The Journal of Emergency Medicine, Vol. 28, No. 2, pp. 169–174, 2005

0736-4679/05 $–see front matter

ELSEVIER

doi:10.1016/j.jemermed.2004.08.018

Selected Topics: Toxicology

ARE ONE OR TWO DANGEROUS? TRICYCLIC ANTIDEPRESSANT EXPOSURE IN TODDLERS

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□ **Abstract—Tricyclic antidepressants (TCA), increasingly prescribed for multiple indications in children and adults, are responsible for many pediatric poisonings. Though the majority of TCA exposures in this age group remain asymptomatic, several reports in the English language literature reveal significant morbidity as well as fatalities in toddlers, primarily from imipramine and desipramine. These few cases indicate that doses of 10–20 mg/kg (one to two pills) have the potential for toxicity and fatalities. More recent studies have focused on the relative safety of small exposures suggesting that with doses less than 5 mg/kg the patient may be safely observed at home. Though further studies are necessary to determine the exact dosing that places the child at risk, the authors recommend a 6-h Emergency Department observation period for children who ingest more than 5 mg/kg of most TCAs, as clinical toxicity becomes evident within this time frame. © 2005 Elsevier Inc.**

□ **Keywords—antidepressants; tricyclic antidepressants; children; pediatrics; toxicity; overdose; poisoning**

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INTRODUCTION

Tricyclic antidepressants (TCAs), known for the three rings in their chemical structure, include imipramine, desipramine, amitriptyline, nortriptyline, doxepin, trimipramine, protriptyline, and clomipramine. Two newer compounds have slightly different structures and toxicity: maprotiline is a tetracyclic and amoxapine is a dibenzoxapine (1–5). All TCAs have a similar side effect profile; however, maprotiline and amoxapine vary slightly. Maprotiline exhibits more severe cardiac toxicity (3,6). Amoxapine has less cardiac toxicity but an increased incidence of seizures (3,7). This article focuses on data for the traditional cyclic antidepressants (amitriptyline, desipramine, and imipramine), as these continue to be the more frequently prescribed and ingested in overdose.

Tricyclic antidepressants have remained a leading cause of poisoning fatalities since they first became available. Lethality derives from cardiovascular and central nervous system toxicity, with an overall fatal toxicity index of 34.1 deaths per million prescriptions (compared to 13.5 for monoamine oxidase inhibitors and 2.0–6.2 for selective serotonin reuptake inhibitors (SSRIs) and atypical antidepressants) (1–4,8,9). Antidepressants (including TCAs) are the second most commonly prescribed psychotropic medication in children (10). A retrospective study over a 5-year period demonstrated an

RECEIVED: 7 October 2003; FINAL SUBMISSION RECEIVED: 30 June 2004;
ACCEPTED: 3 August 2004

overall growth of 200% in the use of antidepressants in children under the age of 6 years (11). Children in this age group constitute 13% of all cyclic antidepressant users in the last 10 years (3). The growth of prescriptions in the over-6 years of age categories represents more siblings on TCAs and thus more chances for unintentional ingestion (10).

Newer antidepressants, namely the SSRIs, have slowly replaced the use of TCAs for treatment of depression in children. Despite this, TCAs continue to be available in American households due to multiple other indications for their use (12). Although TCAs have been relegated to second- or third-line therapy for depression in children, they have become the mainstay of therapy for enuresis and a treatment alternative for a variety of psychiatric conditions such as obsessive-compulsive disorder, attention-deficit hyperactivity disorder, school phobia, and separation anxiety (3,13,14). In adults, these medications are used for depression, neuralgic pain, chronic pain, and migraines, among other indications (3).

A study in the United Kingdom looked at antidepressant overdoses in all ages from 1989 to 1994. It identified an increase in prescriptions, exposures, admissions, and deaths from TCAs (15). A study at Arkansas Children's Hospital looking specifically at the characteristics of pediatric admissions for cyclic antidepressant admissions from 1988 to 1997, found an increase in the number of children younger than 6 admitted for TCA poisoning. In the last 5 years of the study, more children gained access to TCAs from extended family members or older siblings. Amitriptyline is the TCA most commonly implicated (12). The exposures exist, and the question remains whether fatalities occur in children younger than 6 years and, if so, with how much medication.

This article provides a basic overview of the pathophysiology, pharmacokinetics, and clinical manifestations of TCA toxicity. The medical management of TCA overdose has been excluded intentionally as there are many reviews on this topic and so as to allow a focus on exposure. This article reviews the available English literature on TCA exposure in young children to determine whether ingestion of one to two pills can indeed be fatal to children under the age of 6 years.

CHARACTERISTICS OF TRICYCLIC ANTIDEPRESSANTS

Pharmacokinetics

TCAs have a half-life of 7–58 h (54–92 h for protriptyline), which may be shorter in children (16). Rapid absorption occurs in the gastrointestinal (GI) tract with a peak at around 2–8 h. This drug class undergoes extensive first-pass metabolism (3,5). The implication of this in acute ingestions is that GI decontamination becomes crucial because of rapid initial absorption and because anticholinergic effects lead to delayed emptying. In the acute management of overdose, TCA serum levels are not helpful. Not only is there a significant delay in obtaining them, there is also no correlation between drug levels and clinical toxicity due to the large volume of distribution, long half-life, genetic differences, pH-dependent protein-binding, and tolerance (3,17–19).

Pathophysiology

Tricyclic antidepressants affect the autonomic, central nervous, and cardiovascular systems. TCAs have central and peripheral anticholinergic effects. Acting centrally, they inhibit re-uptake of neurotransmitters (the biogenic amines: norepinephrine, serotonin, and dopamine) into presynaptic nerve terminals and inhibit central sympathetic reflexes. Additionally, TCAs block the fast sodium channels of the myocardium, particularly in the distal conducting system (3,9,11,18).

Based on their effects on the various systems, it is clear how TCAs cause toxicity. First, centrally, the change in neurotransmitters causes delirium, psychosis, lethargy, coma, and generalized seizures. The exact mechanism for the seizures is not completely understood. Second, as competitive antagonists of muscarinic acetylcholine receptors and H1-histamine blockers, TCAs exert central and peripheral anticholinergic effects. Finally, the blockade of sodium channels in the heart causes the most dangerous effects: conduction delays and dysrhythmias. The decreased inward movement of sodium at the fast sodium channels slows phase zero of depolarization in the distal conduction system and the ventricle, thus slowing ventricular depolarization and prolonging the QRS complex. Phase 4 is also affected with slowed repolarization that manifests as QT prolongation (3,9,18,20). The pathophysiology also comes into play in the development of Brugada Syndrome (the development of ST changes in leads V_1 to V_3 because of altered sodium channel flow) in TCA overdose (21).

The most common dysrhythmia resulting from TCA overdose is sinus tachycardia secondary to peripheral anticholinergic action; however, wide complex tachycardia is the characteristic cardiac complication. The wide complex tachycardia can be supraventricular tachycardia with aberrancy or actual ventricular tachycardia (3). Much of TCA overdose evaluation and disposition has come to depend on the patient's electrocardiogram (EKG) as illustrated by various studies.

Many studies conducted in adults, and some in children, have helped delineate the use of EKG criteria in