Kansas Journal of Medicine

Volume 3, Issue 3, 2010

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Case Studies

Need of a Revised Bleeding Risk Model in Patients on Warfarin Therapy: Considering Hypertension as an Important Risk Factor

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Introduction

Atrial fibrillation is a well recognized risk factor of stroke.[1] Various risk stratification models have been used but CHADS2 (an acronym for Congestive heart failure, Hypertension, Age over 75, Diabetes mellitus, and prior Stroke or transient ischemic attack) is the most commonly used model, possibly because of its easy scoring.[2] In this system, a point is given for congestive heart failure, hypertension, age over 75 years, and diabetes, and two points for previous history of stroke. CHADS2 scoring places patients in one of three risk categories with a score of 0 as low, 1 as moderate, and more than or equal to 2 as high. Aspirin alone is recommended for low risk, aspirin or oral anticoagulants for moderate risk, and oral anticoagulants for high risk individuals.[3]

Although anticoagulants are superior to aspirin alone or the combination of aspirin and clopidogril, they are associated with a significant risk of intracranial hemorrhage.[4-6] The Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE-W) analysis demonstrated the high efficacy of oral anticoagulation (OAC) over the combination of aspirin and clopidogril in patients with CHADS2 score of 1.[7] Therefore, it is important to keep the balance between risks and benefits of starting warfarin in these patients.

Case Report

An 83-year-old male known to have hypertension, atrial fibrillation, hypothyroidism, parkinsonism, bladder carcinoma (status post resection), diabetes mellitus type 2 on insulin, coronary artery disease (status post coronary artery bypass graph in two vessels) presented with generalized weakness, anorexia, and confusion for the past six months that worsened in the prior two weeks. Review of the rest of systems was non-contributory. He had no allergies. He quit smoking and drinking several years prior.

The patient's father had diabetes mellitus; the rest of the family history was unremarkable. He was taking warfarin 2 mg daily for chronic atrial fibrillation, insulin, levothyroxine, lisinopril, carvedilol, amlodipine, citalopram, levetiracetim, carbidopa/levadopa, and hydrocodone.

On examination, blood pressure was 139/83 mmHg and controlled with medication, heart rate was 75 bpm, respiratory rate was 20 bpm, and temperature was 98^{o}F. Positive physical findings were depressed mood, dry mucous membranes suggestive of mild dehydration, 3/6 holosystolic murmur in the left lower sternal border, and chronic venous stasis changes noted in bilateral lower extremities. The electrocardiogram and chest x-ray were normal.

Blood work was normal except for hemoglobin at 11.4 g/dl and platelets at 96 x 10^9/L. The patient was admitted for IV rehydration. His INR was 2.54 and the following day his brain natriuretic peptide came back 808 pg/mL, therefore careful diuresis with furosemide was started with strict intake and output charting.

On the 5th post admission day, the patient was more confused and disoriented from his baseline mental status. A plain computed tomography (CT) scan of the head revealed intraventricular hemorrhage (Figure 1). His INR that day was 3.5. Therefore, warfarin therapy was discontinued and fresh frozen plasma was given for the reversal of anticoagulation. He was transferred to the neuro-intensive care unit and monitored closely for five days. No improvement in his condition was observed and he was transferred to hospice care. He died a few days later.

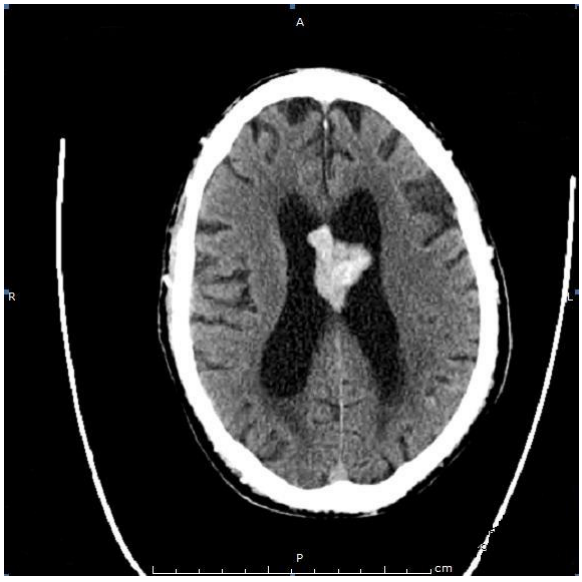

Figure 1. Intraventricular hemorrhage revealed on CT scan.

