Ibutilide Pretreatment to Facilitate Cardioversion of Refractory Atrial Fibrillation in a Patient with Morbid Obesity

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INTRODUCTION

Electrical cardioversion is an effective means for converting atrial fibrillation to normal sinus rhythm, with conversion rates ranging from 70% to 90%.[1] There are a number of treatment alternatives for patients with atrial fibrillation that is refractory to conventional monophasic electrical cardioversion, including external biphasic shock, pretreatment with antiarrhythmic medication, high-energy monophasic shocks, and internal cardioversion. External biphasic shock is becoming the standard of care in the electrical cardioversion of atrial fibrillation.[2] However, even with this modality, atrial fibrillation is resistant to cardioversion in a small proportion of patients. In this setting, use of antiarrhythmic (class III) medication to facilitate cardioversion may be an attractive approach.[1] This report describes the use of ibutilide for atrial fibrillation refractory to cardioversion with both amiodarone and biphasic shock. This case is also important because of the role that obesity played in the patient's recurrent/resistant atrial fibrillation and in the pharmacokinetics of antiarrhythmic agents.

CASE REPORT

A 54-year-old woman had a history of morbid obesity since childhood (in 2004, weight was 185 kg, height 157 cm, and body mass index 75 kg/m²), hypertension diagnosed in 1998, sleep apnea, and hypothyroidism. Her hypothyroidism was relatively well controlled with levothyroxine 50–150 mg/day: thyroid-stimulating hormone was 4.1 mU/L (normal range 0.4–4.2 mU/L) and thyroxine 16 pmol/L (normal range 9.7–25.7 pmol/L) in February 2004. In March 2002 she complained of shortness of breath, dizziness, and sweating. Electrocardiography showed atrial fibrillation

with a rapid ventricular response (heart rate 140/min). The following medications were started: bisoprolol 10 mg/day, diltiazem 240 mg/day, digoxin 0.25 mg/day, furosemide 40 mg/day, and warfarin titrated to an international normalized ratio (INR) of 2 to 3; her heart rate while receiving treatment was 90 beats/min and her blood pressure was 122/70 mm Hg. Echocardiography showed mild left atrial dilatation, mild left ventricular hypertrophy, and normal left ventricular function. In May 2002, after 4 weeks of therapeutic anticoagulation, cardioversion was performed with a biphasic defibrillator. Shocks of 125 and 150 J were applied without successful cardioversion. Cardioversion to normal sinus rhythm was achieved with application of 175 J. At that point, digoxin was discontinued. The patient remained in normal sinus rhythm, and in July 2002 the warfarin was discontinued.

Four days before cardioversion (in May 2002), the patient was enrolled in the Azimilide Cardioversion Maintenance Trial (A-COMET 1), to receive either azimilide 125 mg/day or placebo; the study arm to which the patient was assigned was not known at the time of writing. The purpose of the A-COMET 1 study was to examine the effect of azimilide on the maintenance of normal sinus rhythm in patients who have undergone cardioversion from atrial fibrillation. Azimilide is a novel Vaughn-Williams class III antiarrhythmic agent that blocks cardiac potassium channels and is thought to be beneficial in maintaining normal sinus rhythm after cardioversion.[3] The patient in this case continued receiving the assigned medication or placebo for the full duration of the original study (6 months). Then, in November 2002, she started receiving open-label azimilide 125 mg/day, also as part of the A-COMET 1 study. This medication was continued until

January 2004, at which time the study was halted by the sponsor.* Also in November 2002, the patient's diltiazem was discontinued because of a risk for bradycardia-induced torsade de pointe with concurrent diltiazem and azimilide therapy. Candesartan 16 mg/day was started as a replacement treatment for hypertension.

