

# Torsade De Pointes Following Intravenous Haloperidol Administration in a Patient with Complete Heart Block

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## ABSTRACT

Torsade de pointes (TdP) due to QT prolongation is often a drug-induced ventricular tachyarrhythmia. Different classes of drugs including antiarrhythmics, antipsychotics, and antimicrobials may lead to TdP by a patient-specific response altering repolarization. Combinations of other TdP risk factors such as bradycardia, ischemia, or electrolyte abnormalities are usually also present. In this paper, we describe the development of TdP after the administration of intravenous haloperidol in a patient with complete heart block. The importance of evaluating predisposing risk factors before the administration of any potential QT-prolonging medications is highlighted.

## INTRODUCTION

Torsade de pointes (TdP) is a polymorphic ventricular tachycardia characterized by QRS complexes that twist around an isoelectric line in a sinusoidal fashion. TdP is usually self-limited but may degenerate into ventricular fibrillation. Despite poor sensitivity, QT prolongation remains a useful clinical variable to predict the risk of TdP. The QT interval normally shortens during tachycardia and lengthens during bradycardia. Bazett's formula corrects for these changes by dividing the QT interval by the square root of the preceding rest rate interval. This corrected QT interval remains the gold standard. QTc intervals less than 440 milliseconds are normal, intervals between 440-460 milliseconds in men and 440-470 milliseconds in women are borderline, and longer intervals are considered prolonged.<sup>1</sup>

Many medications have been shown to prolong QTc and induce TdP. Haloperidol is a butyrophenone antipsychotic medication widely used to control delir-

ium and agitation, especially in the intensive care unit.<sup>2</sup> This paper describes a patient with a complete heart block who developed TdP after the administration of intravenous haloperidol.

## CASE

A 74-year-old man with hypertension and chronic renal insufficiency was brought to the emergency department. The patient was confused and unable to provide a coherent history. His cognition had declined over the last 3 months. His primary care physician had decreased his metoprolol dose to 25 mg twice daily the previous day as he was bradycardic. His other medications included lisinopril 40 mg daily and prazosin 5 mg twice daily.

The patient's heart rate was 45 beats per minute and his blood pressure was 144/82 mm Hg. The physical exam was remarkable only for confusion. Potassium was 3.9 and magnesium was 1.9. His creatinine was 2 mg/dl (baseline). His electrocardiogram (ECG) showed sinus rhythm with complete atrioventricular block and a wide QRS escape rhythm at 58 beats per minute. The QT and QTc intervals were prolonged at 590 and 579 respectively (Figure 1). Atropine administration resulted in conversion to second degree atrioventricular (AV) block.

The patient became increasingly agitated and intravenous haloperidol (2 mg) was administered. Shortly thereafter, the patient was found to be unresponsive. Telemetry monitor revealed TdP leading to ventricular fibrillation (Figure 2). He was defibrillated and intubated, and was given intravenous magnesium. An isoproterenol infusion accelerated sinus rates as he continued to have short runs of ventricular tachycardia. An echocardiogram revealed normal left ventricular function with mild concentric hypertrophy. A cardiac catheterization revealed an 80% mid-left anterior descending artery lesion, which was stented. Following the procedure, the AV block resolved. Hence, he was cautiously started on metoprolol for his coronary artery

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disease and runs of nonsustained ventricular tachycardia. He remained in normal sinus rhythm during the rest of his stay and was discharged to a nursing home with outpatient rehabilitation.

