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Case report

ACUTE IZONIAZID POISONING WITH PRESENTATION OF A CLINICAL CASE

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SUMMARY

Rimicid or isonide a group of medications which belong to anti-tuberculosis medicaments. The active substance isoniazid is used to treat pulmonary and extrapulmonary forms of tuberculosis, as well as prophylaxis in case of contact with infected individuals.

Isoniazid is rapidly absorbed, reaching a maximum serum concentration in 2 hours, and penetrates all body fluids. The volume of distribution is approximately 0.6 l/kg.

Isoniazid causes pyridoxine deficiency in two ways:

- by hydrazones, isoniazid metabolites inhibit the pyridoxal kinase, which converts pyridoxine to the active form, pyridoxal-5-phosphate, and

- pyridoxine deficiency disrupts the synthesis and metabolism of GABA, the main inhibitory mediator of the central nervous system.

Isonicotinic acid poisoning metabolism is subject to individualized factors, and in some people, this metabolism can be in a significantly slower.

A clinical case of poisoning with 30 tablets of Rimicid by a 16-year-old girl suicidal attempt was presented. The results of the TC analysis confirm intoxication with the drug, and the retrospective assessment of the concentration over a past period of time using the elimination half-life has revealed an extremely high dose of ingested isoniazid.

Keywords: isoniazid, pyridoxine, poisoning,

INTRODUCTION

Acute exogenous intoxications in childhood are becoming more frequent both around the world and in our country. This is directly dependent on the characteristics of the child's body, the dynamics of their physical and mental development. [1, 2, 3]

Suicidal acts through acute exogenous intoxications in children are a serious challenge for toxicologists, as they include conscious and intentional self-harm associated with many social and medical problems. The most common toxic noxa are drugs that are very affordable and are found in abundance in every home. [1, 2, 4, 5]

We will present a case of attempted suicide with isoniazid in a 16-year-old girl.

Rimicide, isoniazid or isonide are medicinal products that belong to the group of anti-tuberculosis drugs. The active substance is isoniazid and is used for the treatment of pulmonary and extrapulmonary forms of tuberculosis, as well as for the prevention of close contact with infected individuals. [2, 6, 7, 8]

Pharmacokinetics. Isoniazid is a drug that is rapidly absorbed, reaching a maximum serum concentration in 2 hours and penetrating all body fluids. The volume of distribution is approximately 0.6 l/kg. [2, 9, 10]

Isoniazid is insignificantly bound to plasma proteins. The main route of its metabolism is acetylation by the enzyme N-acetyltransferase. Depending on the activity of the enzyme N-acetyltransferase, there are so-called "fast" and "slow" acetylators (genetically determined). [11, 12] In 50-60% of white and black Americans, the activity of acetylating enzymes is low, and they belong to the group of slow acetylators in which the T½ of isoniazid is 180 minutes. In 90% of Asians and Eskimos, this activity is high, and the T½ of isoniazid is equal to 70 minutes - they are defined as fast acetylators. For Bulgaria, the ratio of fast to slow acetylators is approximately 1:1. The end products of degradation are: acetylhydrazine and isonicotinic acid or hydrazine. [2, 9, 13, 14, 15]

Mechanism of toxic effect. Isoniazid causes pyridoxine deficiency in at least two ways:

1. Hydrazones, metabolites of isoniazid, inhibit the pyridoxal kinase, which converts pyridoxine to the active

form, pyridoxal-5-phosphate. In addition, the interaction of isoniazid with pyridoxal phosphate forms an inactive hydrazone complex, which is excreted by the kidneys. [16]

2. Pyridoxine deficiency disrupts the synthesis and metabolism of GABA, the main inhibitory mediator of the central nervous system. Depletion of GABA stores is the most likely cause of epileptic seizures in isoniazid poisoning. [1, 2, 9, 17, 18]

There are also individual features of isonicotinic acid poisoning, and in some people, its metabolism is significantly slower. [6, 9, 19, 20]

Clinical manifestation of acute poisoning. In the case of isonicotinic drug poisoning, the clinical manifestation is dominated by cerebrotoxic syndrome with manifestations of tremor, attacks of tonic-clonic seizures, resistance to conventional treatment, and, respectively, gradual changes in consciousness to coma. These symptoms may occur 30 minutes after taking the drug. [1, 17, 19, 21]

The paraclinic is characterized by severe metabolic acidosis. Early toxic effects include: vomiting, slurred speech, dizziness and tachycardia, but acute overdose may lead to the development of epileptic seizure without any previous symptoms. [2, 9, 17]

In severe poisoning, a coma develops rapidly and lasts 24-36 hours, persisting after cessation of seizures and correction of acidosis. [2, 9, 17]

Acute toxic effects of isoniazid also include hypotension, hyperthermia, acute renal failure, toxic hepatitis, hyperglycemia, glycosuria and ketonuria. [1, 6, 19, 22]

Diagnosis. Acute isoniazid poisoning may be suggested by anamnestic data, clinical manifestations, and chemotoxicological analysis (measurement of isoniazid plasma concentrations and urine screening).

