Use of Intravenous Lipid Emulsion Therapy and Insulin in a Case of Tarka Intoxication

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ABSTRACT

Introduction: Tarka (trandolapril/verapamil hydrohloride extended-release) is a fixed-dose combination antihypertensive drug formed from verapamil hydrochloride and trandolapril. Toxicologic manifestations of Tarka overdose are altered mental status, bradycardia, hypotension, atrioventricular block (first-degree), hyperglycemia, metabolic acidosis, and shock.

Case Presentation: We report a case of Tarka toxicity in a 2-year-old girl who presented with altered mental status, cardiogenic shock, hypotension, bradycardia, severe metabolic acidosis, hyperglycemia, and first-degree atrioventricular block. We started fluid resuscitation, epinephrine, norepinephrine, and insulin. Because of the patient's hyperlactatemia and hypotension despite standard therapies, we initiated intravenous lipid emulsion (ILE) therapy, after which her condition improved promptly.

Discussion: Tarka overdose may be life-threatening as it can cause cardiogenic shock. In our patient, the regression of lactate elevation in a short time with ILE therapy and the improvement of her general condition highlight the importance of ILE.

Conclusions: ILE is an alternative treatment method for acute lipophilic drug intoxications, such as Tarka.

INTRODUCTION

Fixed-dose combination drugs are becoming more common in the treatment of essential hypertension.[1] There are more than 20 combination products available.[2] Tarka is a fixed-dose combination antihypertensive drug formed from verapamil hydrochloride and trandolapril (ranging from 180-240 mg and 1-4 mg, respectively).[2] Compared with monotherapy, fixed-dose combination products have many benefits and are more efficacious when combined versus than the sum of individual drugs.[3] Combined drug preparations also reduce noncompliance by 24% to 26% versus taking both drugs separately.[3]

The toxicologic manifestations of Tarka overdose are lethargy, dizziness, fatigue, headache, constipation, chest pain, cough, altered mental status, bradycardia, hypotension, atrioventricular (AV) block (first-degree), hyperglycemia, metabolic acidosis, and shock.[4] Verapamil is responsible for most of the adverse effects.[4] There are a few case reports about Tarka overdose in adults and children in the literature, as well as a few recent reports of intravenous lipid emulsion (ILE) use in verapamil poisoning in children.[4]

We present the case of a 2-year-old girl who developed altered mental status, hypotension, bradycardia, first-degree AV block, hyperglycemia, metabolic acidosis, and shock and was subsequently treated successfully with ILE and insulin therapy. To our knowledge, there is no previous report in the literature regarding ILE therapy after a Tarka overdose.

CASE PRESENTATION

A 2-year-old girl presented to the pediatric emergency department (ED) due to altered mental status after taking 2 tablets of Tarka (240 mg verapamil, 4 mg trandolapril). She was given 1 g/kg activated charcoal and 20 cc/kg normal saline followed by gastric lavage. There was no known disease in her past medical history.

On examination, the patient's Glasgow Coma Scale score was 9-10, capillary refill time was >3 seconds. Electrocardiography

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showed first-degree AV block (Figure). Venous blood gas was pH 7.08, $PaCO_2$ 44.8 mm Hg, HCO_3 11.8 mmol/L, lactate 9.0 mmol/L, and blood glucose 647 mg/dL. Her white blood cell count was 22.7×103/μL, total neutrophil count was 17.8×103/μL, hemoglobin was 8.7 g/dL, hematocrit was 29.2%, platelet count was 494×103/μL, aspartate aminotransferase was 30 IU/L, alanine aminotransferase was 15 IU/L, urea was 35 mg/dL, creatinine was 0.82 mg/dL, sodium was 131 mmol/L, potassium was 4 mmol/L, chlorine 102 mmol/L, calcium was 8.4 mg/dL, and the C-reactive protein was 3.2 mg/dL. She had hypotension, bradycardia, and hyperglycemia.

On admission to the pediatric intensive care unit (PICU), the patient's vital signs were as follows: heart rate 60 beats per minute, blood pressure 40/20 mm Hg, respiratory rate 40 breaths per minute, body temperature 36.8° C, and oxygen saturation 97% in the non-rebreather mask.