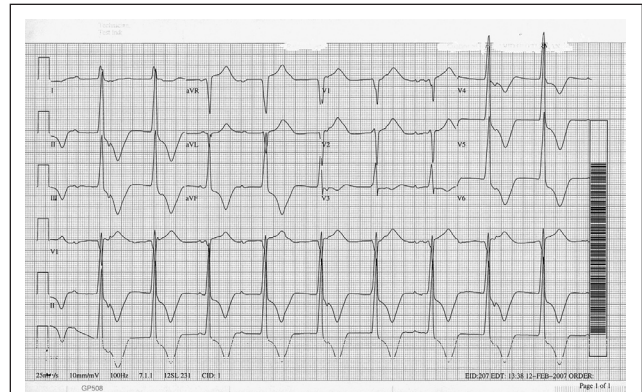
## DISCUSSION

The patient's arrhythmia was consistent with TdP. Intravenous haloperidol was implicated in the setting of heart block due to ischemic heart disease. Electrolytes were normal. Oral and intravenous haloperidol has been reported to cause TdP at high doses; however in this patient, 2 mg of haloperidol administered intravenously precipitated TdP, likely facilitated by the QTc interval prolonged by the bradycardia seen in complete heart block.

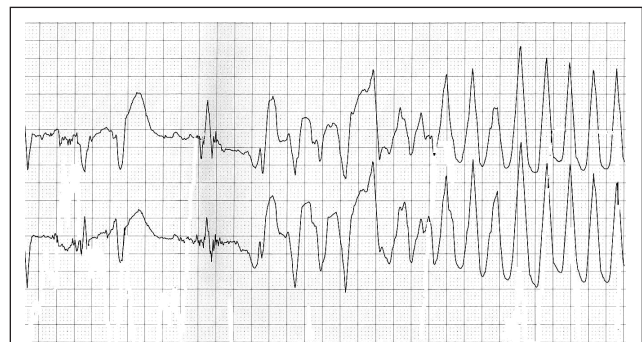
### *Mechanism of QT prolongation and TdP*

The QT interval on the surface ECG represents the summation of action potential duration of the ventricular myocytes. Lengthening of action potential duration is reflected on the ECG by QT interval prolongation.<sup>2</sup> Myocardial repolarization is primarily mediated by efflux of potassium ions through 2 subtypes of the delayed rectifier K<sup>+</sup> current I<sub>Kr</sub> (rapid) and I<sub>Ks</sub> (slow). I<sub>Kr</sub> blockade causes a delay in phase 3 rapid repolarization of the action potential, leading to QT prolongation. Virtually all drugs that prolong QTc block I<sub>Kr</sub>,<sup>1</sup> and a strong correlation has been shown between a drug's ability to block I<sub>Kr</sub> and its potential to cause ventricular arrhythmias.<sup>3</sup> I<sub>Kr</sub> is generated by potassium flow through proteins encoded by the human ether-a-go-go-related gene (HERG, now termed KCNH2). Structural features unique to this channel, like aromatic amino acids with side chains and absence of proline residues may explain why it is susceptible to block by a wide range of compounds.<sup>4</sup> Prolonged repolarization can lead to early afterdepolarizations (EADs). EADs that reach threshold voltage cause ventricular extrasystoles.<sup>5</sup> Purkinje fibers and M cells (midmyocardial) are especially susceptible to drug-induced QT prolongation, EADs, and ventricular extrasystoles. Heterogeneity in ventricular repolarization can create zones of unidirectional block. Repetitive extrasystoles (triggered activity), unidirectional block, and zones of slow conduction can lead to reentry and TdP.<sup>6</sup>

Drug-induced TdP is often preceded by a short-long-short sequence on telemetry, as seen in our patient (Figure 2). This starts with a single or multiple premature ventricular contraction followed by a compensatory pause. The following sinus beat may have deformities of T or U waves and a long QT, followed by another premature ventricular contraction that precipitates TdP.<sup>1</sup>



**Figure 1.** Baseline electrocardiogram showing sinus rhythm with complete atrioventricular block and junctional escape rhythm with QT prolongation.



**Figure 2.** Telemetry strips after 2 mg intravenous haloperidol administration showing Torsade de pointes. Short-long-short sequence preceding initiation of Td.

