

Acute poisoning with cardiotropic agents in children – clinical and paraclinical features

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ABSTRACT

Introduction. A cardiotropic agent is a product that, once absorbed into the body, may alter the proper functioning of the cardiovascular system. The authors report their experience with this acute poisoning at pediatric age.

Materials and methods. This is an 18 month prospective study that included 73 children who developed cardiovascular abnormalities due to acute poisoning with cardiotropic agents. Demographic data, clinical and paraclinical features were collected.

Results. The etiologic agent was a pharmaceutical product in 59 cases, the rest were household and rural toxicants. Sinus tachycardia was the most common cardiac manifestation (37 cases), followed by sinus bradycardia (15 cases). ECG record showed slowed intraventricular conduction in 11 cases, prolongation of QT interval in 7 cases, elevation of the ST segment (> 2 mm) in 3 cases and subepicardial ischemia in 2 cases. In 3 cases of severe poisoning with organophosphate insecticide the evolution was with cardiogenic shock and severe arrhythmia, followed by cardiac arrest and exitus. Systemic arterial hypertension was observed in 3 cases, while hypotension occurred in 5 cases of poisoning. Laboratory tests showed significant electrolyte and acid-base imbalances in 34 cases.

Conclusions. Numerous drugs and environmental toxicants may produce cardiovascular toxicity, which can be explained by various mechanisms of action. In evolution, life-threatening events like severe arrhythmias and cardiogenic shock may occur. A thorough history, physical examination and ECG evaluation are key steps to approach this cases.

Key words: cardiovascular toxicity, electrocardiographic abnormalities, arrhythmia, organophosphate insecticides, intraventricular conduction defects, prolonged QT interval

INTRODUCTION

A cardiotropic agent is a product that, once absorbed into the body, may alter the proper functioning of the cardiovascular system. This entity refers not only to pharmaceutical agents acting on cardiovascular system, but also to other pharmaceutical classes (anticonvulsants, an-

tidepressants, neuroleptics, bronchodilators, decongestants, antihistamines), drugs of abuse (cocaine, amphetamines), rural toxicants (organophosphate and carbamate insecticides, nitrites), industrial toxicants (cyanide, aluminium phosphide), household toxicants (carbon monoxide, trichloroethylene), plants (digitalis, colchicine, aconit) and venoms. (1,2)

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Although there is a wide interest in acute poisoning with cardiotropic agents, there is little information in the literature regarding this pathology in children. In this study we report our experience with this acute poisoning at pediatric age.

MATERIALS AND METHODS

We conducted an 18 month prospective study in the Toxicology Department at „Grigore Alexandrescu” Emergency Children’s Hospital in Bucharest. 73 cases were included in the study on the following criteria: patients 0 to 18 years old, admitted for acute poisoning with cardiotropic agents who developed cardiovascular abnormalities. We excluded from the study patients exposed to cardiotropic agents who did not present any impairment of the cardiovascular system and patients with known heart disease prior to exposure.

We identified the causative agent by history, physical examination and laboratory tests. For each patient we noted age, gender, urban versus rural provenience, method of exposure and intention of poisoning. In order to demonstrate cardiovascular abnormalities, we performed thorough clinical examination with measurement of vital parameters, cardiac monitoring and electrocardiographic (ECG) record in all cases. ECG analysis included the heart rate, rhythm, waves morphology, ST/T abnormalities, measurement of PR and QT intervals and identification of conduction defects. The QT interval was corrected (QTc) according to Bazett’s formula.(3) In order to analyse the data, we used the normal ECG and blood pressure standards for children. (4-8) The acid-base balance, blood gases and serum electrolytes were monitored in each case. We determined the cardiac enzymes in selected cases (ST/T abnormalities on ECG, chest pain). Before being discharged, the patients were examined by echocardiography coupled with Doppler.

For statistical analysis we used Microsoft Excel and SPSS. We compared the continuous variables with t-student test and the categorical variables with Fischer’s exact test, considering results with $p < 0.05$ statistically significant.

