Toxicology Reports 14 (2025) 101891

Contents lists available at ScienceDirect

Toxicology Reports

journal homepage: www.elsevier.com/locate/toxrep

Valproic acid intoxication – The importance of toxicological analysis and correct management: A case report

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ARTICLE INFO

Handling Editor: Prof. L.H. Lash

Keywords:
Valproic acid
Poisoning management
Toxicological analysis
Anamnesis

ABSTRACT

Introduction: Valproic acid (VPA) is an anticonvulsant widely used in treating epilepsy which can occur cases of poisoning in overdose situations.
Case description: A 15-year-old girl purposely ingested about 100 drug tablets according to family members. Gastric lavage with activated charcoal was performed at home using a nasogastric tube and patient just was taken to the hospital around 10 h after drug ingestion, arriving in shock state. All laboratorial parameters were altered together a suspect of aspiration pneumonia with the presence of gross perihilar infiltrated in the right lung. Immunoassay screening test did not detect any substance; LC-UV detected quetiapine (> 150 ng/mL) while GC-MS determined 977.96 μg/mL of valproic acid in the patient's plasma, confirming valproic acid intoxication. Appropriate life support was performed in the patient during hospitalization; however, she died two days later, reaching her suicide.
Conclusions: Prognosis could be favorable if the patient was taken immediately to hospital emergency, considering the complexity of managing poisoning. Patient's anamnesis must be carefully analyzed by the healthcare professional to avoid false conclusions and toxicological analysis is extremely important to clarify suspected poisoning.

1. Introduction

Valproic acid (VPA) is an anticonvulsant used in treatment of epilepsy, bipolar disorder and migraine, which may lead to cases of poisoning in case of overdose, whether accidental or intentional [1]. We report a case of acute intoxication by VPA, associated with other drugs, and raise awareness about the correct management of acute intoxication by exogenous drugs.

2. Case description

On April 07, around 7–8 p.m., a 15-year-old girl (54 kg, 160 cm) purposely ingested about 50, 30 and 20 tablets of VPA (500 mg), quetiapine (QP) (25 mg) and other medications without description according to family members. Patient's mother, a healthcare professional, tried to perform a gastric lavage with activated charcoal was performed at home using a nasogastric tube. Patient was taken to the hospital around 10 h after ingestion, arriving in shock, cyanotic, bradycardia, non-responsive with mydriatic pupils and no photo reagents. Orotracheal intubation was performed along with other therapies.

On April 08, around 6 p.m., patient was admitted to the Intensive Care Unit (ICU) from University Hospital of Santa Maria (HUSM) under mechanical ventilation with central venous catheter, bladder probe of delay, nasogastric probe and presenting dysfunction in multiple organs (liver, kidneys and pancreas). The patient showed electrolyte and coagulation disorder, refractory hypovolemic shock, severe metabolic acidosis and arrhythmia. Also, she was suspected of aspiration pneumonia based in clinical state of shock associated with leukocytosis with left shift and elevated lactate level, initiating antibiotic therapy. Bacterioscopy analysis from tracheal/bronchial secretion showed the presence of gram-negative bacteria while *Escherichia coli* and *Klebsiella oxytoca* were identified in blood culture test. Chest X-ray was performed

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https://doi.org/10.1016/j.toxrep.2025.101891
Received 19 July 2024; Received in revised form 6 December 2024; Accepted 2 January 2025
Available online 4 January 2025

and presented a gross perihilar infiltrated (Fig. 1-I). All laboratorial parameters remained altered during her hospitalization period (Table 1).

Immunochromatographic test for 12 drugs did not detect any substance in plasma and urine samples (amphetamine, barbiturates, benzodiazepines, cocaine, ecstasy, methamphetamine, methadone, morphine, phencyclidine, propoxyphene, tricyclic antidepressants, tetrahydrocannabinol and their respective metabolites). Fluoride plasma samples were used for toxicological analysis to determine only VPA and QP. Gas chromatography coupled to mass spectrometry (GC-MS) after liquid-liquid extraction [2] was employed and demonstrated 977.96 μg/mL of VPA (therapeutic range: 50–100 μg/mL) while liquid chromatography with ultraviolet-visible detector (LC-UV/Vis) [3] identified QP above limit of detection (150 ng/mL) (Fig. 1- II and III).

Patient received life support with orotracheal intubation and mechanical ventilation, hydration, noradrenaline application, metabolite balance and cardiac function monitoring/management were performed.

On April 09, the patient presented cardiorespiratory arrest in asystole that evolved to death at 9:32 p.m. This case report was approved by the Federal University of Santa Maria Ethics Committee, Brazil (Protocol 5.849.073).

