

Pharmacy & Therapeutics Committee
Dofetilide (Tikosyn)
3/2003

Recommendations:

- Dofetilide will be added to formulary for use in the FDA approved indications:
 - Tikosyn is indicated for conversion of atrial fibrillation and atrial flutter to NSR.
 - Tikosyn is indicated for maintenance of NSR in patients with atrial fib/flutter of greater than one week duration who have been converted to NSR. Dofetilide should be reserved for patients who are highly symptomatic.
- A competency test will be provided to all pharmacists and nursing staff where it will be initiated.
- A cardiology consult is recommended for all patients started on dofetilide.
- The patient package insert should be provided and explained to the patient prior to initiation of therapy.
- Orders for dofetilide in a dofetilide naïve patient must be on the preprinted order form.
- Prescribing physicians must be a confirmed dofetilide prescriber.

Findings:

- Tikosyn is indicated for maintenance of NSR in patients with atrial fib/flutter of greater than one weeks duration who have been converted to NSR. Dofetilide should be reserved for patients who are highly symptomatic.
- Tikosyn is indicated for conversion of atrial fibrillation and atrial flutter to NSR.
- *Dofetilide must be started only in patients placed for a minimum of 3 days in a facility that can provide ECG monitoring and in the presence of personnel trained in the management of serious ventricular arrhythmias.*
- Dofetilide is a Vaughn Williams Class III antiarrhythmic and blocks the I_{kr} potassium channel.
- Dofetilide increases the monophasic action potential duration, primarily due to delayed repolarization.
- QT interval prolongation is a result of prolongation of both effective and functional refractory periods in the His-Purkinje system and the ventricles.
- Dofetilide does not increase the electrical energy required to convert electrically induced VF. Dofetilide significantly reduces the defibrillation threshold in patients with VT or VF undergoing implantation of a cardioverter-defibrillator.
- Dofetilide does not effect cardiac output, cardiac index, stroke volume index, or systemic vascular resistance in patient with VT, mild to moderate CHF, angina, or low left ventricular EF.
- *Dofetilide is eliminated by glomerular filtration and active tubular secretion via the cation transport system. This ion transport system can be inhibited by cimetidine, trimethoprim, prochlorperazine, megestrol, and ketoconazole.*
- *QTc interval prolongation and the risk of ventricular arrhythmias are directly related to plasma concentration of dofetilide.*
- *Clearance of dofetilide decreases with decreasing renal function. Dosing should be adjusted for renal function.*
 - *In clinical trials 23% of patients had their initial dosage decreased due to creatinine clearance and 3% due to QTc interval prolongation. Prolongation of QT or QTc interval lead to drug discontinuation in 3% of patients.*
- *Clearance in women 12-18% lower than men after correction for weight and creatinine clearance.*
- *The incidence of torsade de pointes was approximately 3x higher in females than males in clinical studies.*
- *Amiodarone levels are available with a turn around time of 4-5 days.*
- *Dofetilide levels are not available.*
- *Torsade de pointes may be treated with magnesium sulfate infusion or isoproterenol infusion with or without cardiac pacing.*
- The Arizona Health Sciences Center web site www.torsades.org has a list of drugs with associated with torsades graded into four categories. (see attached printouts)

Contraindications:

- *Congenital or acquired long QT syndromes*
 - *Baseline QTc > 440 msec (500 msec in patients with ventricular conduction abnormalities)*
 - *Calculated creatinine clearance < 20 ml/min.*
 - *Patients receiving cimetidine, hydrochlorothiazide, ketoconazole, prochlorperazine, megestrol, trimethoprim, and verapamil.*
- Note: Hydrochlorothiazide increases dofetilide's serum levels and has increased rates of torsades.*

Precautions

- *Tikosyn's use in the conjunction with other drugs that prolong the QT interval has not been studied and is not recommended (phenothiazines, cisapride, bepridil, tricyclic antidepressants, and erythromycin).*
- *Medications secreted by the cationic pathway should be used with caution (triamterene, metformin, and amiloride)*
- *Class I or III antiarrhythmic agents should be withheld for at least 3 half-lives prior to starting Tikosyn.*
- *Tikosyn should be stopped for two days before starting potentially interacting drugs.*
- *Tikosyn should not be initiated following amiodarone until the serum amiodarone levels are < 0.3 mg/l or amiodarone had been withdrawn for at least three months.*
- *Potassium levels should be within the normal range prior to administration of Tikosyn.*