RESULTS

In the 18 month period of study 982 children were admitted with the diagnosis of acute poisoning in our department. In 73 cases (21 boys and 52 girls) we highlighted cardiovascular ab-

normalities. The mean age was 7.5 ± 10.4 years. There was a significant difference in the mean age between boys (4 ± 2 years) and girls (7.5 ± 7.7 years) ($p = 0.0443$). We noticed two peaks of incidence: first in the age group 1-5 years and second in the age group 11-15 years. 59% of cases came from rural environment. The method of exposure was ingestion in the majority of cases ($n = 61, 84\%$), the rest were cases of inhalation, nebulisation or intranasal administration. The exposure was accidental in 42 (58%) cases and it was significantly related to patients’ age: before age 10-41 of 42 cases (98%) were accidental exposures, while after age 11-30 of 31 cases (97%) were intentional poisoning. ($p < 0.0001$) Table I gives the age, gender and urban versus rural distribution patterns, while table II shows the intention of poisoning related to age.

The poisoning was determined, in most patients, by pharmaceutical agents – 59 (81%) cases. (Table 3) Carbamazepine was the most common etiology, followed by salbutamol. In 14 cases, patients were exposed to multiple cardiotropic drugs. One of the most frequent combinations was between anticonvulsants, antidepressants and sedatives. Non-pharmaceutical agents were involved in 13(18%) cases. In one case the etiology was unknown.

The ECG changes and other cardiac manifestations that we objectified in the study are listed in table IV. Sinus tachycardia was the most common cardiac manifestation (37 cases, Figure 1) in our study, followed by sinus bradycardia (15 cases, Figure 2). On ECG records we objectified slowed intraventricular conduction (widened QRS complexes, right bundle branch block) in 11 cases (Figure 3) and prolongation of QTc interval in 7 cases (Figure 4). Elevation of the ST segment (> 2 mm) was present in 3 cases, all of them caused by organophosphate insecticide poisoning. In one case, this abnormality was associated with raised cardiac enzymes. Systemic arterial hypertension was observed in 3 cases with organophosphate insecticide poisoning. Hypotension occurred in 5 cases of poisoning.

In three cases of severe poisoning with organophosphate insecticide (diazinon) the evolution was with cardiogenic shock and severe arrhythmia – ventricular tachycardia, torsades de points, ventricular fibrillation; followed by cardiac arrest and exitus. This 3 cases were the only deaths recorded during the study (4%). One case of severe propafenone poisoning led to hypotension and specific electrocardiographic pattern for the membrane stabilizing activity: widened QRS complex, first degree atrioventricular block, prolonged QT interval. In two cases

TABLE 1. Age, gender and urban/rural distribution

Age groups (years)	Girls	Boys	Girls/Boys ratio	Rural	Urban	Rural/Urban ratio	Total (%)
< 1	0	3	-	2	1	2:1	3(4)
1-5	18	13	1.4:1	15	16	0.9:1	31(42)
6-10	4	4	1:1	3	5	0.6:1	8(11)
11-15	23	0	-	18	5	3.6:1	23(32)
16-18	7	1	7:1	5	3	1.7:1	8(11)
Total	52	31	1.7:1	43	30	1.4:1	73(100)

TABLE 2. Intention of poisoning

Intention	1 year	1-5 years	6-10 years	11-15 years	16-18 years	Total (%)
Accidental	3	31	7	0	1	42(58)
Intentional	0	0	1	23	7	31(42)
Total	3	31	8	23	8	73(100)

of carbon monoxide poisoning the ECG record showed subepicardial ischemia.

Laboratory tests have shown significant abnormalities of serum electrolytes (hyponatremia, hypokalemia) and acid-base balance (metabolic acidosis) in 34 cases (47%). (Figure 5)

At the time of discharge from the hospital, for all 70 surviving patients clinical examination of the cardiovascular system, biological parameters, ECG and echocardiography were within normal limits.

DISCUSSION

A toxic product can cause numerous dysfunctions in the cardiovascular system. (9) This changes can be objectified by clinical examination and paraclinical tests. ECG record plays an important role in the identification of cardiac arrhythmias and conduction defects, events that sign the severity in these cases. Cardiotropic agents can contribute to arrhythmogenesis by various mechanisms: autonomic disturbances, membrane-depressant effect, electrolyte and acid-base imbalances. (10)