3. Discussion

X-ray patient images demonstrated a probable aspiration of activated charcoal that culminated in respiratory failure, even with mechanical ventilation, as evidenced by the blood gases parameters. In addition, she was in a dehydration state that promoted hypovolemia, directly influenced the high concentrations of the most of laboratory biomarkers (Table 1). Probably all these factors indicated that the cardiac function required a high effort because of the higher blood viscosity and lack of oxygen, as demonstrated in other cases [4].

For shock management, 174 mL of fresh plasma was administered in the patient together with hydration, norepinephrine (8 mg/ 4 mL) and dobutamine (10 μg/kg/min). However, the patient's critical condition did not prevent cardiorespiratory arrest. Also, it was observed liver and pancreatic failure, metabolic acidosis and electrolyte imbalance as demonstrated in the laboratory biomarkers (Table 1), similar to the literature [5]. So, kidney damage could be caused by hyperphosphatemia, which in turn led to hyperkalemia and subsequent arrythmias as described in the literature [5], which could have aggravated the cardiac situation.

Polydrug intoxication has been described by family members and no drugs were detected in the 12-drug immunochromatographic test. So, the focus was the VPA and QP quantification to establish the real cause of intoxication. QP plasma level was close to the limit of detection (> 150 ng/mL) and within therapeutic range (100–500 ng/mL) [3]. However, VPA concentration (977.96 μg/mL) was almost 10 times the limit of therapeutic range (50–150 μg/mL) [6], confirming VPA intoxication.

Main approach for VPA intoxication is gastrointestinal decontamination, administration of activated charcoal and urinary alkalinization [7]. However, the delay of more than 10 h for medical search, made the

