TUBERCULOSTATICS ACUTE POISONING: DIAGNOSTIC AND TREATMENT

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ABSTRACT

Introduction. Although the frequency of isoniazid poisoning is not very high, there are life threatening conditions which require a swift diagnosis and treatment.
Material and method. We present the case of a female patient, aged 15 admitted in our clinic, by means of transfer, from another medical unit, due to tonic-clonic generalized seizures, followed by emesis and coma. The patient arrived at the Emergency Admissions Unit of our hospital, in coma, Glasgow 8, orotracheally intubated. She did not respond to verbal stimuli, but she did respond to deep, painful stimuli with marked agitation. The patient has a nasogastric tube, on which an orange liquid is visible on the outside and on the urinary catheter – orange coloured urine. From the patient's medical history, which was obtained from the patient's mother, we noticed that the patient had been, for the past 4 months, under treatment with tuberculostatic drugs (Isoniazid, Rifampicin and vitamin B6). The patient administered the medication herself.
Results. Based on clinical manifestations, i.e. tonic-clonic generalized seizures, incoercible emesis and coma, reddish-orange colour of the gastric fluid and urine, at over 6 hours after the onset, on the patient's medical historyand based on laboratory results which revealed metabolic acidosis the suspicion of acute tuberculostatic poisoning arose. We started antidotal therapy with vitamin B6 with favourable clinical evolution.
Conclusion. Acute isoniazid poisoning must be suspected in the case of any patient who presents the classic triad: refractory seizures, severe metabolic acidosis and coma and the treatment with the specific antidote-pyridoxine, must be available at any emergency unit.

Keywords: isoniazid, metabolic acidosis, generalized seizures, poisoning, vitamin B6

INTRODUCTION

In accordance with the European Centre for Disease Control and Prevention (ECDCP), Romania continues to rank first place among the other European Union member states, with the highest number of tuberculosis cases.

Isoniazid, hydrazide of nicotinic acid, represents the number one therapeutic solution in the treatment and prevention of tuberculosis in the case of adults, as well as in the case of children. Rifampicin is another tuberculostatic drug, with a synergetic action similar to that of Isoniazid; these two compounds are used together in treatment plans.

CASE DESCRIPTION

Female patient, aged 15, is admitted in our clinic, by means of transfer, from another medical unit, due to tonic-clonic generalized seizures, followed by emesis and coma. The sudden onset of the manifestations – prior to this, the patient was in full health – was a tonic-clonic generalized seizure episode, which lasted approximately 4-5 minutes, followed by incoercible emesis. The family requested for an ambulance to transport the patient to the nearest medical unit, where the patient suffered from another episode of tonic-clonic generalized seizures. She was intubated orotracheally; then a

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nasogastric tube and a urinary catheter were also set; intravenous access was established and diazepam treatment and an IV for restoration of fluids and electrolyte balance were initiated; the patient was transferred to our clinic, where she arrived approximately 6 hours after the onset.

The patient arrived at the Emergency Admissions Unit of our hospital, in coma, Glasgow 8, orotracheally intubated. She did not respond to verbal stimuli, but she did respond to deep, painful stimuli with marked agitation. Oxygen saturation levels in the atmospheric air of 97-98%, vesicular murmur present bilaterally, without rales. VR=80 bpm, BP=148/96 mmHg. The patient has a nasogastric tube, on which an orange liquid is visible on the outside and on the urinary catheter – orange coloured urine. Pupils are equal, round, reactive. Deep tendon reflexes are present bilaterally. No signs of meningeal irritation or of focal neurologic signs. Seizures did not occur again during the transfer.

From the patient's medical history, which was obtained from the patient's mother, I noticed that the patient had been, for the past 4 months, under treatment with tuberculostatic drugs (Isoniazid, Rifampicin and vitamin B6). The patient administered the medication herself.

Based on clinical manifestations, i.e. tonic-clonic generalized seizures, incoercible emesis and coma, reddish-orange colour of the gastric fluid and urine, at over 6 hours after the onset and based on the patient's medical history, the suspicion of acute tuberculostatic poisoning arose. The first labs, which were collected at the Emergency Admission Unit, detected the presence of metabolic acidosis pH 7.24, BE-8.2 mmol/l, serum lactate 4.6 mmol/l, HCO3 17.1mmol/l. The liver function tests identified hyperbilirubinemia, with a predominance of direct bilirubin, but with normal transaminase levels. At the same time, creatine kinase and glycaemia levels were higher than the maximum normal level. The rest of the lab results, i.e. full blood count, kidney function test, coagulation profile were in normal value ranges and the quick urine toxicology test tested positive only for benzodiazepine, which was administered to stop the seizures.

