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CASE PRESENTATION – STUDIU DE CAZ – PRESENTATION DE CAS CLINIQUE – ПРЕЗЕНТАЦИЯ СЛУЧАЕВ ИЗ КЛИНИЧЕСКОЙ ПРАКТИКИ

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CASE REPORT: ACUTE LIVER FAILURE INDUCED BY PARACETAMOL TOXICITY

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Key words: *Paracetamol, overdose, N-acetyl-cysteine, hepatotoxicity, acute liver failure.*

Introduction

Paracetamol is the most commonly used drug across Western Europe and North America. There is no such trend of using Paracetamol in the Republic of Moldova, thus overdose cases are extremely rare. The mechanisms leading to overdose episodes might induce hepatotoxicity.

Clinical case

This present article reports a case of acute liver failure induced by Paracetamol overdose. A 46-year-old man presented to the Medpark International Hospital. He was administered Paracetamol 1000 mg, approximately every 4 hours for 2 days, and 1000 mg twice a day for another 2 days, after an intense physical exertion, followed by muscle fever with myalgia and low-grade fever (37.4 °C) The reason for asking the medical care were pronounced fatigue, nausea, loss of appetite, night sweats, and frequent urination.

Conclusion

Eventually, the case was successfully resolved due to N-acetyl-cysteine, administered according to the established treatment scheme, as well as the adjuvant therapy.

Cuvinte cheie:
Paracetamol, supradozaj, N-acetilcisteină, hepatotoxicitate, insuficiență hepatică acută.

INSUFICIENȚĂ HEPATICĂ ACUTĂ INDUSĂ DE SUPRADOZAJUL DE PARACETAMOL: CAZ CLINIC

Introducere

Paracetamolul este cel mai frecvent utilizat medicament în Europa de Vest și America de Nord. În Republica Moldova nu există, însă, această tendință și în consecință, cazuri de supradozaj înregistrate se atestă foarte rar. Mecanismele ce se derulează în timpul episoadelor de supradozaj induc hepatotoxicitate.

Cazul clinic

În acest articol relatăm un caz de insuficiență hepatică acută indusă de supradozajul cu Paracetamol. Un bărbat de 46 ani s-a adresat la Spitalul Internațional Medpark, care în urma unui efort fizic intens, ce a cauzat febră musculară cu mialgii și subfebrilitate (37,4°C), a administrat comprimate Paracetamol, 1000 mg aproximativ la fiecare 4 ore 2 zile, după care câte 1000 mg de 2 ori pe zi încă 2 zile. Ulterior au apărut simptome de fatigabilitate pronunțată, grețuri, inapetență, transpirații nocturne și micțiuni frecvente, acestea fiind motivul solicitării ajutorului medical.

Concluzii

Datorită medicației cu N-acetilcisteină, aplicată conform schemei de administrare instituite, cât și a tratamentului adjuvant, cazul respectiv a fost soluționat cu succes.

INTRODUCTION

Paracetamol (Acetaminophen) is an antipyretic and analgesic drug, used for mild to moderate pain, exhibiting a central action and being an active metabolite of phenacetin. Paracetamol was introduced onto the pharmaceutical market in 1950 and is currently the most widely used drug worldwide, used to treat pain and fever. Acetaminophen toxicity is defined as an excessive drug intake, greater than 4 g/24 h, which has become a common reason for medical referring to Emergency Healthcare Assistance across Western Europe.

CLINICAL CASE

A 46-year-old man referred to the doctor, complaining of pronounced fatigue, nausea, loss of appetite, night sweats, and frequent urination. He claimed that the symptoms occurred about a week ago, after an intense physical exertion, followed by muscle fever with myalgia and low-grade fever (37.4°C). He individually administered Paracetamol 1000mg, approximately every 4 hours for 2 days, afterwards 1000 mg twice a day for another 2 days. 24 hours passed since the last administration of Paracetamol. The objective examination did not reveal any particularities, except for the subicteric tint of the skin.

The complete blood count, urinalysis, urea and creatinine levels showed no pathological changes.

