

Cardiovascular Monitoring of Children and Adolescents Receiving Psychotropic Drugs

A Statement for Healthcare Professionals From the Committee on Congenital Cardiac Defects, Council on Cardiovascular Disease in the Young, American Heart Association

Howard Gutgesell, MD, Chair; Dianne Atkins, MD; Robyn Barst, MD; Marcia Buck, PharmD;
Wayne Franklin, MD; Richard Humes, MD; Richard Ringel, MD;
Robert Shaddy, MD, members; Kathryn A. Taubert, PhD, AHA Staff

Overview

Reports of sudden deaths of children and adolescents treated with psychotropic medications have raised concerns regarding the appropriateness of this therapy, as well as the advisability of baseline and periodic electrocardiographic (ECG) monitoring of such patients.¹⁻⁴ What follows is a review of the drug effects on the ECG, cardiovascular effects of the commonly used psychotropic medications in children and adolescents, a summary of potentially dangerous drug interactions, and recommendations for cardiovascular monitoring.

Potential Mechanisms for Sudden Death

Although medications can potentially cause sudden, unexpected death by a variety of mechanisms (eg, seizures, central nervous system depression, or coronary artery spasm), cardiac arrhythmias are the most frequent cause. In particular, a unique form of ventricular tachycardia termed torsade de pointes has been recognized as the arrhythmia responsible for the so-called proarrhythmic effect of several antiarrhythmia drugs, and recent evidence has pointed to a similar mechanism in syncope and deaths related to other medications⁵ and in the familial long-QT syndromes.⁶ The common feature of these conditions is delayed repolarization of the myocardium (related to abnormal sodium or potassium currents) with resultant prolongation of the QT interval of the ECG. This appears to leave the myocardium vulnerable to ventricular tachycardia, primarily in the setting of bradycardia but occasionally in association with exercise.

Other ECG abnormalities, such as sinus node depression, second- or third-degree heart block, and supraventricular

tachycardia, seem unlikely causes of sudden death in patients receiving psychotropic medications. Additionally, the rSR' pattern in lead V₁, sometimes referred to as incomplete right bundle-branch block or right ventricular conduction delay, is a normal childhood variant and is not a risk factor for sudden death.

Specific Drugs

The major cardiovascular and electrophysiological effects of the commonly used psychotropic drugs are listed in Table 1. Stimulants such as the amphetamines and methylphenidate (Ritalin) cause slight but clinically insignificant increases in heart rate and blood pressure. The tricyclic antidepressants (TCA) imipramine and desipramine have been associated with at least 7 reported deaths in young patients.^{1,7} The precise mechanism of death has not been documented. Some of the patients have had toxic levels of drugs, and at least 2 had risk factors for sudden death (a coronary anomaly in 1 and a family history of sudden death in another). The ECG effects of TCA administration include an increase in heart rate (by 20% to 25%), prolongation of the PR interval (by 5% to 10%), increase in QRS duration (by 7% to 25%), and prolongation of the QT interval (by 3% to 10%). Although 8% of patients have a corrected QT interval (QTc) of >460 ms, the mean value of the QTc remained within normal limits for pediatric patients.^{4,8-11} Malignant arrhythmias, in particular torsade de pointes, have not been documented except for the ventricular fibrillation observed in the emergency room in the patient with a family history of sudden death.

The selective serotonin reuptake inhibitors have minimal cardiovascular effects; deaths have been rare, even with

This statement was approved by the American Heart Association Science Advisory and Coordinating Committee in November 1998. A single reprint is available by calling 800-242-8721 (US only) or writing the American Heart Association, Public Information, 7272 Greenville Avenue, Dallas, TX 75231-4596. Ask for reprint No. 71-0159. To purchase additional reprints: up to 999 copies, call 800-611-6083 (US only) or fax 413-665-2671; 1000 or more copies, call 214-706-1466, fax 214-691-6342, or e-mail pubauth@amhrt.org. To make photocopies for personal or educational use, call the Copyright Clearance Center, 978-750-8400.

(*Circulation*. 1999;99:979-982.)

© 1999 American Heart Association, Inc.