The patient's cardiac status remained stable until August 2004. At that time, she presented with complaints of fatigue, shortness of breath, and a fluttering feeling in her chest. Electrocardiography showed atrial fibrillation, with a heart rate of 111/min. Bisoprolol was increased to 20 mg/day, warfarin (INR target 2 to 3) was restarted, and amiodarone was started at 200 mg tid for 3 weeks, followed by 300 mg/day indefinitely. Because of difficulty in achieving therapeutic INR for 4 consecutive weeks, cardioversion was finally performed in December 2004. Before the planned cardioversion, the patient's INR was 3.1, potassium 4.7 mmol/L, heart rate 90/min, blood pressure 123/55 mm Hg, and QTc 400 ms.

Three shocks were administered by biphasic rectilinear defibrillator (120 J, 150 J, and 200 J, separated by 2-min intervals); however, the patient remained in atrial fibrillation. Therefore, 1 mg of ibutilide was administered intravenously over 10 min. Two minutes after the infusion was completed, 2 more shocks were delivered (200 J each, separated by an interval of 1 min), but cardioversion was not achieved. After a 1-min interlude, a third shock (200 J) was administered, after which the rhythm converted to normal sinus rhythm (heart rate 57/min, blood pressure 100/55 mm Hg, QT 557 ms). The patient was monitored for 4 h after cardioversion; no adverse effects were reported. The patient remained in normal sinus rhythm, and in April 2005 warfarin was discontinued, and enteric-coated acetylsalicylic acid 81 mg/day was started. The amiodarone dose was maintained at 300 mg/day.

DISCUSSION

A number of approaches are available for treating atrial fibrillation that is refractory to electrical cardioversion. The first is biphasic defibrillation. Randomized controlled trials have demonstrated superior efficacy and lower energy requirements for biphasic shocks relative to monophasic shocks (efficacy 94% and 79%, p = 0.005).[5] Biphasic defibrillators are replacing

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*The results of the A-COMET 1 trial, published after this paper was accepted, showed no difference betweeen azimilde and placebo in the maintenance of normal sinus rhythm.[4]

conventional monophasic devices as the standard of care.[2] However, in a small proportion of patients, atrial fibrillation remains refractory to this method. In the patient described here, 3 biphasic shocks (120 to 200 J each) in 2002 caused conversion of atrial fibrillation of less than 2 months' duration. In 2004, atrial fibrillation of 4 months' duration was refractory to cardioversion with 3 external biphasic shocks.

A second approach for refractory atrial fibrillation has been pretreatment with antiarrhythmic medication to facilitate electrical cardioversion. Potassium-blocking agents (class III agents, specifically amiodarone, sotalol, ibutilide, and azimilide) are considered the most effective agents for this purpose because of their ability to prolong the atrial refractory period.[1] Increased refractoriness increases the size of the multiple re-entrant wavelets seen in atrial fibrillation. Larger wavelets make propagation of arrhythmia more difficult, thus facilitating electrical cardioversion. Evidence for this effect was shown in the Sotalol Amiodarone Atrial Fibrillation Efficacy Trial (SAFE-T).[6] Amiodarone, sotalol, or placebo was given to patients for 28 days before electrical cardioversion (monophasic or biphasic). The total rate of conversion to normal sinus rhythm (both before and after electrical cardioversion) was 79.8% for amiodarone, 79.9% for sotalol, and 68.2% for placebo (p = 0.01).[6] These results suggest that both sotalol and amiodarone may have a beneficial effect in facilitating electrical cardioversion. However, in the case reported here, amiodarone did not seem to facilitate cardioversion. Despite a load of 600 mg daily for 3 weeks and 300 mg daily for approximately 3 months, the patient's atrial fibrillation was initially refractory to cardioversion. This situation will be discussed in more detail later in terms of the impact of obesity in this case.

