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The Use of Sodium Benzoate in a Ten-fold Overdose of Asparaginase

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A three year old boy with acute lymphoblastic leukaemia (ALL) was administered chemotherapy consisting of asparaginase, vincristine, daunorubicin and dexamethasone. On day 15 the patient received a tenfold overdose of asparaginase and was hospitalised for care. Despite a very high plasma ammonia level the patient remained well clinically and other biochemical results remained normal. Ammonia-trapping therapy with sodium benzoate at 206 mg/kg/day associated with a low protein diet was undertaken for two days. Once the ammonia level returned to normal, chemotherapy was continued with a reduced dose of asparaginase.

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Introduction

Iatrogenic injuries, including medication errors are an important problem in all hospitalised populations. In a recent paper, most potential adverse events occurred at the stage of drug ordering (79%) and involved incorrect dosing (34%) and intravenous medication (54%)[1]. Furthermore, tenfold errors in paediatric doses are not uncommon[2,3]. In infants and small children, order of magnitude errors are likely to occur because of the small volume of the stock solution involved.

Recently, a three year old patient was administered a dose of asparaginase, ten times higher than the required one in his local hospital. He was immediately transferred to the Haematology Department of the Robert Debré Hospital. The main clinical features following asparaginase overdose are liver disorders and effects on coagulation (both haemorrhage and

thrombosis). After the overdose, the patient was asymptomatic but the investigations showed hyperammonemia. This paper relates the management and outcome of the hyperammonaemia for this paediatric patient.

Case report

A three year old Caucasian boy (14.5 kg, 0.66 m^2) was diagnosed as suffering from acute lymphoblastic leukaemia. A standardised chemotherapy protocol EORTC (European Organization for Research and Treatment of Cancer) was started. The first treatment of induction consisted of: dexamethasone 3 mg/m^2 orally, twice daily, with a progressive decrease from day 22; vincristine 1.5 mg/m^2 intravenously, at days 8, 15, 22 and 29; asparaginase *E. Coli* 10,000 IU/m^2 intravenously, at days 13, 15, 19, 22, 26 and 29; single intrathecal methotrexate injection at day 1; intrathecal injection of the following three mixed all together *i.e* methotrexate 12 mg, cytarabine 30 mg, hydrocortisone 15 mg at days 8 and 22.

On day 15 of the chemotherapy protocol, the child was admitted to his local hospital to receive treatment. There, 66,000 IU of Asparaginase (L-asparaginase amidohydrolase from *E.Coli*) was administered instead of 6,600 IU. Consequently, the physicians decided to transfer him to the Haematology Department of Robert Debré Hospital. When he arrived he was stable haemodynamically, with no intestinal disorders, no haemorrhagic signs and normal neurological examination. Plasma chemistry, haemostasis, hepatic and pancreatic functions were monitored. Biochemical parameters were normal except for hyperammonaemia, as shown in Figure 1, and changes in amino acids (increased levels of glutamic and aspartic acids and low levels of glutamine and asparagine). The highest plasma ammonia level was recorded on day 16 of the protocol, *i.e.* 319 µmol/L (normal range: 14-38 µmol/L-Kodak, Ektachem 700 Analyser C Series).

A wash out period was observed for 3 days after the intravenous administration of asparaginase. Furthermore, a low protein and hypercaloric diet was undertaken in order to favour protein anabolism. Initially, L-glutamic acid was considered as it was thought that neurological disorders induced by asparaginase could be prevented with this amino acid[4].

However, following advice from the neurologist, this treatment was not administered because asparaginase is an enzyme that also catalyses transformation of glutamine into glutamic acid. As the patient had received a large amount of asparaginase, glutamic acid was likely to be present as confirmed on day 1. Instead, sodium benzoate was administered for two days. The dose was 1g given orally, every eight hours (206 mg/kg/day).

