Double, suicidal intoxication with hydroxycarbamide - a case report

Hydroxycarbamide (HCB), also known as hydroxyurea, is an urea derivative used mainly as antineoplastic and antisickling agent. We described a 31 yrs. female, with essential thrombocytopenia, who was admitted to our clinic because of double suicidal ingestion of hydroxycarbamide. First time it was 7.5 g of HCB with coingestion of 50 mg of diazepam, and several glasses of wine, second time it was 10 g of HCB, with coingestion of 100 mg paroxetine and few glasses of vodka. Both suicidal attempts were triggered by multiple reactive factors. At the time of admissions the patient was conscious, restless, with decreased mood. Transient decrease of total leukocyte count was noted on fourth day of first overdose. The second overdose led to no significant changes in blood count. There were no other abnormalities in biochemical results. According to the best of our knowledge this is the first report of acute suicidal intoxication with hydroxy-carbamide in an adult.

Hydroxycarbamide (HCB), znany również jako hydroksymocznik, jest pochodną mocznika, jest środkiem niespecificznym, który ma w efekcie działania uniemożliwiające wzrost promieniowania. W pracy opisano przypadek 31-letniej pacjentki, leczonej z powodu nadpłytkowości samoistnej, która zastała przyjęta do naszego ośrodka w połowie 2012 roku. W obu przypadkach pacjentka była przytomna, niespokojna, z obniżonym nastrojem. W czwartej dobie po pierwszym zatruciu obserwowano przejściowy spadek całkowitej liczby leukocytów. Po drugim zatruciu nie obserwowano żadnych zmian w obrazie morfologicznym krwi obwodowej. Zgodnie z naszą najlepszą wiedzą jest to pierwszy opis samobójczego zatrucia hydroksymocznikiem.

Introduction

Hydroxycarbamide’s action in myeloid tissue leads to inhibition of granulocyte, platelet and erythrocyte production. Antimitotic effect is achieved by inhibition of ribonucleic reductase, while cytotoxic effect is due to direct DNA fragmentation, and breaking and translocations of chromosomes. Cellular growth is stopped in S and G1 phases. RNA and protein synthesis are not affected. Time to peak concentration (tmax) after ingestion of HCB is about 1-2 h, while half-life is approximately 3-4 h [1].

Drug is metabolised to urea both in the liver and the kidneys. About 50-80% of the hydroxycarbamide is excreted unchanged with urine as metabolites and unchanged drug during first 12 h from ingestion. Small part is excreted via lungs as carbon dioxide [2-4].

HCB is distributed into breast milk, it crosses the placenta and blood-brain barrier [2,3,5,6].

The drug’s main application areas are therapy of myeloproliferative disorders like polycythemia vera, essential thrombocythemia with high risk of thrombosis or bleeding, myelofibrosis, resistant chronic myelotic leukaemia and sickle cell disease [1-9].

HCB is also used in patients suffering from malignant melanoma, recurrent, metastatic or inoperable ovarian cancer. If administered concomitantly with irradiation therapy, hydroxyurea is indicated for the local control of primary squamous cell carcinomas of head and neck [1-9]. Other applications include psoriasis and use in combination with antiretroviral drugs because it acts synergistically with nucleoside reverse transcriptase inhibitors [1-9].

According to the best of our knowledge this is the first report of acute suicidal intoxication with hydroxycarbamide in an adult.

Case report

Female aged 31 yrs. was admitted to the Pomorian Centre of Toxicology twice during 6 consecutive months, each time after suicidal ingestion of hydroxycarbamide tablets. According to the anamnesis, 12 months prior to admission, she used to take 500 mg of...
hydroxycarbamide per day, and about 75 mg of acetylsalicylic acid (ASA) per day. The medications belonged to the woman and were prescribed to her because of essential thrombocythaemia. Additionally due to insomnia our patient was treated with benzodiazepines. The dose of diazepam varied from 2.5 to 5 mg before sleep.

After first suicidal attempt psychiatric out-patient care was constituted and treatment with 20 mg of paroxetine per day was started.

**Admission 1.** The female patient ingested: 7 500 mg of hydroxycarbamide (15 tablets á 500 mg), 50 mg of diazepam (10 tablets á 5 mg) and several glasses of wine. It was her first suicidal attempt, and was triggered by multiple reactive factors. For about 6 months preceding poisoning she used to consume several glasses of wine every evening to reduce anxiety and sleep disorders. Additionally she had a history of GERD (gastroesophageal reflux disease) treated with omeprazole. At the time of admission she was conscious, restless, with decreased mood. Transient decrease of total leucocyte count was noted on fourth day after overdose. Only lymphocyte line was significantly affected (lymphocyte count: 1.34 G/l, 1.39 G/l, 1.07 G/l). Macrocytosis was present both before and after overdose and was connected with hydroxycarbamide therapy (MCV 111.5 fl., 109.2 fl., 109.5 fl.). There were no other abnormalities in biochemical results.

**Admission 2.** During the second suicidal intoxication the patient ingested: 10 000 mg of hydroxycarbamide, 100 mg of paroxetine and ethanol. In the time between hospitalisations the female was treated in day care psychiatric ward. The suicidal attempt was again triggered by multiple reactive factors. At the time of admission she was conscious, with elevated psychomotoric drive and decreased mood. No lowering in leucocytes or erythrocytes was noted. Platelet count was elevated up to 453 G/l. Once again macrocytosis was noted (MCV 101.8 fl.). Serum concentration of alcohol on admission she was discharged after 3 days of hospitalization to further psychiatric and hematologic treatment.

**Discussion**

Hydroxycarbamide (HCB), also known as hydroxyurea, is an aza derivative used mainly as antineoplastic and antischickling agent, enzyme and nucleic acid synthesis inhibitor [1-9]. There is no information available in medical literature on acute overdose of hydroxyurea in adults. A PubMed search resulted in only one case report of a 2-year-old girl accidentally received in a single dose of 612 mg/kg of hydroxyurea, which was 35-times her prescribed daily dose. Despite a high serum hydroxyurea level 4-hours post-ingestion (7756 μM) only mild transient myelosupression was reported [4].

Total dose of hydroxyurea ingested by our patient was 7 500 mg (120 mg/kg) during the first time, which was 15 times her prescribed daily dose; and 10 000 mg (160 mg/kg) during the second time, which was 20 times her prescribed daily dose. In both cases there were no important clinical symptoms of acute toxicity. Transient myelosupression with lowering of total leucocyte count was noted 4 days after first overdose. Other laboratory values as well as follow up showed no significant abnormalities.

Macrocytosis which was noted both before and after overdoses are a common side effect of chronic therapeutic use of HCB, and should not be connected with acute poisoning [7].

Based on available data it seems that no significant toxicity is to be expected in acute hydroxycarbamide overdose probably due to its high therapeutic threshold and rapid elimination. More severe outcomes may be observed in chronic overdose, including marrow suppression, secondary leukaemia, severe hepatitis, mucositis, vomiting and diaphoresis [8,9].

Our patient’s case has shown that even repeated acute overdose may not lead to significant bone marrow suppression, however, possible cause for such state may be also connected with lying about ingested amount, or interaction between hydroxycarbamide and ethanol.

**Conclusions**

Double ingestion of high dose of hydroxycarbamide led to no acute toxic effects, although further follow up has to be constituted. The only observed constant effect was macrocytosis, which was most probably an effect of prolonged therapy of essential thrombocythaemia.

**Limitation**

The limitation of our work is lack of the HCB level in the patient’s blood.

**References**