The patient was admitted in the PICU, where the intubation was removed and she was administered a treatment with activated carbon every six hours through the nasogastric tube, in a series of doses, endovenous glucose and electrolytes IV and treatment with intravenous B6 vitamin. 6 hours after the patient's admission in the PICU, due to the fact that the patient's state improved, seizures did not occur, the coma superficialized and the haemodynamic parameters were in normal ranges, it was decided to transfer the patient to the Toxicology Unit.

The para-clinical labs repeated every 8 hours since the patient's admission showed the disappearance of the acidosis ph7.41, BE -4 mmol/l, HCO3 21.1mmol/l, however the bilirubin, creatine kinase values were elevated, and the transaminase levels were also high (Table 1), without any alteration of the cholestatic enzymes: GGT and alkaline phosphatase. The urinalysis showed the presence of glucose, ketone bodies and bilirubin. Subsequently, the para-clinical labs were collected on a daily basis, proving that toxic liver damage and toxic rhabdomyolisis had appeared; the highest levels were registered on the 5th day after the ingestion: AST 747 U/L, ALT 295U/L, creatine phosphokinase 5067 U/L (Table 1). The abdominal ultrasound scan revealed a normally-sized liver, with a diffusedly modified structure, with micro nodular appearance of the parenchyma, without any architectural disorganisation; the rest of the examined structures were of normal appearance.

In the Toxicology Unit the endovenous treatment with glucose and electrolytes, Vitamin B6, 500 mg/day continued; silymarin and arginine were added to the treatment once the liver damage symptoms appeared. The clinical evolution was slowly favourable, as of the 2nd day the nasogastric tube and the urinary catheter were discontinued, the patient became conscious, cooperative, temporo-spatially oriented, presenting, however, muscular pain in her upper and lower limb region, which decreased as of the 6th day after her admission.

During her admission, the patient was psychologically assessed and she initially denied voluntary ingestion, but the psychological assessment determined the self-destructive nature of the act; as a result, her discharge from the Toxicology Unit and transfer to a paediatric psychiatry service was recommended.

On her 8th day of admission, due to the fact that the patient's state was considerably improved and the para-clinical tests showed an improvement of her liver function and a significant decrease of her creatine phosphokinase levels, it was decided to transfer her to the Psychiatry ward, but the patient's parents refused and requested her discharge.

DISCUSSIONS

Isoniazid, hydrazide of nicotinic acid, was introduced in the treatment of tuberculosis in 1952 and, to this day, remains the main therapeutic line used for the treatment and at the same time for the pre-

TABLE 1. *Paraclinical data, day by day, correlated with the clinical manifestations*

	Reference interval	Admission	8 hours	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8 -discharge
pH	7.35-7.45	7.24	7.41	7.40	7.41	-				
Base excess mmol/l	- 3 - +3	- 8.2	-4.9	-1.6	-3.1	-				
Bicarbonate mmol/l	18-23	17	21.1	23	21.6	-				
ALT U/L	0-34	18	19	91	148	228	295	318	231	189
AST U/L	0-31	31	60	362	487	742	747	551	237	111
Total Bilirubin mg/dl	0.3-1.1	1.21	1.72	0.65	0.44	0.29	0.37	0.39	0.47	0.51
Direct Bilirubin mg/dl	0-0.30	0.79	0.81	0.28	0.19	0.16	0.18	0.18	0.39	0.17
Indirect Bilirubin mg/dl	0-0.85	0.42	0.91	0.37	0.25	0.13	0.19	0.21	0.08	0.34
LAP U/L	74-390	-	85	80	71	64	59	64	59	65
GGT U/L	0-32	-	12	11	12	11	12	15	12	10
CPK U/L	0-145	395	3152	1275	1046	533	1280	5076	3175	1061
Urea mg/dl	17-43	21	18	5	10	21	16	14	15	19
Creatinine mg/dl	0.65-1.1	1.31	1.02	0.89	0.81	0.84	0.87	0.86	0.82	0.87
Clinical manifestations		Comatose is not responding to verbal or pain stimuli; IOT; Reddish orange fluid on nasogastric tube and urinary catheter.	Obnubilated with agitation periods; Spontaneous breathing; Red-orange fluid in urinary catheter.	Obnubilated; Stable from a cardiorespiratory and digestive point of view; Normochromic urines.	Present temporospatially stable from a cardiorespiratory and digestive point of view.	Palpable liver with inferior edge 6 cm from the costal margin.	Myalgia in shoulders and thigh muscle area.		Clinically stable.	Conscious; Cooperative; No myalgia; Stable from a cardiorespiratory and digestive point of view; Liver edge at 1 cm from the costal margin.

