Etripamil: Intranasal Calcium Channel Blocker: A Novel Noninvasive Modality in the Treatment of Paroxysmal Supraventricular Tachycardia

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Introduction

Supraventricular tachycardia (SVT) is a wide term that encompasses atrial and/or ventricular rates in excess of 100 beats per minute at rest; which require atrial and/or atrioventricular (AV) nodal tissue for their initiation and maintenance.[1] The incidence of SVT is about 36 cases per 100,000 persons per year, and the prevalence is about 2.29 per 1000.[1] Although atrial fibrillation (AF) is technically an SVT, AF is usually not included when referring to SVT. The term paroxysmal SVT (PSVT) is applied to intermittent SVTs with abrupt onset and offset, and a regular ventricular response, in contrast to AF, atrial flutter, and multifocal atrial tachycardia, which have an irregular ventricular response. The incidence of PSVT is approximately 89,000 new cases per year and prevalence of about 570,000 persons.[2] Patients without underlying cardiovascular disease are typically younger, and studies have found and these patients to have faster rates in PSVT when compared to those with underlying disease.[2] The risk of developing PSVT increases 5-fold in individuals greater than 65 years of age in comparison with younger individuals.[2] Women are at twice the risk of developing PSVT when compared to men.[2] SVT is often recurrent, occasionally persistent, and a

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frequent cause of visits to emergency rooms and primary care physicians. Due to the probability of SVT terminating before presentation, episodes may be misdiagnosed as anxiety.

Atrioventricular nodal reentrant tachycardia (AVNRT) is the most common cause of PSVT, accounting for approximately 60% of cases.[3] The remaining subtypes include atrioventricular reentrant tachycardia (AVRT), which accounts for approximately 30% of cases, and atrial tachycardia, for approximately 10% of SVT cases.[3] AVNRT involves 2 re-entry pathways, namely the slow and fast, in and around the AV node. The fast and slow pathways are located anteriorly near the septal part of tricuspid annulus and posteriorly near the coronary sinus os, respectively. The pathophysiology of AVRT differs by the existence of accessory pathways known as bundles of Kent, in addition to pathway through the AV node.[4]

The noninvasive means of treatment for SVT are limited to vagal maneuvers per current guidelines.[1] Valsalva maneuver is the standard noninvasive modality most commonly utilized for conversion in SVT. Given the variable success rate of vagal maneuvers, more invasive treatment modalities are often used to achieve conversion of SVT. Novel noninvasive drug therapies are needed to provide better alternatives, and etripamil may be a novel option with great promise.[5]

Discussion

Multiple management modalities have been used to help the conversion of SVT or PSVT into normal sinus rhythm.

Vagal Maneuvers

Vagal maneuvers are a Class I recommendation for acute treatment of regular SVT. One of the most commonly used vagal maneuvers in the attempt to convert SVT is the Valsava maneuver. It involves activating the vagal nerve by the patient expiring against a closed glottis (bearing down). The evidence-based model of practice of the Valsalva maneuver for conversion of SVT involves 3 criteria: supine positioning to achieve maximum barosensitivity, duration of strain for at least 15 seconds, and achieving an intrathoracic/intraoral pressure of 40 mm Hg.[6] The conversion rate of Valsalva maneuver can vary widely from 19.4% to 54.3%.[7]

The REVERT trial showed better conversion rates with the modified Valsalva maneuver (43% compared to 17 % in standard Valsalva, odds ratio [OR] 3.7; 95% confidence interval [CI], 2.3-5.8; $P < 0.0001$).[8] This

technique involves passive leg raising in addition to supine posturing to achieve conversion. Other vagal maneuvers involve carotid sinus massaging or the diving reflex which involves submerging patient's head in cold water while breath holding. Carotid sinus massage can be performed in select patients after ruling out the presence of significant obstructive carotid disease which may signify an underlying pathology, or after a carotid doppler. The maneuver can be risky in older patients with extensive cardiovascular disease (ie, previous stroke or transient ischemic attack), as the maneuver can increase the incidence of embolic events. In a trial comparing the efficacy of the different vagal maneuvers, the standard Valsalva maneuver had the highest conversion rate of 54% when compared to right carotid sinus massage, left carotid sinus massage, and diving reflex, which had conversion rates of 17%, 5%, and 17%, respectively.[9]

Intravenous Medical Therapy

Intravenous adenosine is the first-line recommended medical therapy for acute treatment of regular SVT.[1] Adenosine has a high conversion rate of approximately 90% within 30 seconds when using 2 or more doses. Traditional dosing includes a 6-mg IV rapid bolus, injected as proximal or as close to the heart as possible over 1-2 seconds, followed by rapid saline flush. If no response in 1-2 minutes, a second rapid IV bolus of 12 mg may be administered, followed by rapid saline flush.[10,11] In addition to coronary vasodilatation, adenosine also can potentially cause bronchoconstriction, which leads to patient reports of shortness of breath, chest tightness, and flushing. Though there is no absolute contraindication for its use in asthmatics, it is usually avoided.[12] The adverse effects associated with adenosine may be very unpleasant to some patients and they should be cautioned prior to administration.