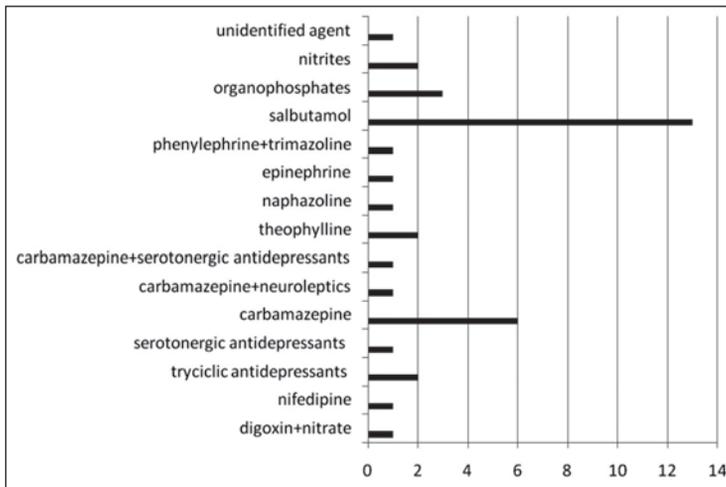


FIGURE 1. Sinus tachycardia

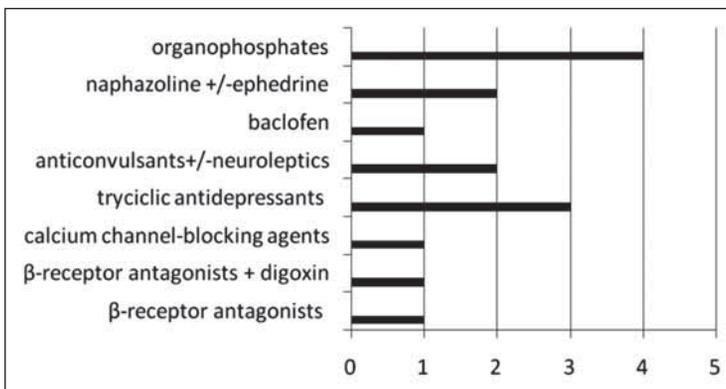


FIGURE 2. Sinus bradycardia

TABLE 3. Etiology of poisoning

Etiology	Number of cases
<i>Cardiovascular drugs</i>	
Digitalis glycosides: digoxin	3
β-receptor antagonists: metoprolol, bisoprolol, propranolol	5
Calcium channel-blocking agents: diltiazem, nifedipine	2
Sodium channel-blocking antidysrhythmics: propafenone	1
Nitrates: pentaerythritol tetranitrate	1
<i>Non-cardiovascular drugs</i>	
Tricyclic antidepressants: amitriptyline, clomipramine, imipramine	5
Serotonergic antidepressants: tianeptin, venlafaxine, paroxetine	3
Neuroleptics: risperidone, levomepromazine+aripiprazole	2
Anticonvulsants: carbamazepine, valproate, oxcarbazepine	18
Methylxanthines: theophylline	2
Neuromuscular agents: baclofen	1
Decongestants: naphazoline	2
Sympathomimetic agents: epinephrine, ephedrine, phenylephrine+trimazoline, salbutamol	17
Local anesthetics: lidocaine	1
<i>Rural toxicants</i>	
Cholinesterase-inhibiting insecticides (organophosphates)	9
Nitrites (well-water)	2
<i>Household toxicants</i>	
Carbon monoxide	2
Unknown agent	1

Autonomic disturbances are mainly caused by toxicants interfering with adrenergic or cholinergic nervous system. The α1- and β1-adrenoceptors overstimulation leads to arterial hypertension and