The diagnosis can be made at plasma concentrations of isoniazid: [2, 9]

- over 10 mg/L, established 1 hour after taking the preparation;
- more than 3.2 mg/L, two hours after taking the preparation,
- and more than 0.2 mg/L after the sixth hour.

Plasma testing of isoniazid is not always possible in the first hours because toxicological testing requires the use of a specialized laboratory, which is not always available and/or requires the transport of samples. On the other hand, in the beginning, the priority is to start treatment due to the urgency of the condition and, in the background - confirmation of the diagnosis. [2, 6, 9]

Seizures may occur with more than 20 mg/kg of isoniazid and always occur with a dose greater than 35-40 mg/kg. A dose of 80 mg/kg is highly toxic and dose above 120 mg/kg is lethal. [6, 9]

Daily dose regimen:

- in children 10 mg/kg/day (10 to 15 mg/kg/day);
- in adults 5 mg/kg/day (4 to 6 mg/kg/day). [3, 6]

CLINICAL CASE

The patient is a girl, T.E.M., 16 years old, who was admitted to the Toxicology Clinic of the University Hospital "Dr G. Stranski" EAD - Pleven with suicidal attempt, realized at home after a family scandal. She is thought to have ingested more than 30 isoniazid (rimicide) tablets, which the mother was taking as maintenance therapy. About 20 minutes after taking the pills, she felt bad and admitted to the relatives what she had done. Within minutes, she fell unconscious and had a tonic-clonic seizure with foaming from the mouth and biting her tongue.

She was brought by private transport to the Emergency Department of the University Hospital "Dr G. Stranski" EAD - Pleven, in a comatose state with tonic-clonic seizures, miotic pupils, with a slow reaction to light. After consultation with a clinical toxicologist, she was treated with diazepam, gastric lavage (after intubation) and, at the same time, started antidote treatment with vit. B6 intravenously. Due to evidence of severe metabolic acidosis, the correction was made with sodium bicarbonate, and she was hospitalized in the Clinic of Toxicology.

A total of 1800 mg of vitamin B6 (36 ampoules of 50 mg/1 mL) was administered until clearing the consciousness. Over the next four days, a further 900 mg (18 ampoules) of pyridoxine was given in decreasing doses as maintenance treatment. Antidote treatment was accompanied by nootropic drugs with non-specific antidote effect, detoxification-depuration, symptomatic and organ protective therapy. Diazepam also continued to be used, as benzodiazepines have been shown to potentiate the action of pyridoxine. [9, 23, 24]

Symptoms of toxic encephalopathy were observed until the third day.

The patient was consulted by a psychiatrist, who stated that it was a "mixed disorder of behavior and emotions "and proposed outpatient monitoring.

DISCUSSION

Paraclinical indicators:

Alkaline-acid balance: pH - 7.263; pCO2 - 32.7 mmHg; pO2 - 111 mmHg; ABC - 14.8 mmol/l; TCO2 - 15.8 mmol/l; BEb - - 11.3 mmol/l; BEecf - -12.4 mmol/l; SBC - 16.2 mmol/l; SAT - 97.6%; (under oxygen); after correction with sodium bicarbonate, the parameters returned to normal.

The blood count was characterized by extreme leukocytosis up to 31 600, which began to normalize the next day, the rest of the blood indicators were normal.

Aminotransferases, bilirubin, urea, creatinine, total protein, albumin, ionogram and hemostasis showed no abnormalities.

Chemical-toxicological analysis:

Blood and urine from the patient were taken and sent for examination to the specialized Chemical Toxicology Laboratory at the Military Medical Academy in Sofia after the sixth hour of taking the drug.

The urine screening test (GC/MS) showed the presence of isoniazid (more than 100 mg/L) and metabolites; paracetamol; lidocaine and metabolites; caffeine, nicotine, cotinine. Immunoassay of the urine sample is negative for illegal drugs.

Testing of the blood sample showed the presence of isoniazid – 0.5 mg/L; paracetamol - below the therapeutic concentration range. The measured value of isoniazid, in accordance with the above-mentioned data for diagnostic clarification, in relation to the values of blood concentration and elapsed time, namely values higher than 0.2 mg/L at the sixth hour, proves overdose and exogenous intoxication. This is also confirmed by the retrospective assessment of the concentration over a past period of time using the elimination half-life.

CONCLUSIONS:

1. The presented case of suicide attempt in a 16-year-old girl with isoniazid overdose has a detailed clinical manifestation of severe intoxication.

2. Toxic noxa was known at home, and the rapid intervention of a clinical toxicologist in the Emergency Department, with the immediate initiation of antidote therapy and subsequent treatment in a specialized toxicology clinic, have led to a favorable outcome.

3. The results of the chemical-toxicological analysis confirm intoxication with the drug, and the retrospective assessment of the concentration over a past period of time using the half-life reveals an extremely high dose of ingested isoniazid.

4. Acute isoniazid intoxications are severe and life-threatening conditions. They require urgent measures and the application of a specific antidote to avoid complications and fatalities.