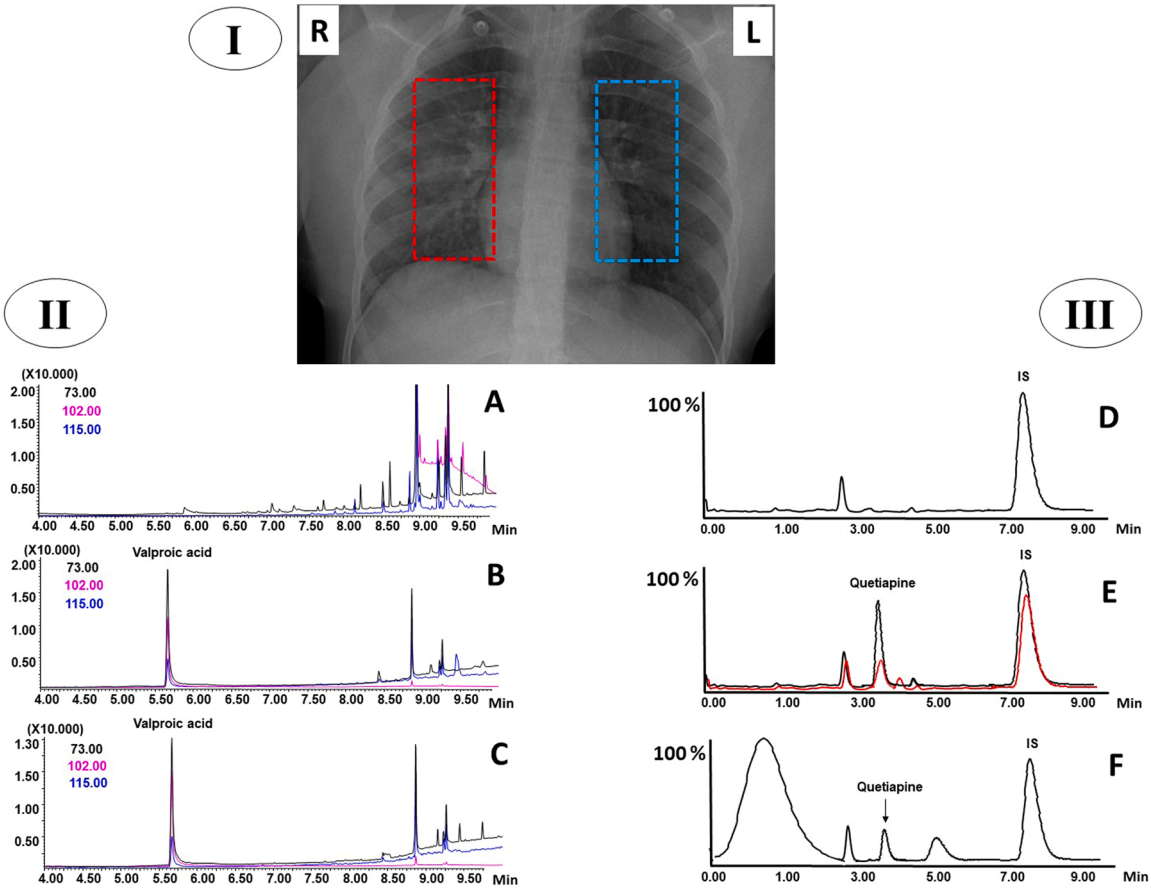

Fig. 1. X-ray from chest patient and respective plasma analysis of valproic acid and quetiapine by GC-MS and LC-UV/Vis. **(I)** X-ray from chest patient demonstrating gross perihilar infiltrate (red line) in right lung of the patient. **(II-A)** Blank plasma for valproic acid analysis by GC-MS; **(II-B)** Blank plasma sample spiked with 50 μg/mL of valproic acid; **(II-C)** Real sample diluted 20 times containing 977.96 μg/mL of valproic acid; **(III-D)** Blank plasma sample spiked with 200 ng/mL of IS for quetiapine analysis by LC-UV/Vis; **(III-E)** Blank plasma sample spiked with 150 and 500 ng/mL of quetiapine; **(III-F)** Real sample detected quetiapine in plasma sample from patient (> 150 ng/mL). GC-MS, gas chromatography coupled mass spectrometry; LC-UV/Vis, liquid chromatography with ultraviolet/visible; L, left; R, right.

Table 1
Physical and laboratorial parameters from patient during hospitalization.

Physical parameters April 08/ around 6 pm	**Max**	**Min**		
Blood presure (mmHg)	65/36	78/42		
Temperature (ºC)	35.5	35.5		
Heart rate (bpm)	79	140		
Respiratory rate (ipm)	25	25		
Laboratorial parameters	**April 08/ 09:51 pm**	**April 09/ 02:33 pm**	**April 09/ 06:38 pm**	**Reference value** [14]
Pyruvic transaminase (U/L)	103	146	-	14–59
Oxaloacetic transaminase (U/L)	387	423	-	15–37
Calcium (mg/dL)	6.5	-	7.4	8.5–10.1
Lactate (mmol/L)	11.6	-	-	0.4–2.0
Creatinine (mg/dL)	1.55	3.41	3.56	0.57–0.89
Urea (mg/dL)	41.0	64.0	64.0	15–39
Potassium (mmol/L)	4.8	6.3	5.3	3.5–5.1
Amylase (U/L)	-	1045	-	25–115
Lipase (U/L)	-	2951	-	73–393
Sodium (mmol/L)	147	148	151	136–145
Chlorine (mmol/L)	-	-	114	98–107
Phosphor (mg/dL)	-	-	9.9	3–6
Arterial blood gasses during hospitalization	**April 08/ 07:26 pm**	**April 09/ 03:22 pm**	**April 09/ 06:38 pm**	**Reference values** [14]
Blood gas values				
Ph	7.039	6.885	6.973	7.53–7.47
PCO_2 (mmHg)	52.5	44.1	26.0	32–45
PO_2 (mmHg)	231.0	122.9	151.0	83–108
Oximetry values				
CtHB (g/dL)	14.6	-	12.5	12.0–16.0
O_2 saturation (%)	99.2	92.3	98.1	95–99
FO_2Hb (%)	98.3	-	97.3	94–99
FCOHb (%)	0.4	-	0.1	0.0–0.8
FHHb (%)	0.8	-	1.9	-
FMetHb (%)	0.5	-	0.7	0.2–0.6
Hctc (%)	44.8	-	38.5	-
Electrolyte values (mmol/L)				
cK+	4.2	6.0	5.1	3.5–5.0
cNa+	150	145	151	136–146
cCl-	125	-	122	98–106
cCa+ +	0.840	0.886	0.920	1.16–1.32
Metabolite values				
CGlu (mg/dL)	223	-	165	70–105
CLac (mmol/L)	9.5	-	24.0	0.5–1.6
State of oxygenation				
CtO2c (mmol/L)	1.15	-	0.97	7.1–8.9
P50e (mmHg)	38.5	-	39.6	24–28
Acid-base State (mmol/L)				
cBase (Efct)c	−15.2	−25.0	−23.5	−2 - + 3
cHCO3-(P)c	13.5	8.2	5.7	21–28
ctCO2 (P)c	15.1	9.5	6.5	-
Blood parameters	**April 08/ 09:51 pm**	**April 09/ 02:33 pm**		**Reference values** [15, 16]
Erythrocytes (millions/mm^3)	4.97	4.93		4.5
Hemoglobin (g/dL)	14.6	14.7		13.2
Hematocrit (%)	47.1	46.3		40.7
Mean corpuscular hemoglobin (pg)	29.4	29.8		29.9
Mean corpuscular volume (micra^3)	94.8	93.9		90.6 (fL)
Mean corpuscular hemoglobin concentration (%)	31.0	31.7		32.4 (g/dl)
R.D.W. (%)	13.5	13.4		13.7
Plateletes (mil/ mm^3)	176	231		239
Mean platelet volume (micra^3)	10.0	9.8		10 (fL)
Leukogram				
Total leukocyte count (cel/mm^3)	16480	10930		4000–11000
Differential leukocyte count (cel/mm^3)				
Rods	1154	7214		0–840
Segmented	14173	2405		3543
Lymphocytes	989	1202		2105
Monocytes	165	109		357
Eosinophils	0	0		0–550
Basophils	0	0		0–72
Coagulation parameters				
Prothrombin time (seconds)	15.7	29.4		10–14
Activity (%)	78	31.0		70–100
INR	1.14	2.04		0.9–1.1
Activated Partial Thromboplastin Time (seconds)	42.3	73.5		21–32