Circulation is available at <http://www.circulationaha.org>

TABLE 1. Cardiac Effects of Psychotropic Medications

Class	Medication	Cardiac Effects and Comments	Recommendations for Cardiovascular Monitoring
Stimulants	Methylphenidate (Ritalin)	Cardiovascular <ul style="list-style-type: none"> ● Mild tachycardia and increase in blood pressure ● Adrenergic blockers are inhibited ● Sympathomimetics are enhanced ● Report of sudden death in 1 child treated simultaneously with clonidine 	No specific cardiovascular monitoring is indicated
	Pemoline (Cylert)	<ul style="list-style-type: none"> ● Minimal cardiac effects ● Hepatotoxicity 	No specific cardiovascular monitoring is indicated
	Dextroamphetamine	<ul style="list-style-type: none"> ● Tachycardia/palpitations 	No specific cardiovascular monitoring is indicated
Antidepressants			
TCAs	Desipramine (Norpramin); imipramine	Cardiovascular <ul style="list-style-type: none"> ● Rare reports of sudden death ● Prolongation of the QTc, PR, QRS ● Sinus tachycardia Other <ul style="list-style-type: none"> ● Cimetidine increases levels of TCA ● Ritalin decreases the metabolism ● May increase action of other sympathomimetic agents ● Watch drug-drug interactions! 	<ol style="list-style-type: none"> 1. Baseline history and physical 2. Current medication history 3. Baseline ECG measuring: <ul style="list-style-type: none"> ● PR \leq 200 ms ● QRS duration \leq 120 ms ● QTc \leq 460 ms 4. Follow-up ECG and history after a steady state is achieved on 3–5 mg/kg for desipramine and 3–5 mg/kg for imipramine
Selective serotonin reuptake inhibitors	Fluoxetine (Prozac)	Cardiovascular <ul style="list-style-type: none"> ● No significant ECG change ● Interacts with protein-bound medications such as digoxin and warfarin 	No specific cardiovascular monitoring is indicated Digoxin and warfarin dose may need adjustment
	Sertraline (Zoloft)	Cardiovascular <ul style="list-style-type: none"> ● No significant ECG abnormalities ● Mild tachycardia Other <ul style="list-style-type: none"> ● No MAOI 	
	Paroxetine (Paxil)	No significant cardiac effects P450: evaluate other medications	Possible interaction with P450 system
Other antidepressants	Bupropion (Wellbutrin)	Little information on cardiac effects Dopamine agonist	No specific cardiovascular monitoring is indicated
	Lithium	Cardiovascular <ul style="list-style-type: none"> ● Reports of arrhythmias ● Flattened T waves Other <ul style="list-style-type: none"> ● Monitor levels ● Diuretics decrease renal clearance (especially thiazide diuretics) 	No specific cardiovascular monitoring is indicated
Other psychotropic agents			
α -2 Adrenergic agonist	Clonidine (Catapres)	Cardiovascular <ul style="list-style-type: none"> ● Hypotension ● Rebound hypertension when discontinuing 	<ol style="list-style-type: none"> 1. Monitor blood pressure when medication is started 2. Monitor blood pressure when weaning from the medication 3. No ECG monitoring is necessary
	Guanfacine (Tenex)	<ul style="list-style-type: none"> ● Similar to clonidine 	
Antipsychotics/ neuroleptics			
Phenothiazines	Chlorpromazine Thioridazine Mesoridazine Perphenazine Trifluoperazine Fluphenazine	Cardiovascular <ul style="list-style-type: none"> ● Tachycardia (anticholinergic) ● Hypotension ● Prolongation of the QTc (be aware of other medications that prolong the QTc) 	<ol style="list-style-type: none"> 1. Baseline history and physical 2. Current medication history 3. Baseline ECG measuring: <ul style="list-style-type: none"> ● PR \leq 200 ms ● QRS duration \leq 120 ms ● QTc \leq 460 ms 4. Follow-up ECG and history after therapeutic levels are reached

