The Journal of Emergency Medicine, Vol. 47, No. 2, pp. 155–162, 2014

0736-4679/$ - see front matter

ELSEVIER

http://dx.doi.org/10.1016/j.jemermed.2014.02.006

Selected Topics: Toxicology

TOXICITY OF ANTIHYPERTENSIVES IN UNINTENTIONAL POISONING OF YOUNG CHILDREN

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☐ **Abstract—Background: Knowledge is limited about the toxicity of unintentional exposure to antihypertensives in young children (0–6 years of age). Objective: Our aim was to research symptoms and poisoning severity in unintentional poisonings in this group of age and determine adequate poisoning management. Methods: We performed a 10-year retrospective, explorative analysis of the Mainz Poison Center/Germany database with regard to circumstances of poison exposure, dosage, symptoms, and treatment. To be able to relate drug exposure with reported symptoms, analyses were restricted to single drug exposures. Written follow-up information was obtained in about 50% of all cases. Results: A total of 1489 cases were analyzed, of which 957 were single drug exposures with 421 exposures to beta-blocking agents, 364 to inhibitors of the renin-angiotensin system, 122 to calcium channel blockers, and 50 to antiadrenergic drugs. No severe (Poisoning Severity Score [PSS] = 3) or fatal poisonings (PSS = 4) were reported and, with the exception of atenolol, propranolol, irbesartan, isradipin, clonidine, and moxonidine, no poisonings with a PSS > 1. We did not find a significant relationship between dosage, release formulation and symptoms, or PSS. All patients fully recovered without specific treatment. Conclusions: In young children with unintentional, single drug exposure to the most popular antihypertensive medication (i.e., metoprolol, bisoprolol, ramipril, enalapril, lisinopril, captopril, candesartan, valsartan, amlodipine, and verapamil), only mild symptoms occurred, and hospital evaluation is not a must. However, children with recent exposure to clonidine or moxonidine should be evaluated at a hospital due to an increased likelihood of poisonings of at least moderate severity.**

☐ **Keywords—beta blocker; calcium channel blocker; renin-angiotensin-aldosterone antagonist; antiadrenergic drugs**

INTRODUCTION

Although it is common sense to keep any medication out of children's reach, it is not uncommon that medication without medical indication is unintentionally ingested by young children. Antihypertensive drugs might endanger young children if swallowed without proper medical indication. Published data on this topic are sparse and our experience is gained mainly from case reports and a few case series (1–3).

Unintentional ingestion of antihypertensive medication without proper medical indication might potentially be harmful when looking at the usually desired effects and possible side effects of this type of medication. The most frequently used antihypertensive medication can be grouped into beta-blocking agents (BBA), inhibitors of the renin-angiotensin-aldosterone system (iRAS), calcium channel blockers (CCB), and antiadrenergic drugs

The manuscript contains data from the doctoral thesis of Nicole Hetterich, MD.

RECEIVED: 9 June 2013; FINAL SUBMISSION RECEIVED: 9 January 2014;
ACCEPTED: 9 February 2014

(AAD). BBA are considered to have a relatively fast onset of action and to effectively lower inotropy, blood pressure, and heart rate. In young children, cases with hypoglycemia after BBA ingestion are reported (4). However, this symptom is not consistently reported with BBA exposure, and there is controversy regarding the toxicity of beta blockers with this patient population in unintentional poisoning (2,4). Poisonings with iRAS are considered relatively nontoxic due to their mechanism of action, and usually delayed full blood pressure−lowering effect (5). Contrary to that, CCB usually have a relatively fast onset of action, and significant blood pressure−lowering effect, and moderate to severe poisonings are reported with higher doses (6). The group of AAD is too heterogeneous to predict any group effect.

This study was designed to study possible symptoms after unintentional ingestion of antihypertensive medication in young children, and to see to what extent monitoring and therapy are required. For this, we retrospectively analyzed antihypertensive medication exposures reported to the Mainz Poison Center/Germany database in a 10-year period.

MATERIALS AND METHODS

Data for this analysis were extracted from the Mainz Poison Center/Germany database system as described elsewhere (7). This Poison Center services two major federal states (Rheinland-Pfalz, Hessen) with 10.09 million inhabitants. Clinical and laboratory data recorded from all telephone consultations are entered in a database system. A dataset comprises information about time and circumstances of drug/substance exposure, age and body weight of the exposed person, amount and (galenic) form of the drugs/substances (7,8). Clinical data include organ-related symptoms, laboratory results (if available) and Poisoning Severity Score (PSS) as follows: none (grade 0), no symptoms or signs related to poisoning; minor (grade 1), mild, transient, and spontaneously resolving symptoms; moderate (grade 2), pronounced or prolonged symptoms; severe (grade 3), severe or life-threatening symptoms; and fatal (grade 4), death. For follow-up information, standardized forms are sent to persons consulting with the Poison Center, and information from returned forms are entered into the database to complete the consultation (7). A case review is carried out daily by a senior toxicologist to ensure the quality of the datasets and to give feedback to the toxicologists on call.

For this study, data acquired during a 10-year period (2001 to 2011) were used. The queries on the database were carried out with the following criteria: newborns to children aged 6 years; exposure to BBA, iRAS (e.g., angiotensin-converting-enzyme [ACE] inhibitors, ATII blockers), CCB, and AAD (e.g., central-acting antihypertensives, peripheral vasodilators). Anatomical Therapeutic Chemical Classification System (ATC) codes were used for the query.

RESULTS

A total of 1489 cases were analyzed, of which 616 were exposures to BBA, 583 to inhibitors of iRAS, 192 to CCB, and 97 to AAD. To be able to relate drug exposure with reported symptoms, we restricted further analyses to single drug exposures. Across all groups, there was no detectable difference in the occurrence and severity of symptoms between immediate release and extended release formulations (data not shown).

BBA

Four hundred and twenty-one cases with beta-blocker exposure (single drug exposure, ATC code EHAC07) were reported to our Poison Center. Follow-up information was available in 202 (48.0%) cases. In general, symptoms were light with BBA intoxications (Table 1), did not exceed PSS 1 (Table 2), and lasted only up to 5 h. Only two cases, one with propranolol and a second with atenolol, had a PSS 2. In the propranolol case with PSS 2, the child experienced mild symptoms at first contact with the Poison Center. This patient was a 17-month-old boy, who was exposed to 4 mg/kg body weight of propranolol. The child started being symptomatic 1 h after exposure with screaming, tachycardia, and shivering; symptoms lasted 4 h. The patient fully recovered without specific treatment. In the atenolol case, a 1.5-year-old female patient was exposed. Her blood pressure was recorded as low as 58/37 mm Hg at a heart rate of 60 beats/min. Unfortunately, no follow-up information was

Table 1. Frequency of Symptoms After Unintentional Ingestion of Antihypertensive Medication in Young Children With Positive Follow-Up

Symptoms	BBA (n = 202)	iRAS (n = 180)	CCB (n = 51)	AAD (n = 50)
Bradycardia	5	1	—	1
Tachycardia	3	4	1	—
Hypotension	5	6	1	3
Hypertension	—	—	1	—
Sleepiness	15	8	5	13
Nausea/vomiting	4	2	2	—
Dizziness	3	3	—	—
Pain	2	2	—	1
Hypoglycemia	1	—	—	—
Flush	—	3	5	—
Nonspecific	7	11	5	6
Total	45	40	20	25

AAD = antiadrenergic drugs; BBA = beta blockers; CCB = calcium channel blockers; iRAS = inhibitors of the renin angiotensin system.