prognosis difficult, since the ingested pills had already been absorbed (absorption time of VPA from 4 to 8 h). So, the goal of medical team was the increase of urinary excretion of VPA employed aqueous $NaHCO_3$ 8.4 % solution (150 mL in 1 h + 150 mL in 23 h) and patient́s general life support, including amiodarone (150 mg/ 3 mL in 2 ampoules) to control arrhythmia condition.

Considering VPA level (977.96 μg/mL), hemoperfusion with continuous hemodialysis is recommended for VPA levels above 800 μg/mL [8], which was requested. However, the patient died before the procedure. Despite high VPA levels, the prognosis could be favorable if the patient was taken immediately to hospital emergency [8].

In this case report, it was tried to perform a gastric lavage with activated charcoal at home using a nasogastric tube by mother before hospitalization. However, these procedures must be performed in a hospital environment due to the risk of inhalation and vomiting of the patient, especially those in a coma state [9]. Also, this condition was aggravated due to long time it took to take patient to hospital (> 10 h), culminating in patient's death.

Despite anamnesis being a fundamental tool for clinical purposes, the report of patient and/or family members should be carefully evaluated by the health professional, especially in situations of intoxication to avoid false conclusions [10]. Our toxicological analysis showed only high VPA levels in plasma sample and a small amount of QP. So, the description reported by the family members does not agree with the laboratory finding regarding QP, demonstrating the importance of toxicological analysis in clarifying a poisoning case, corroborating with other studies [2,6,8–10]. Thus, toxicological analyzes come to elucidate situations involving suicide attempts by xenobiotics administration. However, bureaucratic and logistical aspects (e.g., time between requesting a toxicology test and collecting blood; access to appropriate equipment) should be resolved to establish an efficient toxicological analysis service.

Suicide attempts are the main cause of drug poisoning in young people and adults [11,12] and it is considered a complicated theme to be discussed by family members [13]. Thus, it is necessary to create a public policy both to raise awareness of parents and guardians about drug storage and access of suicide-susceptible patients at home as well as that intoxications are considered serious situations that require immediate hospital care. This approach can prevent future poisoning and possible deaths from suicides attempts.

4. Conclusions

For VPA intoxication, it is essential to seek hospital help immediately, avoiding any procedure at home for the best prognosis of the patient. Patient's anamnesis must be carefully analyzed by the healthcare professional to avoid false conclusions and toxicological analysis is extremely important to help identify/quantify compounds in poisoning cases. Public strategies must be created to prevent suicide attempts with drugs in young and adult's people

Funding

Coordination of Improvement of Personal Higher Education – Brazil (CAPES – Finance Code 001) and Fundo de Incentivo a Extensão for the scholarship provided to Leonardo Corrêa Cardoso and Karol Andriely de Vargas Paier, respectively.

CRediT authorship contribution statement

Leonardo Corrêa Cardoso: Writing – review & editing, Validation, Data curation. **Karol Andriely de Vargas Paier:** Writing – original draft, Methodology, Investigation, Data curation. **Gustavo Andrade Ugalde:** Writing – review & editing, Methodology, Investigation. **Fernanda Ziegler Reginato:** Writing – review & editing, Methodology, Investigation. **André Valle Bairros:** Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization. **Miguel Roehrs:** Writing – review & editing, Validation, Investigation, Formal analysis. **Ivy Bauer Lovatel:** Writing – review & editing, Investigation, Formal analysis.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Leonardo Correa Cardoso reports financial support was provided by Coordination of Higher Education Personnel Improvement. Karol Andriely de Vargas Paier reports financial support was provided by Federal University of Santa Maria. Leonardo Correa Cardoso reports a relationship with Coordination of Higher Education Personnel Improvement that includes: funding grants. Karol Andriely de Vargas Paier reports a relationship with Federal University of Santa Maria that includes: funding grants. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.toxrep.2025.101891.

Data availability

Data will be made available on request.

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