### *Risk Factors*

Several risk factors may predispose patients to drug-induced Long QT System (LQTS) and TdP (Table 1).<sup>7-8</sup> The inability to predict the risk of developing drug-induced QT prolongation for a given individual makes it a particularly vexing problem for clinicians.<sup>9</sup>

### *Bradycardia, LQTS and TdP*

Bradycardia has been shown to be a risk factor for the development of TdP. Complete AV block may lead to TdP by causing downregulation of potassium channels and QT prolongation.<sup>10</sup> Extracellular potassium is a major factor modulating the physiology of I<sub>Kr</sub>, with longer cardiac action potentials at lower extracellular potassium levels, which may be important for the genesis of bradycardia-dependent arrhythmias such as TdP.<sup>1</sup>

Topilski et al noted that patients with complete AV block had a higher risk of TdP than 2:1 AV block or severe sinus node dysfunction. Their studies revealed that the QT, corrected QT (QTc), and T<sub>peak</sub>-T<sub>end</sub> intervals, rather than the severity of bradycardia, correlated with the risk of TdP, and these intervals, along with the presence of notched T waves like those seen in congeni-

**Table 1.** Risk Factors for Acquired QT Prolongation Leading to Torsade de Pointes (TdP)

Female sex increases risk by 2-3 times
Hypokalemia/Hypomagnesemia/Hypocalcemia
Drugs that block potassium efflux (Web sites: Arizona-CERT Web site, www.torsades.org, www.qtdrugs.org, www.longqt.org, www.sads.org)
Structural heart disease
Prolonged baseline (QTc>450 milliseconds)
Family history of congenital long QT syndrome
Prior drug-induced TdP
Hepatic impairment
Bradyarrhythmia
Atrioventricular block
Hypothyroidism
Inhibition of the metabolism of a drug that blocks I <sub>Kr</sub> by another drug that blocks the cytochrome P450 system
Central nervous system tumors and head trauma

tal LQT2 syndrome, could identify patients at risk for TdP with a positive predictive value of 84%.<sup>10</sup>

### *Haloperidol and TdP*

Haloperidol, a butyrophenone antipsychotic widely used in the treatment of agitation and delirium, has been considered a safe drug with a high clinical index. Upon reviewing the literature, the risk of TdP is greater with intravenous rather than oral haloperidol, especially with doses of  $\geq 35$  mg/day, a QTc of  $\geq 500$ , or in patients with hepatic insufficiency.<sup>2,11-12</sup> There were no reports documenting TdP after intramuscular haloperidol administration. Other haloperidol-induced cardiac arrhythmias observed were atrial ectopy, third-degree AV block, ventricular tachycardia and ventricular fibrillation. Haloperidol blocks I<sub>Kr</sub> with the concentration that produces 50% inhibition (IC<sub>50</sub>) of 1 nmol/L of haloperidol.<sup>13</sup>

### *Management of LQTS and TdP*

Clinicians should be familiar with the list of constantly evolving medications that can predispose to LQTS and TdP. Prompt treatment is critical once TdP develops but prevention remains the best strategy.<sup>1</sup>

## **CLINICAL IMPLICATIONS AND CONCLUSION**

Although haloperidol has demonstrated efficacy in the treatment of agitation and delirium, it is important to recognize its potential to induce QTc prolongation and TdP.<sup>12</sup> Physicians should consider ordering a baseline ECG and if the QTc interval is prolonged >450 milliseconds, alternative drugs should be considered. If the QTc lengthens by >15-20% above baseline, espe-

cially if accompanied by the development of flattened T-waves or U-waves, haloperidol should be discontinued. Patients should have their electrolytes—especially magnesium, calcium, and potassium—measured and corrected prior to the administration of QT prolonging medications.<sup>2</sup> Special attention should be paid to patients with bradycardia associated with QT interval >510 milliseconds, QTc interval >400, or T<sub>peak</sub>-T<sub>end</sub> >85 milliseconds if they also have LQT2-like “notched T waves,” as they may be at sufficiently high risk for developing TdP to justify urgent pacemaker implantation even if symptoms or additional indications are absent.<sup>10</sup> These patients should not be given any QT prolonging medications and should be brought to the notice of an electrophysiologist for immediate evaluation.

**Funding/Support:** None declared.

**Financial Disclosures:** None declared.

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