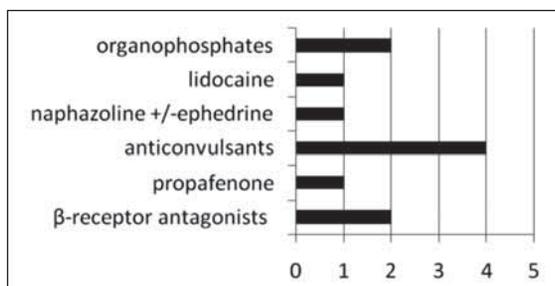


FIGURE 3. Slowed intraventricular conduction

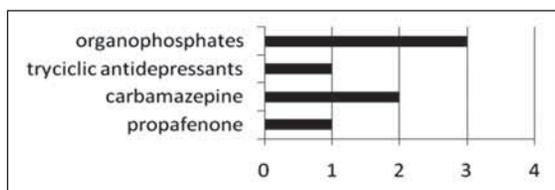


FIGURE 4. Prolonged QTc interval

tachyarrhythmias. Toxicants that inhibit cholinergic receptors may have the same effect. (1,2,10-12) In our study, we identified this overstimulation of adrenergic activity in patients admitted for acute poisoning with epinephrine, phenylephrine + trimazoline, ephedrine, salbutamol and theophylline. The most frequently involved agent was salbutamol, a β2-receptor agonist, which in high doses produces β1-agonist effects. Sinus tachycardia was objectified in all 13 cases caused by this medicine. On the other hand, α2-adrenoceptors overstimulation has a different clinical picture: initial hypertension and reflex tachycardia, followed by hypotension with bradycardia. (13,14) We objectified this clinical feature in 2 cases of naphazoline acute poisoning. The α1- and β1-adrenoceptors blockade leads to bradyarrhythmias and arterial hypotension. Overstimulation of the parasympathetic system may have the same effect. (1,2,10) In our study, β-receptor antagonists were involved in 5 cases. Some cardiotropic agents have both sympathetic and parasympathetic clinical features. In this study, we observed this effect in acute poisoning with organophosphate insecticides. Their mechanism of cardiotoxicity consists in a short period of increased sympathetic tone characterized by tachycardia and arterial hypertension, followed by a prolonged period of parasympathetic activity, during which bradycardia, arterial hypotension, ST/T changes and severe arrhythmias may occur. (15,16) The 3 deaths recorded during the study were due to cardiogenic shock and severe ventricular arrhythmias caused by acute poisoning with organophosphate insecticides.

Other neurotransmitters are also involved in the occurrence of cardiovascular manifestations. Serotonin reuptake inhibiting effect may produce autonomic disturbances in acute poisoning with serotonergic antidepressants. (17) In our study, sinus tachycardia was noticed in 3 cases caused by this drugs. We also objectified sinus bradycardia and first degree atrioventricular block in one case of acute poisoning with baclofen, which is a structural analogue of the main inhibitory neurotransmitter γ-aminobutyric acid. (18)

The manifestations due to membrane-depressant effects vary depending on the toxic agent and its place of action. Inhibition of the sodium channels in the myocardium slows the cardiac conduction. This effect can be seen on the ECG record as widening of the QRS complexes, atrioventricular or bundle-branch blocks and prolongation of the QT interval. In evolution, this type of poisoning may lead to arterial hypotension, ventricular tachyarrhythmias (ven-

TABLE 4. Electrocardiographic and clinical features

<i>ECG changes</i>	
Prolonged QTc interval	propafenone, carbamazepine, imipramine, organophosphate insecticide.
Prolonged PR interval (first degree atrioventricular block)	propafenone, imipramine, baclofen, organophosphate insecticide.
Right bundle-branch block	β -receptor antagonists, carbamazepine, naphazoline + ephedrine.
Widened QRS complexes	carbamazepine, oxcarbazepine, lidocaine, propafenone, organophosphate insecticide.
Elevated ST segment	organophosphate insecticide.
Atrial premature beats	carbamazepine.
Ventricular premature beats	carbamazepine, organophosphate insecticide.
Junctional rhythm	propafenone.
Ventricular tachycardia	organophosphate insecticide.
Torsades de points	organophosphate insecticide.
Ventricular fibrillation	organophosphate insecticide.
<i>Other cardiac manifestations</i>	
Sinus tachycardia	digoxin+nitrate, salbutamol, nifedipine, naphazoline, epinephrine, phenylephrine+trimazoline, carbamazepine, theophylline, tricyclic and serotonergic antidepressants, neuroleptics, nitrites.
Sinus bradycardia	diltiazem, β -receptor antagonists, digoxin, naphazoline +/-ephedrine, tricyclic antidepressants, carbamazepine, neuroleptics, baclofen.
Systemic arterial hypotension	β -receptor antagonists, propafenone, organophosphate insecticide.
Systemic arterial hypertension	organophosphate insecticide