The laboratory biochemical findings revealed changes in liver functioning, suggesting hepatic cytolysis syndrome: Alanine aminotransferase (ALT) – 8009 U/L (normal range: 0.1-41 U/L), Aspartate aminotransferase (AST) – 3792 U/L (normal range: 0,1-41 U/L) (fig. 1); cholestasis: Gamma-glutamyl transferase (GGT) test – 210 U/L (normal range: 15-85 U/L) (fig. 2), total serum bilirubin level – 92 µmol/L (normal range: 3-17µmol/L), and conjugated bilirubin – 80 µmol/L (fig. 3). Moreover, the patient exhibited coagulopathy syndrome, confirmed by the quantitative D-Dimer assay: 7615 µg FEU/mL (norm <500µg FEU/mL) on the first day of admission and ranging values on the subsequent days of treatment. Prothrombin index made up 34.4% (70-130%) (fig. 4) and INR – 2.07. The albumin level showed the lowest value in the first days of treatment. Markers of viral hepatitis: Total anti-HCV, HBsAg, Total Anti-HBc, Total Anti-HDV were negative. The chest X-ray revealed no particular features. Magnetic resonance cholangiopancreatography (MRCP), performed to exclude gallstone disease and other etiologies, registered severe edema of the gallbladder wall (13 mmthick) and a vermicular lumen. A detached gallbladder and inability to visualize the intrahepatic bile ducts were reported. Periportal inflammation and edematous liver hilum. Early hepatomegaly. Were these MRI signs of acute hepatitis/acute liver failure?

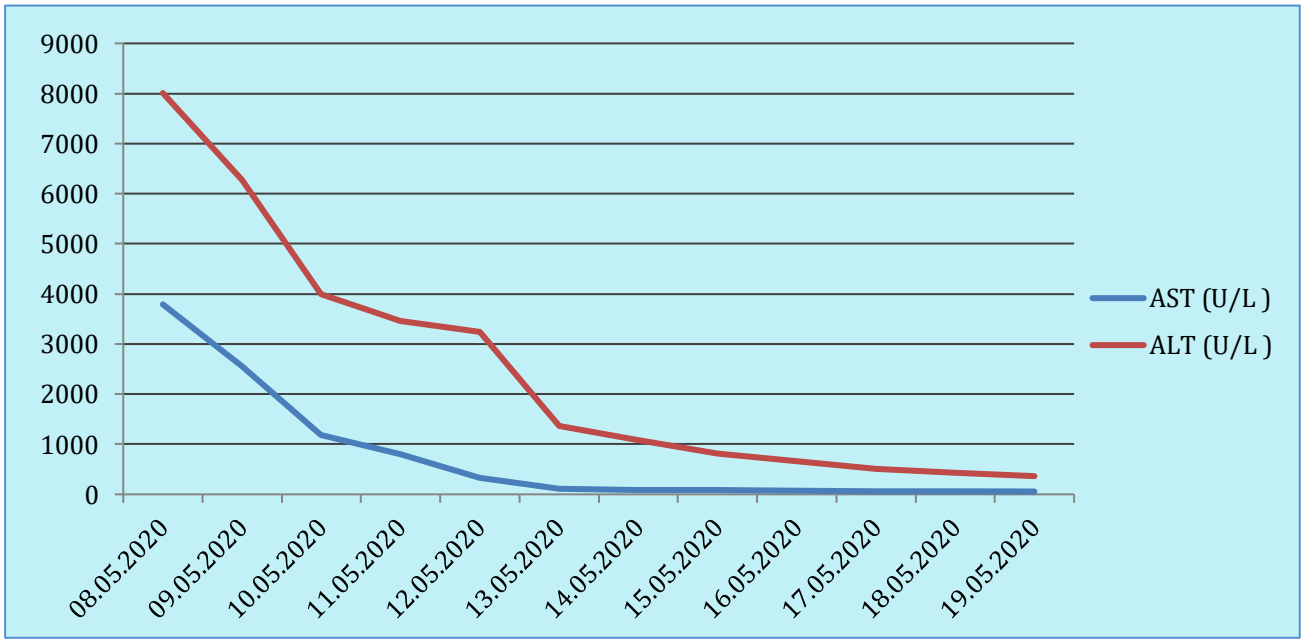

Figure 1. The dynamic changes of Alanine Aminotransferase and Aspartate Aminotransferase levels in patient with acute Paracetamol toxicity.

Severe acute liver injury was determined by elevated transaminases and INR=2.07 (>1.5) and jaundice (1). In this case, severity score for drug induced liver injury was moderate-severe (2). There were no clear signs of hepatic encephalopathy. The Glasgow Coma Scale didn't change.