TABLE 1. Continued

Class	Medication	Cardiac Effects and Comments	Recommendations for Cardiovascular Monitoring
Butyrophenones	Haloperidol (Haldol)	Cardiovascular <ul style="list-style-type: none"> ● Tachycardia (anticholinergic) ● Hypotension ● Prolongation of the QTc (be aware of other medications that prolong the QTc) 	<ol style="list-style-type: none"> 1. Baseline history and physical 2. Current medication history 3. Baseline ECG measuring: <ul style="list-style-type: none"> ● PR \leq200 ms ● QRS duration \leq120 ms ● QTc \leq460 ms 4. Follow-up ECG and history after therapeutic levels are reached
Diphenylbutylpiperidine	Pimozide (Orap)	Cardiovascular <ul style="list-style-type: none"> ● Prolongation of QTc (be aware of other medications that prolong the QTc) 	<ol style="list-style-type: none"> 1. Baseline history and physical 2. Current medication history 3. Baseline ECG measuring: <ul style="list-style-type: none"> ● PR \leq200 ms ● QRS duration \leq120 ms ● QTc \leq460 ms 4. Follow-up ECG and history after therapeutic levels are reached
Dihydroindolone	Molindone (Moban)	Sinus tachycardia One of the few tranquilizers without a warning about the QTc	No specific cardiovascular monitoring is indicated

MAOI indicates monoamine oxidase inhibitor.

massive overdose. Clonidine, a widely used antihypertensive medication, has been associated with 2 deaths in patients who also received methylphenidate, but the mechanism for these deaths is unknown and may have been sudden cessation of treatment.

Drug Interactions

Many psychotropic medications are metabolized by the cytochrome P450 system, an enzyme system that may be inhibited by a multitude of medications¹² (Table 2). Adverse effects have occurred when the P450 system is inhibited, which leads to elevated levels of medications that prolong the QT interval and produce ventricular tachycardia (torsade de pointes). Most notable have been deaths related to torsade de pointes from nonsedating histamine-blocking agents such as terfenadine (Seldane) and astemizole (Hismanal).¹³ Many of these episodes were associated with coadministration of other medications such as macrolide antibiotics or imidazole antifungal agents (Table 2). Other classes of medications that inhibit or are metabolized by the P450 cytochrome system include antidepressants, calcium channel blockers, histamine blockers, gastrointestinal motility agents, and steroids. Prolongation of the QT interval and torsade de pointes have been reported in young children taking cisapride.

Antiarrhythmic drugs of class Ia (eg, disopyramide, procainamide, and quinidine) and class III (eg, amiodarone and sotalol) likewise prolong the QT interval, and therefore concomitant use of psychotropic medications with these drugs is not recommended.

Family History

In some families, syncope and sudden death have been related to familial prolongation of the QT interval and torsade de pointes. Such individuals are at increased risk for arrhythmias due to medications that prolong the QT interval. Drugs that

prolong the QT interval are contraindicated in patients with familial long-QT syndrome.

Recommendations

1. Before therapy with psychotherapeutic agents is initiated, a careful history should be obtained, with special attention to symptoms such as palpitations, syncope, or near syncope. Medication use (prescribed and over-the-counter) should be determined. The family history should be reviewed with reference to the long-QT syndrome or other causes of sudden, unexplained death. Detection of these symptoms or risk factors warrants a cardiovascular evaluation by a pediatric cardiologist before initiation of therapy.
2. At follow-up visits, patients receiving psychotropic drug therapy should be questioned about the addition of any drugs and the occurrence of any of the above symptoms. The physical examination should include determination of heart rate and blood pressure.
3. Despite the lack of understanding of the mechanism of sudden death in young patients taking TCAs or demonstration that ECG monitoring could prevent these deaths, ECG monitoring at baseline and during chronic therapy has been recommended.^{4,14,15} Until more data are available, it seems prudent to obtain an ECG at baseline before TCA or phenothiazine therapy is begun (primarily to detect unsuspected instances of long-QT syndrome) and another when steady state is achieved. If the sustained resting heart rate is >130 bpm, the PR interval is >200 ms, QRS is >120 ms, or QTc is >460 ms, or if symptoms such as palpitations, near syncope, or syncope develop, alternative therapy may need to be considered along with pediatric cardiology consultation.
4. Concomitant use of psychotropic drugs and other drugs that are metabolized by or inhibit the P450 enzyme system should be avoided.