Intravenous nondihydropyridine calcium channel blockers (CCB), diltiazem and verapamil, may be used to achieve conversion, when adenosine is ineffective or is contraindicated. The literature reveals similar conversion rates of nondihydropyridine CCB when compared to adenosine.[13,14] The onset of action is slower for verapamil or diltiazem, 2-5 minutes compared to 10 seconds for adenosine. Patients receiving CCB often experience greater hypotension; however, this may be reduced by slow infusion of CCB, rather than bolus dosing.[14,15] Slow infusion also showed successful conversion rates of 98%.[15] The slow infusion of CCB allows minimal dosage of the drug to be delivered required for conversion of SVT, minimizing systemic side effects. Both verapamil and diltiazem are equipotent in termination of SVT, but verapamil may have an

advantage in patients with dual AV nodal pathways by increased effectiveness in prevention of SVT and an increase in the antegrade refractoriness of the slow AV nodal pathway.[16]

Intravenous beta blockers are alternatives when conversion is not achieved by either adenosine or CCBs.[1] Esmolol is a selective beta-1 adrenergic receptor, with a rapid onset, but a very short duration of action. Although esmolol can terminate an acute SVT, its efficacy compared to intravenous CCB was found to be inferior.[17] Yet beta blockers remain in the guidelines given their relative safety.[1] IV metoprolol is usually reserved for arrhythmias with rapid ventricular rate, (ie, AF or multifocal atrial tachycardia, therefore the role in acute termination of PSVT is limited.[1] Propranolol, an oral nonselective beta blocker, has a role for ongoing, outpatient management of PSVT, but has no role in acute termination.[1] A combination of oral beta blocker, propranolol 80 mg, and CCB, diltiazem 120 mg, may be effective in termination of acute SVT with conversion rate as high as 94% ($P< 0.001$), when compared to placebo and fleicanide.[18,19]

If no conversion is achieved by intravenous adenosine, CCB, and beta blockers, IV amiodarone can be tried to abort the acute event of PSVT.[1] Amiodarone is a Vaughan-Williams Class III antiarrhythmic with multiple mechanisms of action that prolongs the phase 3 action potential of cardiac muscle. A study found that amiodarone was effective in terminating an acute event of SVT, AVNRT though contraindicated in AVRT.[20] Amiodarone produces profound systemic side effects, those long-term complications are not observed with the short period use.[20] The usual presentation of a patient with SVT of unknown mechanism might limit its use.

Direct Current Cardioversion

Conversion is successful in most patients (80%-98%) without out the use of synchronized direct current cardioversion for regular SVT; however, it is necessary when pharmacological methods are contraindicated or fail to achieve conversion.[1] Synchronized cardioversion is usually reserved for SVT resulting in hemodynamic instability. The recommended energy levels used to perform synchronized cardioversion vary from 50 to 200 J biphasic, or 100-200 J monophasic.[1]

Etripamil

Etripamil is a novel CCB agent acting on the L-type calcium channel primarily on AV nodal conduction. Etripamil prolongs refractory periods

through inhibition of calcium ion influx through the calcium slow channels to terminate SVT.[5] It is short acting with a half life of less than 5 minutes. Etripamil selectively affects the slow pathway bridge sharing voltages in the surrounding coronary sinus and fast pathway region. A high-density mapping of the slow pathway in a patient with AVNRT 3 minutes postadministration of intranasal etripamil showed drastic loss of voltage in the slow pathway, resulting in a picture similar to postablation.[21] The voltage in this area has a slow recovery after several minutes, with gradual recovery of conduction through AV node.

The NODE-1 trial was a phase 2 dose-finding study in which 104 patients in sustained SVT for 5 minutes were randomized to either 4 various strengths of intranasal etripamil (35 mg, 75 mg, 105 mg, or 140 mg) or placebo. The conversion rates were 35% in the placebo group, compared to 65% of the 35-mg etripamil group (OR not reported; P= 0.1128), 87% of the 70-mg etripamil group (OR 12.38; 95% CI, 2.28-82.26; $P < 0.0006$), 75% of the 105-mg etripamil group (OR 5.57; 95% CI, 1.19-27.63; $P < 0.0248$), and 95% of the 140-mg etripamil group (OR 37.14; 95% CI, 3.84-1654.17; $P < 0.0001$). Fifty percent of the patients were converted in <3 minutes.