Ibutilide is a novel class III antiarrhythmic intravenous agent for the pharmacological cardioversion of atrial fibrillation and atrial flutter. By itself, this drug has a conversion rate of 40% to 50% for atrial fibrillation.[7] It can also lower the threshold for electrical cardioversion.[1] Ibutilide was highly effective in facilitating monophasic electrical cardioversion in a randomized controlled trial (n = 100), in which there was 100% cardioversion among patients who were pretreated with ibutilide 1 mg IV.[8] This effect was confirmed in 2 case series (with monophasic shocks, 92% to 95% effectiveness).[9,10] Pretreatment with ibutilide has lowered the defibrillation threshold with internal biphasic cardioversion, both in animal and human studies.[11,12] The adverse event of most concern associated with ibutilide is ventricular tachycardia: in ibutilide-treated

patients the incidence of ventricular tachycardia was 9.2%, of nonsustained monomorphic ventricular tachycardia 4.9%, of nonsustained polymorphic ventricular tachycardia 2.6%, and of sustained polymorphic ventricular tachycardia 1.7%.[7] Factors that could put a patient at higher risk for torsade de pointe include low left ventricular ejection fraction, bradycardia, long QT interval, and hypokalemia.[7] In the patient described here, pretreatment with ibutilide resulted in successful cardioversion after 3 additional biphasic shocks. There were no reported side effects. This case report confirms the results of a recently published study that examined the efficacy of biphasic cardioversion at the Mayo Clinic.[13] As part of the protocol in that study, patients who had atrial fibrillation resistant to electrical cardioversion were given ibutilide 1 mg, after which a second attempt at electrical cardioversion was made. In that study, ibutilide was needed only infrequently for biphasic cardioversion, which had an efficacy rate of 93% for atrial fibrillation. However, of the patients for whom biphasic cardioversion failed and who then received 1 mg ibutilide, 75% underwent conversion to normal sinus rhythm, either before or after a second attempt at electrical cardioversion. Both that recent study and the current case report confirm the utility of ibutilide in facilitating cardioversion in those few patients with atrial fibrillation refractory to biphasic shock.

An issue of concern raised by this case is the use of ibutilide in a patient with atrial fibrillation that is refractory to amiodarone. Since both amiodarone and ibutilide are class III antiarrhythmics that prolong the QT interval, the combination might result in a higher risk of torsade de point. Also, the question of efficacy of an additional class III antiarrhythmic should be addressed. The use of ibutilide after amiodarone loading failed to convert atrial fibrillation/flutter has been reported twice.[14,15] Ibutilide treatment before electrical cardioversion resulted in total conversion rates of 91% and 100%, respectively. Rates of nonsustained torsade de pointe were 1.4% and 11%, respectively. There were no cases of sustained ventricular tachycardia. The addition of ibutilide for patients already receiving amiodarone seemed to be effective, with only moderate toxic effects. Thus, even though ibutilide is generally contraindicated with other medications that prolong the QT interval, it may be considered for patients with atrial fibrillation refractory to amiodarone-facilitated cardioversion.

Another issue that should be explored is why cardioversion was unsuccessful on the first 2 discharges yet successful on the third attempt. The reason for this delay in cardioversion is unclear. Use of electrical cardioversion immediately after the 10-min ibutilide infusion followed the protocol of a randomized trial that demonstrated 100% effectiveness of this drug in facilitating monophasic cardioversion.[8] Still, it is possible that this particular patient required more time for the drug to reach high enough levels in heart tissue to facilitate cardioversion. This might have been related to the effect of obesity in the pharmacokinetics of ibutilide, as discussed in the next paragraph.

Morbid obesity (body mass index 75 kg/m²) probably played an important role in this case.[16] Obesity certainly plays a role in atrial fibrillation itself, including increased risk for this condition[17,18] and increased risk for shock-resistant atrial fibrillation. The increased risk of atrial fibrillation is suggested to occur through left atrial distension: the larger the atrium, the higher the risk for the sustained re-entrant wavelets associated with atrial fibrillation. There is also an association between obesity and failure of external electrical cardioversion,[19] thought to be due to increased electrical transthoracic impedance of the chest wall in obese patients. Hence, this patient's obesity may have contributed to the recurrent and refractory atrial fibrillation.