TABLE 2. Potential Drug Interactions

Group A. Drugs metabolized by the cytochrome P450 enzyme systems*

1. Psychotropics	
Amitriptyline	Clomipramine
Desipramine	Imipramine
Nortriptyline	Thioridazine
2. Antiepileptics	
Carbamazepine	Phenytoin
Valproic acid	
3. Antiarrhythmics	
Amiodarone	Diltiazem
Encainide	Felodipine
Flecainide	Metoprolol
Nifedipine	Propranolol
Quinidine	Timolol
Verapamil	
4. Other	
Cisapride	Cyclosporine
Lovastatin	Omeprazole
Tacrolimus	Terfenadine
Warfarin	

Group B. Drugs inhibiting the cytochrome P450 enzyme systems*

1. Antibiotics	
Clarithromycin	Erythromycin
Fluconazole	Itraconazole
Ketoconazole	Miconazole
2. Psychotropics	
Fluoxetine	Fluvoxamine
Haloperidol	Paroxetine
3. Other	
Cimetidine	Grapefruit juice
Quinidine	

*Concomitant use of drugs from group A and group B may result in augmentation of pharmacological and toxic effects of group A drugs. Drug reduction and careful monitoring is required.

References

- Popper CW, Zimnitzky B. Sudden death putatively related to desipramine treatment in youth: a fifth case and a review of speculative mechanisms. *J Child Adolesc Psychopharmacol*. 1995;5:283-300.
- Werry JS, Biederman J, Thisted R, Greenhill L, Ryan N. Resolved: cardiac arrhythmias make desipramine an unacceptable choice in children. *J Am Acad Child Adolesc Psychiatry*. 1995;34:1239-1245; discussion 1245-1248.
- Biederman J, Thisted RA, Greenhill LL, Ryan ND. Estimation of the association between desipramine and the risk for sudden death in 5- to 14-year-old children. *J Clin Psychiatry*. 1995;56:87-93.
- Biederman J, Baldessarini RJ, Wright V, Knee D, Harmatz JS, Goldblatt A. A double-blind placebo controlled study of desipramine in the treatment of ADD, II: serum drug levels and cardiovascular findings. *J Am Acad Child Adolesc Psychiatry*. 1989;28:903-911.
- Roden DM, Thompson KA, Hoffman BF, Woosley RL. Clinical features and basic mechanisms of quinidine-induced arrhythmias. *J Am Coll Cardiol*. 1986;8(suppl A):73A-78A.
- Keating MT, Sanguinetti MC. Molecular genetic insights into cardiovascular disease. *Science*. 1996;272:681-685. Review.
- Riddle MA, Nelson JC, Kleinman CS, Rasmusson A, Leckman JF, King RA, Cohen DJ. Sudden death in children receiving Norpramin: a review of three reported cases and commentary. *J Am Acad Child Adolesc Psychiatry*. 1991;30:104-108.
- Schroeder JS, Mullin AV, Elliott GR, Steiner H, Nichols M, Gordon A, Paulos M. Cardiovascular effects of desipramine in children [see comments in *J Am Acad Child Adolesc Psychiatry* 1989;28:964-965]. *J Am Acad Child Adolesc Psychiatry*. 1989;28:376-379.
- Wilens TE, Biederman J, Baldessarini RJ, Geller B, Schleifer D, Spencer TJ, Birmaher B, Goldblatt A. Cardiovascular effects of therapeutic doses of tricyclic antidepressants in children and adolescents. *J Am Acad Child Adolesc Psychiatry*. 1996;35:1491-1501. Review.
- Wilens TE, Biederman J, Baldessarini RJ, Puopolo PR, Flood JG. Electrocardiographic effects of desipramine and 2-hydroxydesipramine in children, adolescents, and adults treated with desipramine. *J Am Acad Child Adolesc Psychiatry*. 1993;32:798-804.
- Fletcher SE, Case CL, Sallee FR, Hand LD, Gillette PC. Prospective study of the electrocardiographic effects of imipramine in children. *J Pediatr*. 1993;122:652-654.
- Slaughter RL, Edwards DJ. Recent advances: the cytochrome P450 enzymes. *Ann Pharmacother*. 1995;29:619-624.
- Woosley RL, Chen Y, Freiman JP, Gillis RA. Mechanism of the cardiotoxic actions of terfenadine [see comments in *JAMA* 1993;269:1550-1552]. *JAMA*. 1993;269:1532-1536.
- Wagner KD, Fershtman M. Potential mechanism of desipramine-related sudden death in children. *Psychosomatics*. 1993;34:80-83.
- Elliott GR, Popper CW. Tricyclic antidepressants: the QT interval and other cardiovascular parameters. *J Child Adolesc Psychopharmacol*. 1990;1:187-189.

KEY WORDS: AHA Scientific Statements ■ psychotropic drugs ■ death, sudden