Dofetilide Package Insert Data				
Dofetilide Conversion to Normal Sinus Rhythm				
Dofetilide Dose	125 mcg BID	250 mcg BID	500 mcg BID	Placebo
Study 1	6%	10%	30%	1%
Study 2	6%	11%	29%	1%
Median Time (days) to Recurrence of AF/AFI				
Study 1	31	179	>365	27
Study 2	182	>365	>365	34
Study 1 (Dofetilide and electrical cardioversion)				
Randomized	82	82	77	84
Achieved NSR	60	61	61	68
6 months				
Still on treatment in NSR	38%	44%	52%	32%
D/C for recurrence	55%	49%	33%	63%
D/C for AE	3%	3%	8%	4%
12 months				
Still on treatment in NSR	32%	26%	46%	22%
D/C for recurrence	58%	57%	36%	72%
D/C for AE	7%	11%	8%	6%
Study 2 (Dofetilide and electrical cardioversion)				
Randomized	135	133	129	137
Achieved NSR	103	118	100	106
6 months				
Still on treatment in NSR	41%	49%	57%	22%
D/C for recurrence	48%	42%	27%	72%
D/C for AE	9%	6%	10%	4%
12 months				
Still on treatment in NSR	25%	42%	49%	16%
D/C for recurrence	59%	47%	32%	76%
D/C for AE	11%	6%	12%	5%

Summary of Torsade de Pointes in Patients Randomized to Dofetilide by Dose in patients with Supraventricular Arrhythmias				
Dose	< 250 mcg BID	250 mcg BID	> 250-500 mcg BID	> 500 mg BID
Number of Patients	217	388	703	38
Torsade de Pointes	0	0.3%	0.9%	10.5%

Incidence of Torsade de Pointes Before and After Introduction of Dosing According to Renal Function			
	Total	Before	After
Supraventricular Arrhythmias	11/1346 (0.8%)	6/193 (3.1%)	5/1153 (0.4%)
Diamond CHF	25/762 (3.3%)	7/148 (4.7%)	18/614 (2.9%)
Diamond MI	7/749 (0.9%)	3/101 (3%)	4/648 (0.6%)
Diamond AF	4/249 (1.6%)	0/43 (0%)	4/206 (1.9%)

Dofetilide's Pharmacokinetic Parameters	
Oral Bioavailability	> 90%
Time to Cmax post dose	2-3 hours
Half-life (creatinine clearance > 60 ml/min)	10 hours
Time to Steady State (creatinine clearance > 60 ml/min)	2-3 days
Protein Binding	60-70%
Volume of distribution	3 liters/kg
Renal Elimination	80%
Fraction Excreted Unchanged	80%
Normal Therapeutic Levels	1-3.5 ng/ml