Obesity can have highly complex effects on the pharmacokinetics of drugs, including the volume of distribution, metabolism, and renal excretion.[20] There is minimal published information on dosing of amiodarone for patients with obesity. Therefore, extrapolation from the pharmacokinetic properties of the drug is required. As a general rule, the greater the lipophilicity of a medication, the greater the likelihood that obesity will increase the volume of distribution.[20] Amiodarone is a highly lipophilic drug that is distributed extensively in the fatty tissues of the body (volume of distribution 50 to 100 L/kg).[21] In particular, accumulation in adipose tissue is 125 times that in blood.[21] It seems reasonable, then, that a patient with morbid obesity would have a larger volume of distribution for amiodarone, and a larger volume of distribution would necessitate higher doses of the drug to achieve therapeutic levels. It is conceivable that the amiodarone dose for this obese patient (600 mg/day for 3 weeks, then 300 mg/day for 3 months) was insufficient to reach therapeutic levels. Therefore, one of the reasons that amiodarone did not facilitate cardioversion might have been modest dosing in a patient with large body stores of fat.

The influence of weight on the dosing of ibutilide should also be examined. Ibutilide is rapidly and extensively distributed extravascularly (volume of distribution 11 L/kg), although not to the same extent as

amiodarone.[22] Thus, although obesity probably affects ibutilide pharmacokinetics, this effect would probably be less than the effect on amiodarone, which has a much larger volume of distribution.[21] One way to assess the effect of weight on ibutilide would be dose-ranging studies. As stated earlier, ibutilide was developed for the chemical cardioversion of atrial fibrillation and atrial flutter.[7] Pharmacokinetic studies with ibutilide have shown a dose-dependent, weight-based response in chemical cardioversion. A dose–response trial examined the effects of single doses of ibutilide, ranging from 0.005 to 0.025 mg/kg (total body weight), on the rate of chemical cardioversion of atrial fibrillation. Doses of 0.025, 0.015, and 0.01 mg/kg were superior for cardioversion to doses of 0.005 mg/kg or placebo (cardioversion rates of 46%, 45%, 33%, 12%, and 3% respectively).[23] The recommended dose of ibutilide for the chemical termination of atrial fibrillation is 1 mg for patients with body weight of 60 kg or more and 0.01 mg/kg for those with body weight less than 60 kg.[22] A second dose of the same strength can be given to patients in whom cardioversion is not achieved after the first dose. There are no specific dosing recommendations for patients who are obese. Furthermore, the optimal dose of ibutilide in the setting of facilitated cardioversion is not known. The greatest weight documented in a published trial examining ibutilide for this indication was 140 kg.[9] A 1-mg dose of ibutilide was chosen for the patient described here, who had a body weight of 185 kg. This is equivalent to a weight-based dose of 0.0054 mg/kg. This weight-based dose would have been inferior to higher doses if the aim had been pure chemical cardioversion.[23] However, there have been no dose–response studies examining ibutilide in facilitating electrical cardioversion. In previous reports of ibutilide for facilitation of electrical monophasic cardioversion, the dose was 1 mg. This dose resulted in electrical cardioversion rates between 95% and 100%.[8-10] In fact, for the patient described here, conversion to normal sinus rhythm was achieved after pretreatment with ibutilide (1 mg or 0.0054 mg/kg) with no untoward effects. Weight-based doses of less than 0.01 mg/kg may have efficacy for this indication while reducing cost and toxic effects. However, it may take longer for the drug to reach full effectiveness. Further research may be required to examine the optimal dose of ibutilide for facilitated cardioversion.

In summary, this case demonstrated the beneficial effect of ibutilide in a patient resistant to oral amiodarone and biphasic cardioversion. It also highlighted some of the ways in which obesity affects the treatment of atrial fibrillation, including pharmacokinetics.

Finally, it suggests the benefit of a 1-mg pretreatment ibutilide dose in the setting of morbid obesity.

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