vention of the tuberculosis infection. It has a good digestive absorption and the optimal plasmatic levels are achieved between 1 and 2 hours after ingesting a therapeutic dose. It crosses through the hematoencephalic barrier and reaches, at cephalorachidian liquid level, similar concentrations with the plasmatic ones. Elimination occurs, at a rate of 75-90%, through the renal flow, especially in the form of metabolites resulted after the hepatic biotransformation through acetylation and hydrolysis.

Rifampicin is a broad spectre antibacterial, derived from Rifampicin B extracted from Streptomyces mediterranei. It is used to treat gram positive or negative bacterial infections, but it is especially used for micro bacterial infections, in association with Isoniazid. Digestive absorption is good and it is quickly dispersed in all tissues and fluids, including in the cephalorachidian liquid (1). Elimination occurs mostly through the biliary system, but it can also occur through the renal flow, in an active form or as an active metabolite (desacetyl rifampicin) or inactively (formyl rifampicin). Urine samples collected every 3-6 hours after the administering of Rifampicin have brownish-red coloration (1).

The main organs affected by the accidental or voluntary ingestion of a toxic dose of isoniazid are the liver and the nervous system, through the hepatotoxic metabolites or through the interaction with pyridoxine. Toxicity symptoms appear due to 1500 mg doses. Doses higher than 30 mg/kg or a serum level of over 10 ug/ml, determine seizures, while doses of 80-150 mg/kg are associated with a guarded prognosis and death (2). In the case of the presented patient, the ingested dose remains unknown, neither was the determining of the isoniazid or rifampicin serum levels possible.

Pyridoxine (B6 Vitamin), though its active metabolite – pyridoxine phosphate, is an essential cofactor for the emergence of gamma-amino butyric acid (GABA), the main neurotransmitter which inhibits the nervous system. IHN produces a pyridoxine and pyridoxine phosphate deficit, by increasing its elimination through the renal flow, but also by inhibiting the pyridoxine kinase involved in the creation of the active metabolite and, consequently, the levels of gamma-amino butyric acid decrease.

The clinical manifestations may appear in an interval of 30 minutes up to 2 hours after ingestion and they are represented by the classic triad: recurrent seizures, metabolic acidosis and coma (3). Our patient had two episodes of generalised tonic-clonic seizures, followed by coma, and the para-clinical labs collected at admission showed the presence of metabolic acidosis and an accumulation of lactic acid, which are typical in IHN poisoning.

Hepatic damage appears secondary to the emergence and accumulation at this level of an active metabolite, acetyl hydrazine. Due to the fact that the emergence of these hepatotoxic metabolites is

stimulated by rifampicin, when these two substances are associated, the incidence and severity of liver damage increase (4). Rifampicin usually determines increases of bilirubin and alkaline phosphatase levels, and increases of transaminases can be determined both by rifampicin and isoniazid, but especially when they are associated (5). The rifampicin's hepatotoxicity was first described by Scheuer in 1974 in a study which analysed 11 patients under rifampicin treatment. (6)

In the patient's case, I noticed a transaminase increase on the 5th day, maximum, after ingestion – ALT 318 U/L, AST 747 U/L, as well as elevated levels of total bilirubin (1.72 mg/dl) and conjugated bilirubin (0.81 mg/dl), without any modification to the cholestasis enzymes. Other toxic effects of rifampicin, described in specialised literature such as thrombocytopenia, damage to the renal function or red man syndrome were not noticed in the patient's case presented here.

Rarely, in the clinical picture of isoniazid poisoning, rhabdomyolisis may appear, secondary to the direct toxicity of isoniazid or of the metabolites, but mostly as a result of the seizures (7). The patient presented elevated levels of creatine phosphokinase, but which had a non-linear evolution: 8 hours since her admission CPK= 3152 U/L, after which the values started to decrease and on day 3 they were 533 U/L; after this, once the muscle pain in the upper and lower limbs began, the values peaked at 5067 U/L, on day 6. This evolution is similar to that of other cases described in the specialised literature, in which CPK reaches maximum levels on day 5-6. Also, there are statistically significant correlations between the CPK levels and the isoniazid dosage (over 2.4 grams) as well as the length of seizures (8); in the case of our patient, such a correlation couldn't be established, because the isoniazid dosage and the exact length of the seizures were unknown.