Discussion

The estimation of bleeding risk related to warfarin therapy is important. Risk is different for individual patients. To help physicians in risk stratification, various bleeding risk models for patients on warfarin have been developed. An early outpatient bleeding risk index for warfarin-treated patients provided an evidence-based starting point for warfarin therapy rather than relying on the physician's prediction.[8] Four risk factors were identified, including age over 65, history of stroke, history of gastrointestinal bleeds, and one of the following: diabetes mellitus, creatinine over 1.5 mg/dL, hematocrit over 30%, or recent myocardial infarction. According to this model, patients were classified as low risk (no risk factor), intermediate risk (1-2 risk factors), and high risk (3-4 risk factors) for bleeding.

Another model predicts the risk of bleeding for patients receiving warfarin.[9] This model considered age over 60, sex, and malignancy in their formula, (1.6 X age) + (1.3 X female sex) + (2.2 X malignancy), to calculate the score and subsequent stratification of the patients as high (more than 3 points), intermediate (1-3 points), or low risk (0 points).

In 2006, Shireman and colleagues[10] proposed a new model to simplify the queries regarding risks of warfarin therapy. Eight factors including age over 70 years, gender, remote bleed, recent bleed, alcohol/drug abuse, diabetes, anemia, and anti-platelet therapy use are considered. Bleeding rates then are compared with rates derived using other models.

All these models have clinical implications. Hypertension was not studied in any of these models. Hypertension is the single most important risk factor for the intracerebral hemorrhage (ICH).[11-13] It is one of the components of CHADS score and a very important risk factor for ICH. A revised bleeding risk model should be designed to address hypertension as one of the risk factors for bleed in patients receiving warfarin.

Conclusion

The risk of intracranial bleeding is associated with oral anticoagulation therapy with warfarin. Multiple risk factors have been associated with the risk of bleeding. Association between hypertension and intracranial bleeding is well established. Various bleeding risk models in patients on warfarin have been developed, but the relationship of high blood pressure with warfarin therapy and the risk of intracranial bleed has not been studied comprehensively. Further studies are needed to guide physicians and avoid grave complications like intracranial bleed.

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Keywords: anticoagulants, warfarin, intracranial hemorrhages, hypertension

Acknowlegments: The authors thank Dr. Jeremiah Kempke who provided patient information for this case report.

Side Effects of Adalimumab Masquerading as Lymphoma

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Introduction

Adalimumab (HUMIRA®) is a TNF-α blocking agent approved for several autoimmune conditions such as rheumatoid arthritis, psoriasis, ankylosing spondylitis, and Crohn's disease. The common side effects of adalimumab are headache, rash, upper respiratory tract infections, and injection site reaction. More cases of malignancies, especially lymphoma and non-melanoma skin cancer, have been observed among patients receiving TNF blockers compared to control patients in clinical trials.[1] The clinical manifestations of the side effects of adalimumab, at times, can be diagnostic dilemmas.

Case Report

A 68-year-old man presented to the emergency room with a three-month history of unintentional weight loss, low-grade fevers, night sweats, and lymphadenopathy. He also reported generalized abdominal pain and anorexia. His past medical history was significant for rheumatoid arthritis (RA), hypertension, and depression. He had no previous surgery. Vital signs on admission were stable. The physical examination was remarkable for enlarged axillary, cervical, and inguinal lymph nodes. Initial laboratory tests results revealed pancytopenia and slightly elevated creatinine.

The differential diagnoses at this stage included, but was not limited to, malignancy (particularly lymphoma), tuberculosis (TB), HIV, and thyroid disorders. The patient also had a history of depression which could explain some of his symptoms, such as anorexia and weight loss.

The patient was initially anemic and leukopenic. An HIV test was negative. A Quantiferon-Gold test for TB was also negative. A CT scan of the abdomen/pelvis showed multiple small lymph nodes in the aortocaval region. Subsequently, a bone marrow aspirate was normocellular. A lymph node biopsy did not reveal any evidence of lymphoproliferative disorder. The patient's abdominal symptoms improved with two days of supportive management.