The patient was given an emergency assistance within the Intensive Care Unit, by administering N-Acetyl-cysteine (NAC) at a loading dose of 150 mg/kg over the first 15 minutes, then 50 mg/kg – over the next 4 hours, and 100 mg/kg NAC – during the following 16 hours, thus, the total dose amounted for 300 mg/kg over 20 hours. On the third day of hospital stay, the treatment was combined with semi-pulse therapy with Methylprednisolone 500 mg for 3 days, which was further gradually reduced. Furthermore, on the 4th day of hospitalization, plasmapheresis and albumin transfusion, amino acids and anticoagulation with Enoxaparin, caused by the existing thrombotic risk (D-Dimer assay: 7615 µg FEU/mL) were carried out, showing a positive dynamic in patient's condition. The patient was discharged after 11 days of treatment with ALT – 371 U/L, AST – 57 U/L, GGTP – 233 U/L, the total serum bilirubin level being 50 µmol/L. The patient exhibited satisfactory overall condition and no adverse reactions were reported.

A follow-up treatment was recommended, by administering ademetionine and enterosorbents, as well as by maintaining the anticoagulation level by taking prophylactic doses of Enoxaparin for 1 month. Additionally, a dynamic monitoring of transaminases, bilirubin, GGTP levels, as well as a magnetic resonance cholangiography were performed.

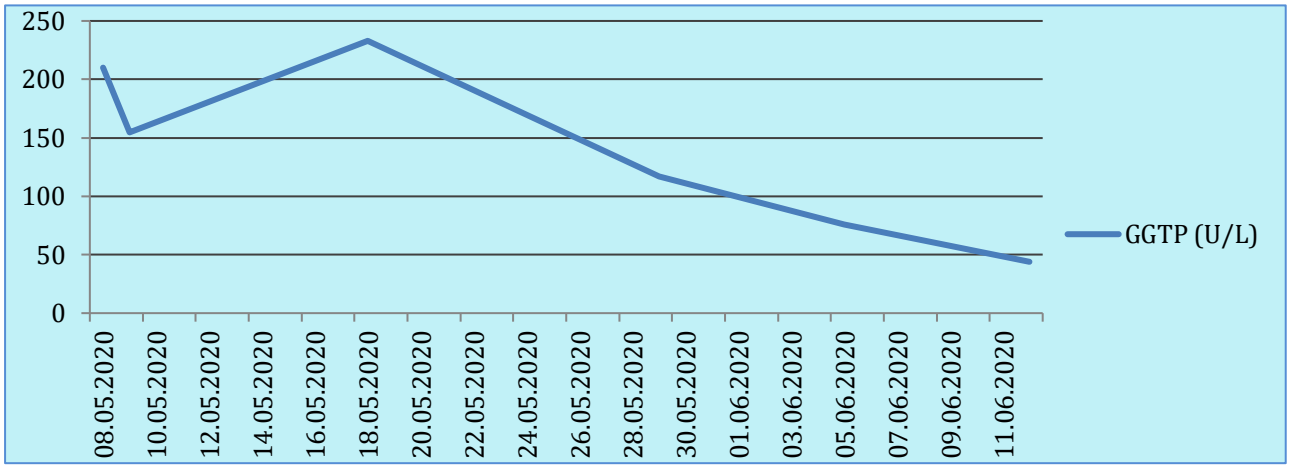

Figure 2. Dynamic changes of Gamma-glutamyltranpeptidaselevels in patient with acute toxicity.

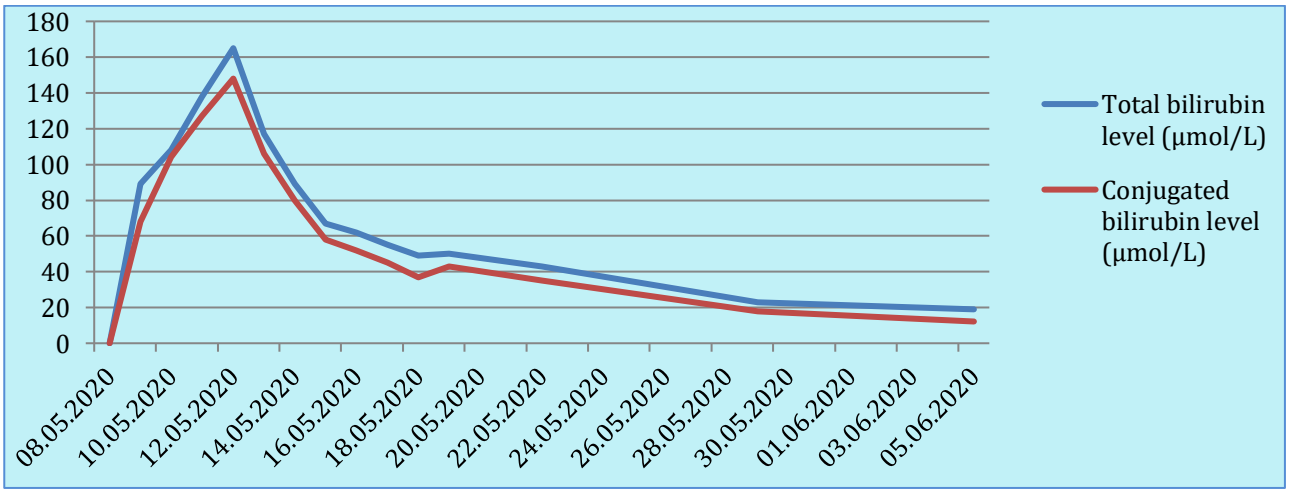

Figure 3. Dynamics of serum bilirubin levels in patient with acute Paracetamol toxicity.

