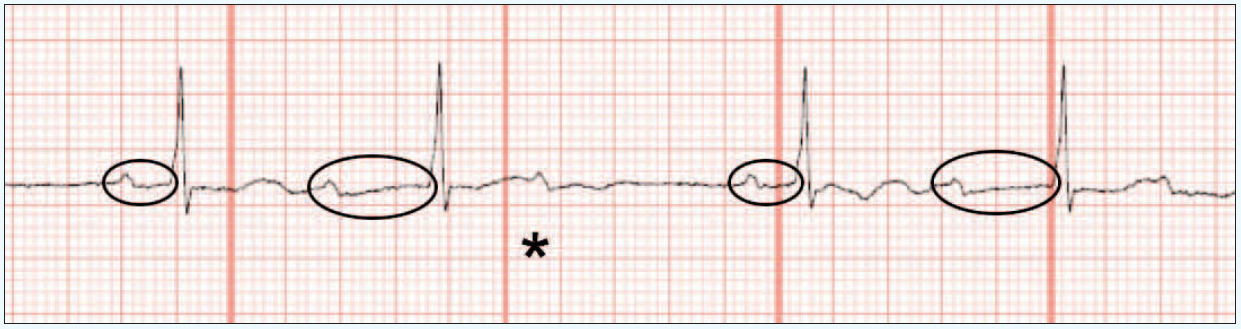

Figure 4. Ovals designate the progressively prolonging PR interval until a ventricular beat is dropped. The nonconducted P wave is indicated by the asterisk.

but consistent PR intervals when conducted. Mobitz II usually occurs with preexisting conduction disease (eg, combination of bundle branch and fascicular blocks), is always pathologic, and is more likely to progress to complete heart block.

When AV block occurs in a 2:1 ratio (Figure 2), it is impossible to distinguish between Mobitz I and Mobitz II; therefore, 2:1 AV block is simply referred to as "2:1 AV block.

When the QRS is narrow, as in this case, Mobitz I is more likely; however, it is prudent to assume the worst scenario (ie, Mobitz II) and transfer for an electrophysiology study and/or pacemaker placement unless more information suggests otherwise.[1-3]

In this case, another ECG was performed after a short period of time, which revealed Mobitz I conduction (**Figure 3** and **Figure 4**).

In Figure 3, there are periods of 3:2 block, where the PR interval prolongs before the QRS is dropped. This confirms the diagnosis of second-degree atrioventricular block, Mobitz type I (Wenckebach). This is illustrated again in Figure 4.

Although Mobitz I is often benign, this patient is 79 years old with known coronary artery disease and is symptomatic with nausea and vomiting. Therefore, he was transferred for pacemaker placement.

Learnings/What to Look for

- The presence of more P waves than QRS complexes should prompt consideration of an atrioventricular block
- In general, a first-degree AV block and second-degree Mobitz I block are unlikely to progress to complete heart block, especially in young and healthy patients
- It is impossible to distinguish between Mobitz I and Mobitz II with a fixed 2:1 ratio. Serial ECGs may help make the diagnosis
- With a fixed 2:1 AV block, it is safest to assume Mobitz II due to its high risk of progression to third-degree AV block

"In a young patient, first-degree AV block is likely a benign finding. It may, however, represent serious pathology in an older patient with known heart disease and/or with preexisting conduction disturbances."

Pearls for Initial Management and Considerations for Transfer

- Consider patient demographics when analyzing AV nodal blocks; in a young patient, first-degree AV block is likely a benign finding. It may, however, represent serious pathology in an older patient with known heart disease and/or with preexisting conduction disturbances
- Patients with 2:1 AV block should be transferred to a facility capable of pacemaker placement

References

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Case courtesy of ECG Stampede (www.ecgstampede.com).

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