The patient had been treated with adalimumab previously for rheumatoid arthritis. He stopped taking this medication five days prior to admission for anticipated knee replacement surgery. After three days of hospitalization, anemia and leukopenia improved spontaneously and the patient was discharged in stable condition. A rheumatology consult recommended discontinuing adalimumab and initiating steroids for rheumatoid arthritis. The patient's lymphadenopathy resolved after two weeks.

Discussion

This case illustrated the potential for recognition of serious side effects of adalimumab in particular and biologic therapies in general. As reported earlier[2], the risk of developing lymphoma is

increased in several autoimmune diseases. However, the French RATIO registry[1] suggested increased incidence of lymphomas with the use of anti-TNF monoclonal antibody.

Examining the risk of lymphoma with biologic use is complicated by several factors. First, although lymphoma is of public health importance (it is the fifth most common cause of cancer), it is statistically rare, affecting about 1 in 5000 people per year.[3,4] Therefore, very large studies are necessary to yield adequate statistical power to detect clinically significant lymphoma risks of biologics.

Second, many patients treated with biologics have received immuno-suppressants such as methotrexate (MTX), cyclosporine, or azathioprine, either in the past, or concurrently with biologics, which themselves potentially can increase the risk of lymphoma. Consequently, it is difficult to determine which drug, or combination of treatments, meaningfully impacts lymphoma risk.

Although the patient described in the above case had a negative work-up for lymphoma, it was imperative to recognize such predictable side effects of adalimumab use. Identifying the side effects of biologic therapy is critical to the institution of appropriate management of acute illness and further follow-up.

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Keywords: adalimumab, lymphoma, adverse effects, case report

Utilization of Fosphenytoin for Digoxin-Induced Ventricular Arrhythmia

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Introduction

Digoxin is a class-IV anti-arrhythmic which has indications for use in congestive heart failure and atrial dysrhythmias including atrial fibrillation, atrial flutter, and atrial tachycardia.[1] It was prescribed first by Dr. William Withering for hydrops pectoris and described in *An Account of the Foxglove and Some of Its Medical Uses* in 1785.[2] Though digoxin has been used for over 200 years, its properties and benefits continue to be investigated. Digoxin inhibits the sodium-potassium ATPase pump, thereby increasing intracellular sodium-calcium exchange in the cardiac myocyte. The resultant increase in intracellular calcium causes increased contractility. Digoxin also exerts an anti-adrenergic action in patients with heart failure by inhibiting sympathetic outflow.[1,3]

While benefits of digoxin therapy were anecdotal for decades, in the early 1990s, PROVED, RADIANCE, and DIG trials showed prevention of clinical deterioration, decrease in hospitalizations, and improved exercise tolerance in digoxin treated patients despite the absence of an absolute survival advantage.[4-6] Notwithstanding these proven benefits, digoxin utility has been restricted by a narrow therapeutic window. Most cases of toxicity involve serum digoxin levels greater than two ng/mL, although digoxin's interaction with many commonly used medications, including but not limited to verapamil, diltiazem, erythromycin, and tetracycline may precipitate toxicity at therapeutic serum drug levels. The mechanism of action may involve precipitating the AV-blocking effect (e.g., verapamil, diltiazem) or increasing the bioavailability of digoxin (e.g., macrolide antibiotics). Advanced age, renal failure, ischemic heart disease, cardiomyopathy, and electrolyte disturbances including hypo-kalemia, hypomagnesemia, and hyper-calcemia also may predispose to toxicity. Toxicity may lead to neurologic, gastrointestinal, and/or cardiac symptoms, including headaches, dizziness, ataxia, yellow-green chromatopsia, nausea, vomiting, diarrhea, various cardiac dysrhythmias, and cardiac death.[3,7]

Though gastrointestinal manifestations are often the first sign of digoxin toxicity, patients may present with cardiac arrhythmias which rapidly can progress to a fatal arrhythmia if unrecognized. Premature ventricular beats or atrioventricular block are the earliest and most common abnormal rhythms found in up to 30-40% of verified cases of toxicity.[7] Up to 80-90% of toxicity cases involve some type of cardiac arrhythmia.[8] Treatment can prove challenging and may need to be multi-faceted due to the many potential manifestations of digoxin toxicity. Supportive care, correction of electrolyte disturbances and use of digoxin-specific antibody Fab fragments to bind free digoxin

and aid in excretion are well documented. Fab fragments are pieces of the antibody that contain the antigen binding site.