MANAGEMENT OF DRUG-INDUCED TORSADE DE POINTES

- PATIENT DATA/BACKGROUND:
- How is drug-induced torsade de pointes managed?
- RESPONSE:
- Overall, treatment of torsade de pointes (TDP) is aimed at: 1) diagnosing TDP by means of its characteristic electrocardiogram (ECG) tracing, 2) identifying and discontinuing any drugs known to cause the arrhythmia, 3) correcting any electrolyte disorders that may cause or contribute to the dysrhythmia, 4) increasing the patient's heart rate until the risk for recurrent TDP has dissipated, and 5) providing continuous ECG monitoring until no further episodes of TDP have occurred for at least 48 hours (Stratmann & Kennedy, 1987).
- Torsade de pointes, literally meaning "twisting around the points", is a distinctive ventricular dysrhythmia. TDP occurs in the presence of delayed repolarization, represented by a prolonged QT interval on ECG tracing, that leads to a polymorphous ventricular tachycardia (Tzivoni, 1988). The ECG tracing of torsade de pointes is characterized by a discernible ECG tracing depicting a sinusoidal-shaped twisting of ventricular complexes around the isoelectric line. TDP is suggested to be due to either a dispersion of repolarization or early after-depolarizations occurring within ventricular muscle (Surawicz, 1989). Some authors refer to TDP as recurrent ventricular fibrillation or a transitional stage between ventricular tachycardia and ventricular fibrillation (Kossman, 1978; Ranquin, 1978).
- TDP may occur in association with several disease states, electrolyte disorders (eg, hypokalemia or hypomagnesemia), or as a complication of treatment with drugs that affect ventricular repolarization. With drug-induced TDP, the proarrhythmia may occur at therapeutic concentrations and is not necessarily related to elevated concentrations of the culprit medication. Medications implicated in causing TDP include (Stratmann & Kennedy, 1987; Raehl et al, 1985):
ANTIARRHYTHMICS:
 - Type IA
 - Quinidine (high incidence: 1.5% to 8%)
 - Procainamide
 - Disopyramide
 - Type IC
 - Encainide
 - Flecainide
 - Type III
 - Ibutilide (Prod Info Covert(R), 1996)
 - Amiodarone
 - Sotalol
 - Sematilide
 - Other
 - Adenosine (Wesley & Turnquest, 1992)
- VASODILATORS: Prenylamine, lidoflazine, fenoxedil, and bepridil
- PSYCHOTROPICS: Antipsychotics (eg, thioridazine, haloperidol, pimozide (Krahenbuhl et al, 1995) and antidepressants (eg, maprotiline, amitriptyline).
- ANTIHISTAMINES: Terfenadine and astemizole (Tech Info Seldane(R), 1996; Prod Info Hismanal(R), 1996).
- ANTIBIOTICS: Erythromycin, spiramycin, pentamidine, and sulfamethoxazole-trimethoprim (Lopez et al, 1987)
- MISCELLANEOUS DRUGS: Corticosteroids, diuretics (via Electrolyte disorders), chloroquine, suxamethonium, isoproterenol, amantadine, chloral hydrate, vasopressin, atropine, cisapride (Ahmad & Wolfe, 1995), halofantrine (Toivonen et al, 1994), and tacrolimus (Johnson et al, 1992).
- Clinical outcomes with drug-induced torsade de pointes range from asymptomatic, self-terminating arrhythmias to ventricular fibrillation resulting in cardiac arrest (Raehl et al, 1985). Risk factors include electrolyte or metabolic disturbances such as hypomagnesemia, hypokalemia, anorexia, and liquid protein diets; congenital long QT syndrome; underlying cardiac conditions such as bradycardia, myocardial ischemia, and mitral valve prolapse; administering any of the above drugs in combination, or administering any of the above drugs concurrently with drugs known to inhibit the culprit drug's metabolism.
- The combination of terfenadine and erythromycin would be an example of where two drugs known to cause TDP are being used concurrently with one of the medications (erythromycin) inhibiting the metabolism of the other medication (terfenadine), further increasing the risk for TDP to occur (Smith, 1994).
- Prevention of TDP includes identifying the risk factors, obtaining the baseline ECG and measuring the QT intervals before and while giving a drug known to cause TDP, avoiding supratherapeutic drug levels, and avoiding simultaneous use of drugs known to produce TDP individually (eg, combination of disopyramide and amiodarone) (Stratmann & Kennedy, 1987).
- With respect to acute therapy of TDP, electrical cardioversion may be performed if the patient becomes hemodynamically compromised during the rhythm disturbance, but this therapy would only be a temporary measure and would not prevent recurrences of TDP as long as the patient was still at risk for TDP due to the continued presence of an instigator of TDP. Specific emergent treatment to prevent recurrences of TDP until contributing factors have been removed or corrected include isoproterenol and/or atrial and ventricular overdrive pacing to increase heart rate and prevent any abnormal repolarization

and/or early after- depolarization. Magnesium sulfate (2 grams intravenous bolus) has also been promoted as a first line emergency treatment of drug-induced TDP. One 2-gram bolus intravenously abolished TDP immediately in 9 patients; three others responded to another 2-gram intravenous bolus of magnesium, 15 minutes after the initial bolus. The use of magnesium sulfate infusion was rapid and simple, and was not associated with adverse effects (Tzivoni et al, 1988). Alternative therapies, such as lidocaine, mexiletine, verapamil, bretylium, phenytoin, propranolol, calcium gluconate, and atropine, have been tried, but their efficacies are questionable and inconsistent and therefore cannot be recommended as routine therapy (Stratmann & Kennedy, 1987).