REFERENCES:

1. Monov A. [Clinical toxicology.] Vol. 1. Venel, Sofia. 1995: pp.85-90. [in Bulgarian]

2. Ellenhorn MJ. Ellenhorn's Medical Toxicology: Diagnosis and Treatment of Human Poisoning. 2nd Edition. Schonwald S, Ordog G, Wasserberger J. (Editors). Williams & Wilkins. January 1, 1997. [Internet]

3. Alao AO, Yolles JC. Isoniazid-induced psychosis. *Ann Pharmacother*. 1998 Sep;32(9):889-91. [PubMed]

4. Steichen O, Martinez-Almoyna L, De Broucker T. [Isoniazid induced neuropathy: consider prevention.] [in French] *Rev Mal Respir.* 2006 Apr; 23(2 Pt 1):157-60. [PubMed]

5. Iannaccone R, Sue YJ, Avner JR. Suicidal psychosis secondary to isoniazid. *Pediatr Emerg Care.* 2002 Feb;18(1):25-7. [PubMed]

6. Luzhnikov E. [Medical toxicology.] *Moskva: Publishing group: GEOTAR-Media*. 2012: 265, 271, 314. [in Russian]

7. Trevor A, Katzung B, Masters S, Knuidering-Hall M. Katzung & Trevor's Pharmacology Examination and Board Review. 10th Edition. (Lange Medical Books) McGraw-Hill Education / Medical. December 21, 2012. [Internet]

8. Sykes JE, Gunn-Moore DA. Chapter 44 - Mycobacterial Infections. In: Canine and Feline Infectious Diseases. Part II. Section 2: Bacterial Diseases. Elsevier. 2014. p.425. [Crossref]

9. Hoffman R, Nelson L, Howland M-E, Lewin N, Flomenbau.m N, Goldfrank L. Goldfrank's Manual Toxicologic Emergencies. McGRAW-HILL Medical. 2010; pp.734-739. [Crossref]

10. Trends and Changes in Drug Research and Development. Walker SR, editor. Springer. October 1, 2011. [Internet]

11. Hamilton RJ. Tarascon Pocket Pharmacopoeia 2020 Deluxe Lab-Coat Edition. 21st Edition. Kindle Edition. Jones & Bartlett Learning. April 30, 2020. [Internet]

12. Shah I, Jadhao N, Mali N, Deshpande S, Gogtay N, Thatte U. Pharmacokinetics of isoniazid in Indian children with tuberculosis on daily treatment. *Int J Tuberc Lung Dis*. 2019 Jan 1;23(1):52-7. [PubMed]

13. Moncrieff J. The creation of the concept of an antidepressant: an historical analysis. *Soc Sci Med.* 2008 Jun;66(11):2346-55. [PubMed]

14. Villar D, Knight MK, Holding J, Barret GH, Buck WB. Treatment of acute isoniazid overdose in dogs. *Vet Hum Toxicol.* 1995 Oct;37(5):473-7. [PubMed]

15. Polat E, Senel S. Suicide attempt with isoniazid in adolescents receiving tuberculous prophylaxis: three cases. *Paediatr Int Child Health.* 2021 Aug;41(3):228-230. [PubMed]

16. William Andrew Publishing. Pharmaceutical Manufacturing Encyclopedia (3rd ed.). Norwich, NY: Elsevier Science. 2008:1968-1970.

17. Asiimwe E, Koh M, Patel R. A Case of Accidental Isoniazid Overdose Presenting With Non-specific Symptoms. *Cureus.* 2022 Mar 16; 14(3):e23218. [PubMed]

18. Cade CE, Dlouhy AC, Medzihradszky KF, Salas-Castillo SP, Ghiladi RA. Isoniazid-resistance conferring mutations in Mycobacterium tuberculosis KatG: catalase, peroxidase, and INH-NADH adduct formation activities. *Protein Sci.* 2010 Mar;19(3):458-74. [PubMed]

19. Aleksandrov N. [Practical emergency toxicology.] *Sofia: Znanie*. 2000: 63-66. [in Bulgarian]

20. Rozwarski DA, Grant GA, Barton DH, Jacobs WR Jr, Sacchettini JC. Modification of the NADH of the isoniazid target (InhA) from Mycobacterium tuberculosis. *Science*. 1998 Jan 2;279(5347):98-102. [PubMed]

21. Kwo PY, Cohen SM, Lim JK. ACG Clinical Guideline: Evaluation of Abnormal Liver Chemistries. *Am J Gastroenterol.* 2017 Jan;112(1):18-35. [PubMed]

22. Mihov Hr, Shmilev T. [Poisonings and accidents in childhood.] *Plovdiv: Vasil Petrov.* 2003: 269-271. [in Bulgarian]

23. Sekaggya-Wiltshire C, von

Braun A, Scherrer AU, Manabe YC, Buzibye A, Muller D, et al. Anti-TB drug concentrations and drug-associated toxicities among TB/HIV-coinfected patients. *J Antimicrob Chemother.* 2017 Apr 1;72(4):1172–1177. [PubMed]

24. D'Orazio JL, Hayoun MA. Isoniazid Toxicity Clinical Presentation. *Medscape.* Feb 07. 2019. [Internet]

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