Hyperglycaemia, glycosuria, ketonuria are also modifications which can occur in isoniazid poisoning and which, along with metabolic acidosis, can be mistaken for diabetic ketoacidosis (3). All of these modifications appeared in the presented case, but the values stabilised in the first 48 hours of admission.

In the case of isoniazid poisoning, pyridoxine (B6 vitamin) is the specific antidote, because the clinical manifestations, such as seizures, metabolic acidosis and altering of consciousness, are secondary to the deficit of pyridoxine and pyridoxine phosphate (its active metabolite). The necessary dose of pyridoxine depends on the isoniazid quantity ingested. If the dosage is known, then for each gram of isoniazid, 1 gram of pyridoxine will be administered. Intravenous administration is preferred, if the substance is available, but it can also be administered orally, through the nasogastric tube. In the event in which the ingested isoniazid quantity is unknown, a first dose of B6 vitamin of 5 grams must be administered, intravenously (70 mg/kg body in the case of children), a dosage which can be repeated if needed every 5-20 minutes, until the seizures stop (9). In the presented case, the isoniazid, rifampicin and vitamin 6 doses the patient ingested were unknown, the seizures were short termed and they were stopped through the administering of benzodiazepine, before she arrived in our clinic, where the seizures did not occur again. Based on this, vitamin B6 was administered in 250 mg doses, intravenously, every 12 hours.

Beside the antidote treatment, the rest of the supporting measures are similar to those used in any case of acute poisoning: securing the respiratory tract, obtaining an IV line and monitoring the vital signs.

The administering of activated carbon in doses of 1-2 g/kg is recommended, because it adsorbs the isoniazid efficiently, limiting its absorption. The patient received a series of activated carbon doses, administered through the nasogastric tube, at a 6 hour interval in the first 48 hours. Increasing the elimination of the toxic substance through haemodialysis can be efficient, because isoniazid creates a weak connection to plasma proteins and it has a low distribution volume. However, this procedure is rarely necessary, because maintaining an adequate diuresis is enough to eliminate the toxic substance (10).

As to correct the severe metabolic acidosis, a result of seizures, as well as of lactate dehydrogenase inhibition, caused by the isoniazid, it is necessary to intravenously administer sodium bicarbonate 1-2 mmol/kgc; in this case, the seizure must be stopped, through the administering of pyridoxine and anticonvulsants. Benzodiazepines are administered, as a first resort, intravenously, because they act at GABA receptors level, thus amplifying the effect of the pyridoxine. Diazepam is used in doses of 0.25- 0.5 mg/kg up to a maximum of 10 mg/dose. Phenytoin, acting through the sodium channels and not on the GABA receptors, has a limited efficiency in the treatment of seizures triggered by isoniazid (3). The patient received 2 intravenous diazepam doses of 10 mg before her admission in our clinic, which were enough to stop her seizures;

the patient didn't require further anticonvulsant treatment.

The damage to the liver function described in isoniazid or rifampicin poisonings appeared in the case of the presented patient. The severity may vary towards acute liver failure, which requires liver transplant or may lead to death in 20% of the cases (11). In the case of less severe liver damage, the evolution is a favourable one, without any long term issues. Our patient presented a moderate form of liver damage, with an increase of transaminase and bilirubin levels, but without any damage to the synthesis function of the liver. She received a treatment with 210 mg/day of silymarin three times during her admission and she received the recommendation to continue with the treatment for another 14 days at home.

CONCLUSIONS

Because tuberculosis represents, both at worldwide level and at a national level a public health issue, tuberculostatic drugs, especially isoniazid, are used on a large scale. Although the frequency of isoniazid poisoning is not very high, there are life threatening conditions which require a swift diagnosis and treatment. Acute isoniazid must be suspected in the case of any patient who presents the classic triad: refractory seizures, severe metabolic acidosis and coma. The treatment of this type of poisoning entails gastrointestinal decontamination, controlling the seizures, correcting the acidosis and administering an antidote treatment of pyridoxine, which must be available at any emergency unit.

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