- Amiodarone, which has been shown to cause drug-induced TDP, has been demonstrated to be effective in chronic antiarrhythmic management in patients with a history of drug-induced TDP. In a study, 12 patients with drug-induced TDP received amiodarone 1200 milligram to 1600 milligram/day loading dose for 7 to 14 days, followed by a maintenance dose of 400 milligrams to 600 milligrams/day (5 days per week) for 3 months for therapy of serious, persistent cardiac arrhythmias. Only one patient had long-term adverse effects (pulmonary toxicity) requiring discontinuation of amiodarone. This study suggests that amiodarone can generally be used safely and effectively for long-term antiarrhythmic therapy in patients who had developed drug-induced TDP with other medications (Mattioni et al, 1989).

- **CONCLUSION:**

- Prevention of TDP includes identifying the risk factors, obtaining a baseline ECG and measuring the QT intervals before giving a drug known to cause TDP, and avoiding the use of combination drugs known to produce TDP individually. Standard emergency therapy typically includes: correcting electrolyte disorders, the administration of magnesium sulfate, and increasing the heart rate through administration of isoproterenol and/or atrial and ventricular overdrive pacing until the cause of TDP has been corrected. Electric shock may be necessary if the patient becomes hemodynamically compromised during the rhythm disturbance.

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TORSADE DE POINTES - DRUG OF CHOICE

RESPONSE:

Many cases of drug induced Torsade de Pointes will resolve spontaneously once the offending agent has been discontinued and eliminated from the body. Occasionally episodes degenerate into ventricular fibrillation (150 to 300 beats/min). Where drug-induced polymorphous ventricular arrhythmias leads to life-threatening conditions and there is no underlying organic abnormality, magnesium in the form of magnesium sulfate (1 gram, repeated once if necessary) is the drug of choice due to its low toxicity and wide therapeutic margin (Anon, 1996).

Ventricular pacing may be considered as a second line alternative if the patient does not have another underlying cardiac problem.

Ventricular pacing may be accomplished either by electronic or drug-induced methods. A transvenous pacemaker may be placed or isoproterenol may be administered to cause a drug-induced tachycardia. Extreme caution should be used with patients having mitral valve prolapse, myocardial ischemia, or abnormal atrioventricular conduction.

Potassium chloride should be given cautiously at 10 to 20 mEq/hour to maintain serum potassium between 4 to 5.5 mEq/L (Anon, 1996).

Pharmacist Work Sheet for Tikosyn

Patient _____ MR# _____ Room# _____
 Physician _____ Admission Date _____
 Age _____ Gender: M / F Height _____ LBW _____ Actual Weight _____
 Calculated Creatinine Clearance: _____ Treatment Diagnosis _____

1. The preprinted order form must be use for all dofetilide naïve patients.
2. Verify physician enrollment (1-888-609-4375) or www.Tikosynlist.com. You will need the physician's and our DEA number BB5796896.
3. Calculated the patient's creatinine clearance and verify dosage is appropriate.
4. Screen profile for contraindicated drugs (cimetidine, hydrochlorothiazide, ketoconazole, prochlorperazine, megestrol, trimethoprim, and verapamil)
5. Screen for precautionary drugs. Drug lists are available at www.torsades.org
6. Screen that antiarrhythmics have been held for 3 half-lives as noted below.

Class Ia	Class Ib	Class Ic	Class III
Procainamide 18 hours	Lidocaine 6 hours	Flecainide 81 hours	Amiodarone (90 days or level < 0.3 mg/l)
Quinidine 21 hours	Mexiletine 30 hours	Propafenone 96 hours	Sotalol 36 hours
Disopyramide 30 hours	Tocainide 42 hours		

7. Verify that the Tikosyn Resource Kit is delivered to the nursing unit. Nursing staff will educate the patient.
8. Provide 7 days of medication.
9. Fax Stadlanders Pharmacy Service Enrollment Form 1/800/221/0504. Additional Stadlanders Pharmacy Services Enrollment Forms may be obtained by calling 1/800/238/7828
10. Fax outpatient prescription to Stadlanders 1-800-426-9613 or call 1-888-671-7465. This should be done the first day of admission or as soon as it is known the patient requires Tikosyn.