Two weeks after discharge, the total serum bilirubin was 43 µmol/L, GGTP – 117 U/L, ALT – 343 U/L, AST – 76 U/L, whereas one month later since the disease onset, the biochemical assay revealed no signs of cholestasis and a low-level cytolytic syndrome (ALT – 59 U/L, AST – 32 U/L), without any differences from the laboratory reference ranges.

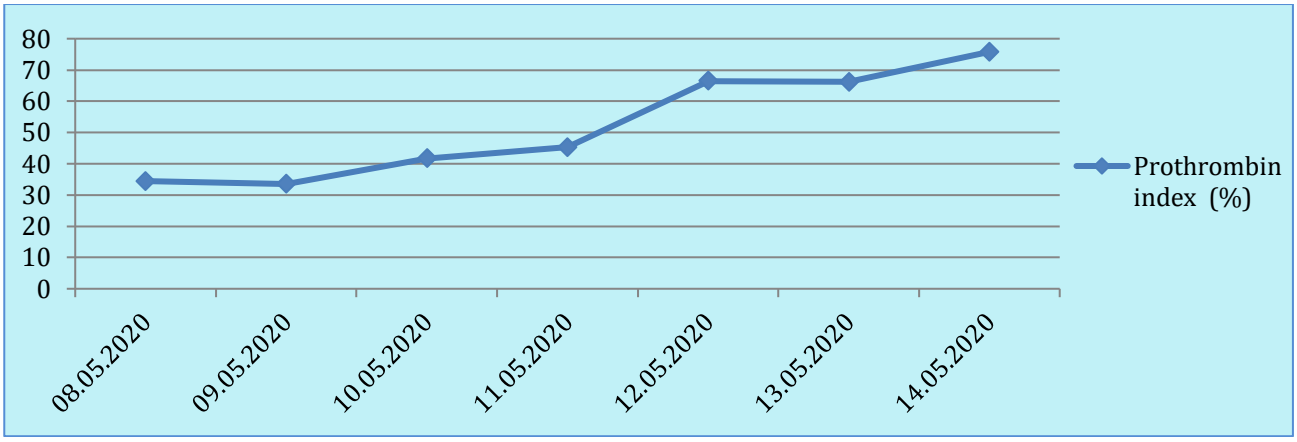

Figure 4. Dynamics of Prothrombin index throughout the treatment period.

DISCUSSIONS

There are approximately 100,000 referrals to the Emergency Department in the UK annually, caused by Paracetamol intoxication, resulting in about 150 deaths. The causes of overdose might be either due to unintentional use a wide range of drug availability containing acetaminophen, as well as due to a deliberate suicidal desire (3). In the United States, approximately 74-92% of Acetaminophen overdoses result from suicide cases, thus approximately 39% cases of acute liver failure are caused by Acetaminophen overdose (4, 5). However, Acetaminophen toxicity is not caused by only overdose. Sometimes, other reasons might occur, which lead to hepatotoxicity due to a definite therapeutic dose. Cases of Paracetamol toxicity have been reported in doses less than 4.0 g/24 hours in patients with Gilbert's syndrome, polymorphism in cytochrome P-450 (as well as other enzymes involved in hepatic metabolism), in malnourished patients, in people with chronic alcohol abuse, in elderly people, etc. (6). Paracetamol-induced acute hepatic failure cases quite rarely occur in the Republic of Moldova. After the drugs ingested per oral, it is absorbed very fast, reaching the highest plasma concentration in about one hour. The bioavailability is about 75%. When a healthy person administers a therapeutic dose of Paracetamol, it is conjugated directly into the liver to form sulfate and glucuronide derivatives. Thus, when administering a therapeutic dose, 55% of drug will be excreted as glucuronide, 30% as sulfate and 4% as metabolic oxidation by-products. The half-life (t½) is about 1.5-2.5 hours, however it might be prolonged in case of overdose (7, 8). The minimum toxic dose of Paracetamol is considered 10 g. The first symptoms appear within 4-12 hours after the first ingestion, featured by dyspeptic symptoms. Liver involvement occurs within 24-48 hours; however, symptoms of acute liver, kidney and heart failure might occur even over 4-6 days after ingestion (6).