tricular tachycardia, ventricular fibrillation, torsades de pointes) or bradyarrhythmias (bradycardia, junctional rhythm, asystole). (19,20) We identified in our study the following cardiotropic agents with sodium channel-blocking properties: propafenone, lidocaine, tricyclic antidepressants, carbamazepine and oxcarbazepine. Calcium channel blockade results in negative chronotropy and dromotropy. The ECG record may demonstrate sinus bradycardia an/or prolonged PR interval. (10,21) We objectified this pattern in one case of diltiazem poisoning. Reflex tachycardia was the only clinical sign noticed in nifedipine poisoning in our study. Another mechanism of arrhythmogenesis in acute poisoning is abnormal initiation of cardiac impulses as an effect of afterdepolarization. Early afterdepolarization results from potassium channel blockade, which can precipitate severe arrhythmias like torsades de pointes. Delayed afterdepolarization appears in conditions of intracellular calcium overload, which may be a result of sodium-potassium ATPase blockade in digitalis poisoning. (10,22)

The mechanisms of cardiac toxicity described above overlap frequently, which explains the polymorphic manifestations of the patients admitted for acute poisoning with cardiotropic agents. (10) In digoxin poisoning we observed sinus bradycardia due to sodium-potassium ATPase blockade, but we also noted sinus tachycardia caused by increased sympathetic activity and decreased parasympathetic activity. (23) In acute poisoning with tricyclic antidepressants we noticed various clinical and ECG manifestations, that have been listed in Table 4. This features are due to multiple mechanisms of toxicity as anticholinergic activity, catecholamines and serotonin reuptake inhibition, blockade of peripheral α 1-adrenoceptors and sodium channel-blocking effect. (17,24)

Besides the direct cardiovascular effects of cardiotropic agents, coexisting systemic factors such as hypoxia, hypovolemia, metabolic acidosis, hypothermia, hypo- and hyperkalemia, hypomagnesemia, hypo- and hypercalcemia may influence and exacerbate cardiotoxicity. (1,10, 25) In our study, we noticed electrolyte and

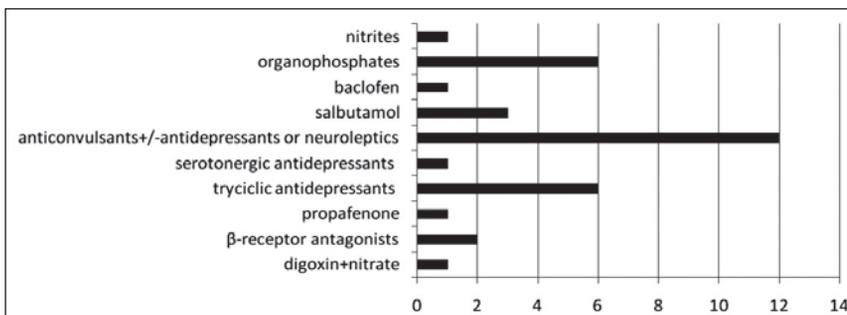


FIGURE 5. Serum electrolytes and acid-base balance abnormalities

acid-base imbalances in 47% of cases. (Figure 5)

In acute poisoning with carbon monoxide, cardiac injuries are caused not only by myocardial hypoxia due to carboxyhemoglobin formation, but also by direct effect of carbon monoxide on the heart as a result of the mitochondrial dysfunction and oxidative stress. (26,27) In our study, two patients had evidence of subepicardial ischemia on ECG.

Well-water contamination with nitrites can produce severe, even fatal methemoglobinemia in infants. (28) Methemoglobin is not able to transport oxygen to tissues. In moderate cases of poisoning cardiac manifestations consists in sinus tachycardia and mild hypertension. A methemoglobin fraction over 40% may produce bradycardia, ventricular dysrhythmias and hypotension, while a fraction over 70% is lethal. (29) In our study, sinus tachycardia was the only cardiac manifestation caused by nitrite poisoning.

CONCLUSIONS

Numerous drugs and environmental toxicants may produce cardiovascular manifestations, when they are involved in a case of acute poisoning. Cardiovascular toxicity may be explained by various mechanisms of action. In evolution, life-threatening events like severe arrhythmias and cardiogenic shock may occur. A thorough history, physical examination and ECG evaluation are key steps to approach this cases.

Acknowledgement

This paper is supported by the Sectoral Operational Programme Human Resources Development (SOP HRD) 2007-2013, financed from the European Social Fund and by the Romanian Government under the contract number POSDRU/107/1.5/S/82839.

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