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...
<table>
<thead>
<tr>
<th>Class</th>
<th>Medication</th>
<th>Cardiac Effects and Comments</th>
<th>Recommendations for Cardiovascular Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stimulants</td>
<td>Methylphenidate (Ritalin)</td>
<td>Cardiovascular ● 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</td>
<td>No specific cardiovascular monitoring is indicated</td>
</tr>
<tr>
<td></td>
<td>Pemoline (Cylert)</td>
<td>● Minimal cardiac effects ● Hepatotoxicity</td>
<td>No specific cardiovascular monitoring is indicated</td>
</tr>
<tr>
<td></td>
<td>Dextroamphetamine</td>
<td>● Tachycardia/palpitations</td>
<td>No specific cardiovascular monitoring is indicated</td>
</tr>
</tbody>
</table>
| Antidepressants       | Desipramine (Norpramin); imipramine | Cardiovascular ● Rare reports of sudden death ● Prolongation of the QTc, PR, QRS ● Sinus tachycardia ● Other ● Cimetidine increases levels of TCA ● Ritalin decreases the metabolism ● May increase action of other sympathomimetic agents ● Watch drug-drug interactions! | 1. Baseline history and physical  
2. Current medication history  
3. Baseline ECG measuring: ● PR =200 ms ● QRS duration ≤120 ms ● QTc ≤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 |
|                       | Fluoxetine (Prozac) | Cardiovascular ● No significant ECG change ● Interacts with protein-bound medications such as digoxin and warfarin | No specific cardiovascular monitoring is indicated  
Dioxin and warfarin dose may need adjustment |
|                       | Sertraline (Zoloft) | Cardiovascular ● No significant ECG abnormalities ● Mild tachycardia ● Other ● No MAO! | Possible interaction with P450 system |
|                       | Paroxetine (Paxil) | No significant cardiac effects P450: evaluate other medications                               | No specific cardiovascular monitoring is indicated                                      |
| Other antidepressants | Bupropion (Wellbutrin) | Little information on cardiac effects Dopamine agonist                                        | No specific cardiovascular monitoring is indicated                                      |
|                       | Lithium          | Cardiovascular ● Reports of arrhythmias ● Flattened T waves ● Other ● Monitor levels ● Diuretics decrease renal clearance (especially thiazide diuretics) | No specific cardiovascular monitoring is indicated                                      |
| Other psychotropic agents | Clonidine (Catapres) | Cardiovascular ● Hypotension ● Rebound hypertension when discontinuing                        | 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) | ● Similar to clonidine                                                                       |                                                                                       |
| Antipsychotics/ neuroleptics | Chlorpromazine | Cardiovascular ● Tachycardia (anticholinergic)                                                | 1. Baseline history and physical  
2. Current medication history  
3. Baseline ECG measuring: ● PR =200 ms ● QRS duration ≤120 ms ● QTc ≤460 ms  
4. Follow-up ECG and history after therapeutic levels are reached |
|                       | Thoridazine      | ● Hypotension                                                                               |                                                                                       |
|                       | Mesoridazine     | ● Prolongation of the QTc (be aware of other medications that prolong the QTc)               |                                                                                       |
|                       | Perphenazine     |                                                                                               |                                                                                       |
|                       | Trifluoperazine  |                                                                                               |                                                                                       |
|                       | Fluphenazine     |                                                                                               |                                                                                       |
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 medications (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). 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. 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

<table>
<thead>
<tr>
<th>Group A. Drugs metabolized by the cytochrome P450 enzyme systems*</th>
<th>Group B. Drugs inhibiting the cytochrome P450 enzyme systems*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Psychotropics: Amitriptyline, Desipramine, Nortriptyline</td>
<td>1. Antibiotics: Clarithromycin, Fluconazole, Ketoconazole</td>
</tr>
<tr>
<td>Clomipramine, Imipramine, Thioridazine</td>
<td>Erythromycin, Itraconazole, Miconazole</td>
</tr>
<tr>
<td>2. Antiepileptics: Carbamazepine, Valproic acid</td>
<td>Fluoxetine, Fluvoxamine, Haloperidol</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Haloperidol, Paroxetine</td>
</tr>
<tr>
<td>3. Antiarrhythmics: Amiodarone, Encainide, Flecaïnide, Nifedipine, Quinidine, Verapamil</td>
<td>Fluoxetine, Fluvoxamine, Haloperidol</td>
</tr>
<tr>
<td>Diltiazem, Felodipine, Metoprolol, Propranolol, Timolol</td>
<td>Haloperidol, Paroxetine</td>
</tr>
<tr>
<td>4. Other: Cisapride, Lovastatin, Tacrolimus, Warfarin</td>
<td>Cimetidine, Cyclosporine, Omeprazole, Tacrolimus, Warfarin</td>
</tr>
<tr>
<td>Cyclosporine, Omeprazole, Tacrolimus, Warfarin</td>
<td>Cimetidine, Grapefruit juice</td>
</tr>
<tr>
<td>Group B. Drugs inhibiting the cytochrome P450 enzyme systems*</td>
<td>3. Other: Cimetidine, Grapefruit juice</td>
</tr>
<tr>
<td>1. Antibiotics: Clarithromycin, Fluconazole, Ketoconazole</td>
<td>Quinidine</td>
</tr>
</tbody>
</table>
| Erythromycin, Itraconazole, Miconazole                        | *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


Key Words: AHA Scientific Statements ■ psychotropic drugs ■ death, sudden
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, Dianne Atkins, Robyn Barst, Marcia Buck, Wayne Franklin, Richard Humes, Richard Ringel, Robert Shaddy and Kathryn A. Taubert
membersAHA Staff

*Circulation*. 1999;99:979-982
doi: 10.1161/01.CIR.99.7.979

*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1999 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/99/7/979

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Circulation* is online at:
http://circ.ahajournals.org//subscriptions/