Treatment of dysrhythmias, if persistent despite administration of digoxin-specific antibody Fab fragments, is less standardized.[8] Research has investigated the use of phenytoin to slow the development of digoxin-induced arrhythmias. The suspected mechanism of action involves a suppression of central sympathetic outflow, thereby decreasing ventricular automaticity.[8] The utility of fosphenytoin, the pro-drug of phenytoin, for treatment of digoxin-induced arrhythmias has not been established.

Case Report

A 78-year-old Caucasian male was admitted with digoxin toxicity. The patient was unable to provide a history. His wife had observed one week of progressive weakness, lethargy, confusion, and anorexia. His past medical history was significant for ischemic cardiomyopathy with an ejection fraction of 10%, for which he took digoxin 0.125 mg daily. He also had mitral valve regurgitation, hyperlipidemia, hypertension, hypothyroidism, and peptic ulcer disease. In addition to digoxin, his home medications included carvedilol, clopidogrel, furosemide, spironolactone, potassium chloride, gemfibrozil, hydrochlorothiazide/lisinopril, levothyroxine, and omeprazole.

The patient was afebrile, with a pulse of 59, blood pressure of 105/45 mmHg, respiratory rate of 8, and oxygen saturation of 99% on two liters per minute of oxygen via nasal canula. The physical examination revealed a notably thin individual. He was alert, however, oriented only to person and place. His heart rate was bradycardic with a regular rhythm; no murmur, rub or gallop was present. Serum chemistry revealed: BUN 193 mg/dL, creatinine 11.9 mg/dL, potassium 8 mEq/L, calcium 9.4 mg/dL, and magnesium 2.9 mg/dL. The digoxin level was elevated at 4.5 ng/mL.

The initial electrocardiogram showed a left bundle branch block, unchanged from the month prior. Chest radiograph showed cardiomegaly, without pulmonary vascular congestion.

Intravenous fluids, albuterol solution via nebulizer, intravenous insulin with 50% dextrose and oral sodium polystyrene sulfonate (SPS) were administered to treat the hyperkalemia. Since the patient's hyperkalemia responded to medical treatment, emergent dialysis was not performed. Confusion and hyperkalemia were presumed to be consequences of digoxin toxicity and digoxin Immune Fab was administered immediately using the following dosing formula: serum digoxin concentration in ng/mL multiplied by weight in kg divided by 100.

Despite digoxin-specific antibody Fab fragments, ventricular arrhythmias commenced with premature ventricular contractions (PVC), followed by ventricular bigeminy and brief runs of wide complex bradycardia (see Figure 1). Shortly thereafter, the patient had a six beat run of ventricular tachycardia.

Intravenous phenytoin was not readily available. There was concern for use of lidocaine in the setting of progressive renal failure. Fosphenytoin was given in a bolus at a dose of 20mg/kg IV. Within one hour of the loading dose, a significant decrease in PVCs, bigeminy, and ectopy was noted (see Figure 2). Digoxin Immune Fab treatment was repeated. Fosphenytoin was continued every 12 hours for the remainder of the hospitalization. Telemetry remained stable with infrequent PVCs over the duration of the hospital stay.

Despite medical management of electrolytes and fluid balance, the patient's renal function and uremia worsened and hemodialysis was initiated late on hospital day two. Despite hemodialysis, the patient