Rare adverse events encountered were local irritation like nasal congestion, oropharyngeal pain, cough, rhinorrhea, dysgeusia, lacrimation, vomiting, and nausea. Only one patient had an episode of hypotension with type II degree AV block 5 minutes after administration of etripamil 140 mg. There was no demonstrated decrease in systolic blood pressure compared to baseline from 2 to 16 minutes after drug administration in the 35 mg and 70 mg groups. Based on the trial results, the 70-mg dosing strategy has proceeded to phase 3 trial for termination of PSVT.[22]

Based on the results from theNODE-1 trial, etripamil appears to be an effective noninvasive model for conversion of SVT. In cases of PSVT where symptoms may be sporadic, etripamil poses a viable outpatient medication that can be easily used intranasally. Although Valsalva maneuver can also still be performed by the patient without the aid of a medical practitioner, the need to lie down and its variable success in conversion does not make it as effective and easy to use as an intranasal medication. The modified Valsalva has a better conversion rate compared to the standard, but it requires assistance of a medical practitioner and yet the conversion rate is not as high as etripamil. Therefore, intranasal etripamil seems to be an easy, effective mode of conversion that can be administered by the patient in case of PSVT without warranting a trip to the Emergency Department (ED).

Furthermore, etripamil is relatively safe compared to other medications used in the acute conversion of SVT. The local irritative side effects

were noted to be due to the presence of drug in the throat, which can be avoided counseling on better positioning of the head during administration through elevation of bed to 30˚, bringing the chin close to the head, and avoiding swallowing.

Conclusion

Etripamil appears to be an effective and safe noninvasive mode for conversion of SVT. Valsalva and modified Valsalva maneuvers are

Table 1. Different modalities in treatment of SVT

Treatment modality	Clinical trials	Conversion rate	Side effects
Valsalva maneuver	Smith et al (2015)	19.4% and 54.3%. What is 19% refer to?	Relatively safe
Modified valsalva maneuver	Appelboam et al (2015) Revert Trial	Modified – 43% Standard – 17%	Relatively safe
Intranasal etripamil	Stambler et al (2017) Node 1 Trial	Placebo – 35% 35 mg – 65% 70 mg – 87% 105 mg – 75% 140 mg – 95%	Nasal congestion, oropharyngeal pain, cough, rhinorrhea, dysgeusia, lacrimation, vomiting, and nausea. Episode of hypotension with II-degree AV block with 140 mg etripamil.
Adenosine	Cairns et al (1991) Gausche et al (1994)	Adenosine – 96% Adenosine – 85% ≈90% (85-96%)	Bronchoconstriction, shortness of breath, chest tightness, and flushing.
Verapamil	Lim et al (2009)	Verapamil ≈90% - as high as 98% on slow infusion	Hypotension, AV block.
Beta-blocker	Gupta et al (1999)	Not as efficacious as CCB, in termination of SVT. Which BB? Would like to have %	Hypotension, increased sweating, nausea, dizziness, and drowsiness
Amiodarone	Gambhir et al (1996)	78% in AVNRT	Bradycardia, AV block, QT prolongation, Torsades de pointes, hypotension, pulmonary fibrosis in long-term use.
Combination oral diltiazem and propanalol	Alboni et al (2001)	Diltiazem+ Propranolol – 94% Placebo – 52% Fleicanide – 61%	Hypotension, AV block, sinus bradycardia.

limited by low success rates and may require the assistance of a medical provider. In cases of PSVT where symptoms may be sporadic, etripamil'sease of intranasal administration and effectiveness in conversion may be a viable option for outpatient use and avoid a trip to the ED. The efficacy of etripamil is comparative to other available intravenous medications (Table 1) without the profound systemic side effects, specifically hypotension, which is notoriously associated with the other intravenous agents who share its same mechanism. Not only does etripamil represents a novel treatment potential for the outpatient setting but also a viable treatment option in the ED. Intranasal delivery is becoming more widespread in drug delivery for the ED and its effectiveness demonstrated by high-density mapping is comparative to postablation will convince providers of its utility. Therefore, etripamil is a novel intranasal CCB for the acute setting of regular SVT that appears to be a safe and effective drug that can be readily self-administered by patients in an outpatient setting, as well as by physicians at the bedside, without concerns of severe side effects.

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