A central venous catheter was inserted into the right internal jugular vein, and 150 cc/kg fluid therapy, epinephrine, norepinephrine, and insulin (0.1 U/kg/h) were started. Inotrope doses were increased to provide normal blood pressure values. Complete blood cell count, liver and renal function tests, serum electrolytes, and coagulation parameters were normal. The follow-up venous gas still showed metabolic acidosis and hyperlactatemia, despite vasopressor and intravenous fluid therapy; therefore, we decided to start ILE therapy. ILE was given as a 1.5 mL/kg (during 5 minutes) and 0.25 mL/kg/min infusion (during 60 minutes). After the ILE therapy, there was significant improvement in the patient's metabolic acidosis (7.08 to 7.40), a significant decrease in lactate (9.9 to 3), and a significant increase in blood pressure values and Glasgow Coma Scale scores (10-13).

The patient was hyperglycemic and had mild metabolic acidosis on admission. Insulin treatment was continued due to hyperglycemia. Acidosis regressed at the 24th hour of admission and insulin treatment was discontinued but had to be restarted 1 hour later as she became hyperglycemic.

Figure. First-Degree Atrioventricular Block on Electrocardiography (25 mm/s, 10 mm/mV) of the Patient Before Intravenous Lipid Emulsion Therapy

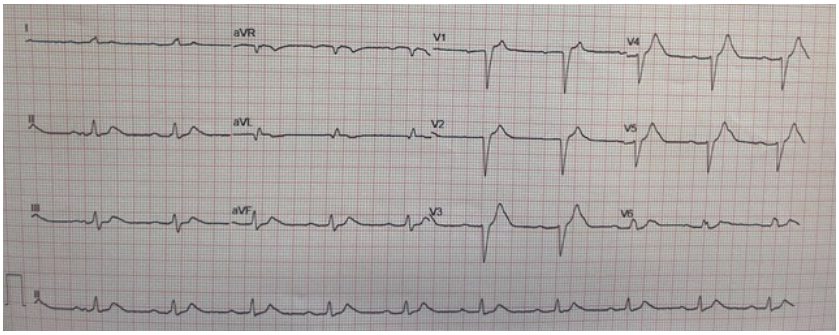

Table 1. Laboratory Results and Treatment Timeline

Time (hour)	pH	$PaCO_2$ mmHg	HCO_3 mmol/L	Lactate mmol/L	Glucose mg/dL	Insulin U/kg(h)	BP S/D	NE	E	ILE Therapy
Admisson	7.14	32.5	11.9	9.9	253		40/20		0.1	**
1	7.40	16	13.7	3.2	243	0.1	67/31	0.1	0.3	
2	7.17	50	15.8	3.5	385	0.1	73/32	0.1	0.3	
7	7.25	45.2	18.1	1.9	399	0.1	80/34	0.1	0.3	
12	7.34	24.9	16	2.9	284	0.1	82/35	0.1	0.3	
18	7.37	30.9	19.3	2.0	176	0.1	77/39	0.1	0.3	
24	7.36	29	18.3	1.9	147	[a]	75/59	0.05	0.2	
36	7.46	33	25	2.9	145	stopped	80/44	off	0.2	
60	7.45	36	25	0.8	95		90/50		off	

Abbreviations: BP, blood pressure; S, systolic; D, diastolic; NE, morepinephrine (mcg/kg/min); E, epinephrine; ILE, intravenous lipid emulsion; U, unit.

[a]One hour after the patient's insulin was discontinued, it was started again after she became hyperglycemic.

[b]1.5 ml/kg (within 5 min) and 0.25 ml/kg/min infusion (60 min).

Table 2. Timeline of Laboratory Results

Time (hour)	Leukocyte Count	Hemoglobin	Platelet Count	Sodium	Potassium	Urea	Creatinine	ALT	AST	CRP
Admisson	22.7	8.7	494 000	131	4	35	0.82	15	30	3.2
6	29.3	13.5	546 000	127	[a]	48	0.69	36	58	6.5
24	41.4	8.2	422 000	138	4.11	48	0.38	26	50	10.4
48	26.7	8	384 000	138	3.37	13	0.25	30	41	4.6
60	16.3	7.9	282 000							

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein.