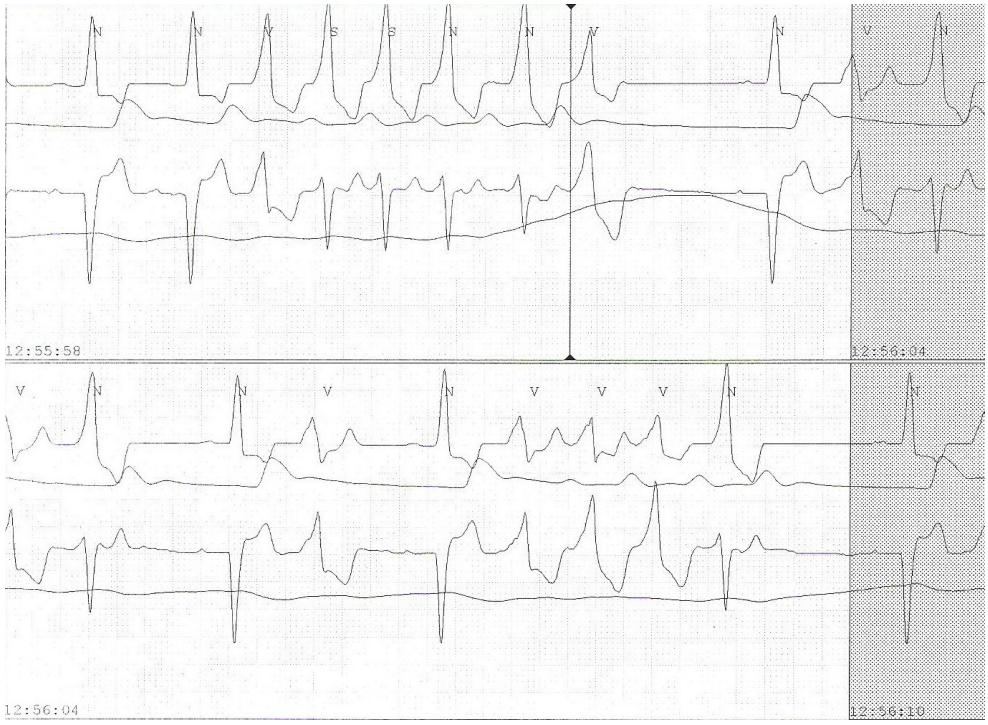

Figure 1. Telemetry demonstrating non-sustained ventricular tachycardia in addition to multiple premature ventricular beats.

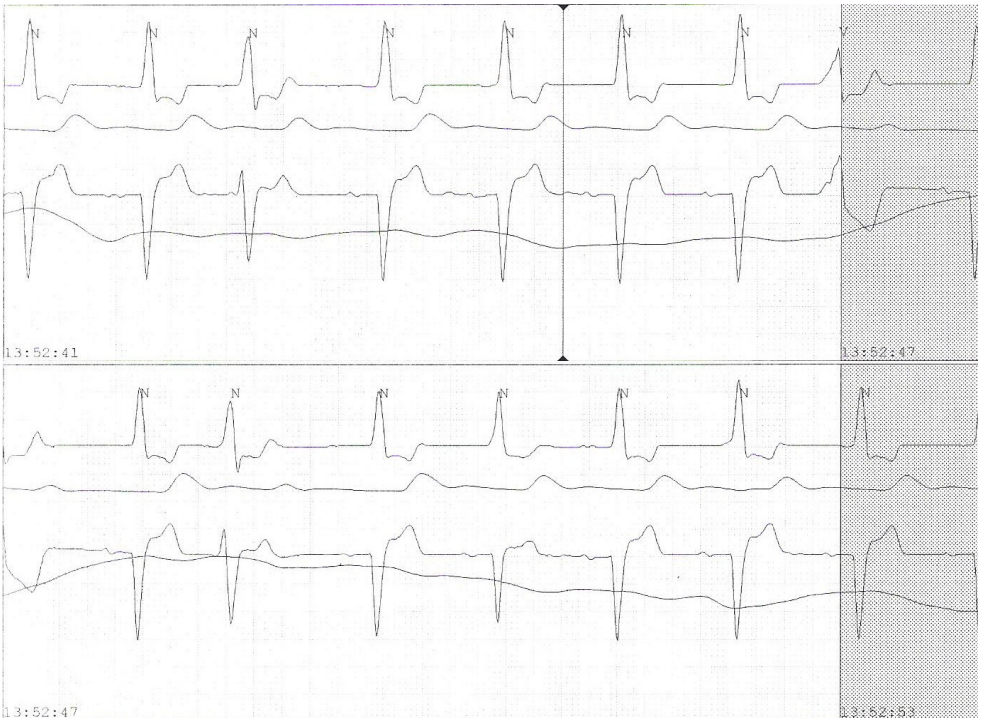

Figure 2. Telemetry demonstrating a substantial decrease in ventricular ectopy less than one hour after fosphenytoin loading.

remained somnolent and confused. A decision was made by the family to change goals of care to comfort measures, and the patient expired on hospital day three.