The acetaminophen-induced hepatotoxicity mechanism leads to formation of toxic metabolite N-acetyl-para-benzo-quinone by cytochrome P-450, which induces oxidative stress, ATP depletion and mitochondrial dysfunction. This product is conjugated by hepatic glutathione and transformed into complexes that are excreted by the kidneys. This is a dosage-dependent mechanism. Another mechanism results in the production of peroxynitrite, which is a toxic free radical that induce oxidative stress via mitochondria dysfunction and DNA fragmentation. All these changes lead to an increased membrane permeability, vacuolation, caryolysis and, eventually, cellular apoptosis (2). NAC acts as a glutation donor, thus being an effective antidote. However, there are differences regarding the drug administration schemes. The recent studies state that NAC administration should be elective within the first 24 hours after ingestion of Acetaminophen (3, 9).

The homeostasis disorder between procoagulant and anticoagulant factors is mainly caused by liver failure. Moreover, the circulating endotoxins might also cause hypercoagulant effect, which might be also induced by acute liver failure (10). The specialized studies reported an increased heterogeneity of coagulation system abnormalities, ranging from a hypercoagulant to hypocoagulant status or the alternation of both. However, thrombosis is the most commonly reported complication. Prophylactic correction of coagulation is not recommended, however a reasonable monitoring and correction of coagulogram markers should be carried out (1, 7).

Both oral and parenteral administration of NAC are available. The disadvantage of oral administration is that a lower drug dose will be absorbed in case of vomiting episodes. The research studies, conducted since the 1970s, were aimed at identifying an effective antidote for Paracetamoltoxicity, by studying cysteine, methionine, and cysteamine, which have proven to have satisfactory treatment outcomes in small randomized trials. However, despite the effectiveness, there have been alsoreporteda series of side effects such as severe headaches, nausea and vomiting, thus leading to search for a new antidote. NAChas become the elective antidote, since it can be also administered intravenously and due to its rarely occurring side effects for the same therapeutic effect. The first 20-hour intravenous NAC regimen was based on the 4-hour Paracetamol half-life used by the British researchers. In the United States, another treatment scheme was developed on the prolonged half-life of Paracetamol, which can last for 12 hours in case of overdose. Despite minor changes in the administration regimen, it is still used effectively nowadays, except for some situations requiring abatement from the standard scheme. As for example in patients who continued to exhibit elevated plasma levels of Paracetamol or non-decreasing transaminases. These situations require an on-going NAC i.v. infusion until over 20-21 hours.

The length of the loading dose has been changed over time, ranging from 15 minutes (the traditional scheme) up to one hour to reduce the administration errors, which is still a controversial issue due to the adverse reactions. Other disputes have arisen regarding the reduction of NAC administration time to 12 hours, whether to switch from the so-called "three bag-regimen" to "two-bag regimen" scheme in order to minimize side effects. A number of randomized studies have been carried out in this regard, which resulted in positive treatment outcomes. The emergence of a great number of changed regimens confirm the low rate of adverse reactions, however showing a decreased therapeutic efficacy (11).

Corticosteroids are admitted in idiosyncratic drug-induced acute liver failure, when other treatments fail, showing clinical benefits (1, 2). In our clinical case, the use of Metilprednisolone was reasoned by the worsening of cholestatic and hepatodepressive syndrome on the third day.

The increasing number of drug abuse and toxicity cases worldwide, has determined the Food and Drug Administration (FDA) to establish the following criteria, in 2011: any drug containing Paracetamol, combined with other substances should not exceed the dose of 325 mg of Paracetamol per tablet. Thus, according to FDA decision, since January 2014, more than half of the pharmaceutical companies have limited the amount of Paracetamol in combined medications (3). However, drug availability and presence of acetaminophen in multiple combined pharmaceutical drugs of different brands poses a significant risk for over dosage. Furthermore, as a result of hepatotoxicity-related cases reported when using common therapeutic doses, current medicine tends to focus on precision medicine. It aims to study the human genome by genetic sequencing (6) in order to obtain data on the possibility of safe administration of Acetaminophen, if this medication is required to be administered.

CONCLUSIONS

The multitude of therapeutic regimes indicates a lack of a "gold standard", but medical practice shows that each patient require a customized treatment regimen due to a series of factors such as genetic, demographic and biological, as well as due to the amount of Paracetamol administered.

CONFLICT OF INTERESTS

The authors declare no conflict of financial or non-financial interests.

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