[a]Hemolysis.

Echocardiography showed the patient's ejection fraction was 60% while receiving inotrope treatment. Within the 1st hour of admission, a calcium gluconate (1 cc/kg) infusion was started, after which she vomited. Glucagon was not started due to her high blood glucose. Her hypotension and bradycardia regressed at the 4th hour of admission, as did her AV first-degree AV block. Inotrope doses were gradually reduced after the 24th hour of hospitalization. Insulin treatment was stopped at 36 hours, and inotrope treatment was stopped at 60 hours. On the 4th day

of admission, she was discharged. See Tables for vital and laboratory signs and treatment.

DISCUSSION

Tarka is an oral, fixed-dose combination therapy consisting of the long-acting lipophilic angiotensin-converting enzyme (ACE) inhibitor trandolapril and sustained-release calcium channel antagonist verapamil.[5-7] Tarka is indicated for the treatment of essential hypertension in patients who need more than monotherapy to control normal blood pressure.[6] Trandolapril decreases vasopressor activity and aldosterone release and inhibits the conversion of angiotensin I to angiotensin II.[6] By contrast, verapamil leads to dilatation of peripheral vessels and coronary vasculature and so diminishes systemic vascular resistance and blood pressure by blocking the influx of calcium ions via L-type calcium channels.[6,7]

The clinical manifestations of trandolapril intoxication are hypotension, bradycardia, lethargy, fatigue, altered mental status, and severe angioedema.[2,4] Treatment of trandolapril intoxication includes fluid resuscitation and vasopressors.[8] Naloxone may be used in ACE I– induced hypotension.[8]

The clinical features of verapamil intoxication are hypotension, cardiac rhythm disturbances ranging from sinus bradycardia to complete heart block and asystole, hyperglycemia, metabolic acidosis, shock, hypokalemia, renal failure, seizure, stroke, noncardiogenic pulmonary edema, and acute respiratory distress syndrome.[2,4,9] In verapamil intoxication, heart failure due to decreased myocardial contractility or complete heart block is a possible mechanism leading to death.[2] Treatment of verapamil intoxication includes glucagon, calcium, hyperinsulinemia/euglycemia therapy (HIET), and vasopressors.[8,9]

There are no data available on the use of Tarka in children.[6] There is, however, an existing case report involving Tarka overdose in a child.[2] Dogan et al reported a 3.5-year-old girl who presented with hypotension and bradycardia. A temporary pacemaker was implanted due to a complete AV block in the patient.[2] Cohen et al reported the case of a 60-year-old man who presented with hypotension and bradycardia due to a Tarka overdose.[8] Our patient presented with altered mental status, cardiogenic shock, hypotension, bradycardia, severe metabolic acidosis, hyperglycemia, and first-degree AV block. She was started on fluid resuscitation, epinephrine, norepinephrine, and insulin. After the lipid treatment, her general condition, hyperlactatemia, and hypotension improved.

What makes our case interesting is the clinical improvement achieved with ILE, demonstrating that toxicity from lipophilic drugs such as trandolapril and verapamil can be treated successfully with ILE.[10] It has been reported in the literature that ILE treatment also has been used to treat toxicity of local anesthetics, β-blockers, cocaine, lamotrigine, butyrophenones, diphenhydramine, olanzapine, amitriptyline, and atypical antipsychotics.[10] The effectiveness of ILE may be explained by two theories. The first is that it causes a "lipid sink" for toxic, lipophilic drugs, dramatically keeping toxic and lipophilic drugs out of the periphery.[10] Thus, the distribution of lipophilic drugs is reduced by ILE treatment.[10] The second theory is that ILE prevents myocardial inhibition because it provides a high concentration of myocardial substrate.[10]

CONCLUSIONS

Tarka overdose may be life-threatening as it can cause cardiogenic shock. ILE is an alternative treatment method for acute lipophilic drug toxicity, such as Tarka. In our patient, the rapid regression of lactate elevation with ILE therapy and the improvement of her general condition highlight the importance of this treatment.

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