Discussion

Historically, digoxin has been implicated as one of the most common causes of adverse drug reaction.[9] Toxicity can be acute or chronic and symptoms of digoxin toxicity include gastrointestinal upset, neurologic findings, including visual disturbance and confusion, and cardiac dysrhythmia.[10] In 10-15% of cases of documented toxicity, an ectopic cardiac rhythm is the first sign of intoxication.[7]

Digoxin-induced arrhythmia occurs due to a depression of the sinoatrial node and its conduction which can lead to atrioventricular (AV) block and ventricular ectopy. In turn, this can lead to increased automaticity, extra-systoles and tachy-arrhythmia induced by the initiation of ectopic atrial pacemakers. While PVCs, AV block, atrial tachycardia, and ventricular ectopy commonly are identified rhythms in digoxin toxicity, there are more specifically associated arrhythmias, including bi-directional ventricular tachycardia usually resulting from an alteration of the intraventricular conduction pathway. Furthermore, ventricular ectopy may be more common in those patients with pre-existing heart disease, as in our patient.[7]

In this case, ventricular arrhythmias started with PVCs, followed by ventricular bigeminy and brief runs of wide complex tachycardia. The presence of a non-sustained ventricular tachycardia prompted initiation of antiarrhythmic treatment. In digoxin-induced arrhythmia, Class IA agents such as procainamide are contraindicated due to their impact of decreasing conduction, thereby propagating AV block. In cases of severe bradyarrhythmia, atropine can be useful. The first line agents to treat ventricular ectopy are phenytoin and lidocaine; phenytoin has been shown to be more effective.[7, 11]

Phenytoin's efficacy in suppressing cardiac ectopy is proposed to be related to its effect on resting membrane potential, the action potential amplitude, and the upstroke velocity in phase 0 of the cardiac cycle. In the presence of a low serum potassium, phenytoin can increase the action potential of both atrial and Purkinje fibers, enhancing conduction and increasing the phase 0 upstroke velocity. Less is known about the effect of phenytoin on a reentrant circuit in the presence of normal serum potassium. (In our patient, serum potassium had been normalized by the time of fosphenytoin administration).

Phenytoin may improve conduction of premature impulses and in the setting of digoxin toxicity depress spontaneous diastolic depolarization. Though phenytoin has been effective for ventricular ectopy associated with digoxin overdose, little effect has been seen in treating atrial arrhythmia or ventricular arrhythmia in the setting of chronic cardiac disease.[11] The reported dose of phenytoin is 250 mg IV over 10 minutes which can be repeated in boluses of 100 mg every five minutes up to one gram.[7] Intravenous phenytoin must be used with caution in patients with pre-existing hypotension and may cause hypotension if it is administered at rates exceeding 50 mg/min. Fosphenytoin for the treatment of digoxin-induced cardiac arrhythmia has not been reported.[7]

Fosphenytoin is a pro-drug of phenytoin, hydrolyzed into phenytoin in-vivo. Benefits of intravenous fosphenytoin treatment as compared to intravenous phenytoin are related to an increased water-solubility, thus decreasing injection site reactions and allowing faster administration. The intra-venous preparation of phenytoin contains approximately 40% propylene glycol in

addition to ethanol, leading to an alkaline pH of 12. Fosphenytoin, with a pH of 8.8, is compatible with most intravenous fluids.[12] The propylene glycol in intravenous phenytoin has been shown in some cases to lead to increased hypotension and cardiac arrhythmia in studies on acute seizure treatment.[12,13] Fosphenytoin is less likely to cause hemodynamic instability. The lack of immediate availability of intravenous phenytoin and the ability to infuse fosphenytoin more rapidly prompted treatment with this agent. This resulted in a substantial reduction in the patient's ventricular ectopy, presumably by the same antiarrhythmic mechanism as phenytoin. He was treated with fosphenytoin through the duration of his hospitalization with no known direct complications of therapy.

Conclusions

This case was a 78-year-old male with digoxin toxicity who developed ventricular arrhythmias. The presence of the elevation of free digoxin with the risk of further dysrhythmia precludes the use of many traditional antiarrhythmics. This patient's deteriorating renal function cautioned use of lidocaine. At this institution, limited availability of intravenous phenytoin prompted use of intravenous fosphenytoin which decreased the ventricular ectopy. Administration of intravenous fosphenytoin, shown to result in fewer incidences of infusion site phlebitis and rate-dependent hypotension as compared to intravenous phenytoin, may be an alternative therapy in an attempt to suppress ventricular ectopy associated with digoxin toxicity.

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Keywords: fosphenytoin, digoxin, drug toxicity, cardiac arrhythmia, case report