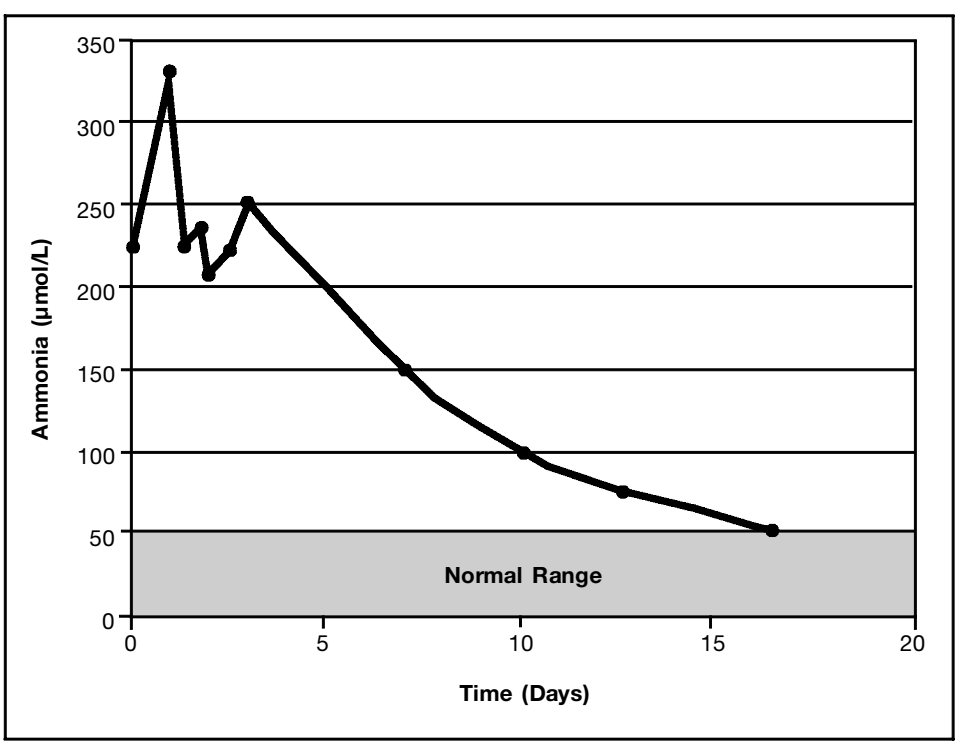

Figure 1. Plasma ammonia concentration following a tenfold overdose of asparaginase.

Figure 1 depicts the short and long term changes in plasma ammonia concentration. The highest level was recorded about 15 hours after the overdose and 8 hours after the start of sodium benzoate. Initially the level dramatically decreased and subsequently the fall was more gradual.

When, the chemotherapy was started again, with a half-dose of asparaginase, a moderate increase in the ammonia level was observed. 18 days after the overdose, the ammonia level was back to normal.

Following the overdose, asparagine and glutamine were undetectable. Aspartic and glutamic acids levels were at their highest the first day after the overdose. One week after the overdose, amino acid levels were back to normal. The child had no serious adverse effects and continued to receive his chemotherapy. At present, the patient is in complete remission.

Discussion

Since 1961, L-asparaginase has been used as an effective agent in addition to other cytotoxic drugs to treat acute lymphoblastic leukaemia and non-Hodgkin lymphomas[5]. Usual paediatric doses are 500 to 1000 IU/kg per day IV or IM during 6 to 21 days[6]. L-asparaginase is an enzyme, extracted from *Escherichia Coli* that catalyses the hydrolysis of L-asparagine to L-aspartate and ammonia and exhibits glutaminase activity as well. Normal human cells get L-asparagine directly from the blood pool or by transamination from L-aspartic acid and L-glutamine. In contrast, L-asparagine is an essential amino acid for leukaemia cells. In the presence of L-asparaginase, the malignant cells's DNA, RNA and protein synthesis are inhibited, leading to cell death[7].

The main adverse effects of this drug are hypersensitivity, pancreatic, haemorrhagic or thrombotic, hepatic disorders and central nervous effects. Neurological toxicity (electroencephalogram changes) was observed by Haskell et al, in 1969, in adults[8]. In addition, hyperammonaemia, related to the administration of asparaginase is likely to increase the neurotoxicity. In our case, it was the main hazard.

After the diagnosis of hyperammonaemia is made, treatment must be started quickly. The choice of treatment should be based on the plasma ammonia concentration, age of the patient, other laboratory test results and clinical condition of patient. The aim of the treatment is to decrease the plasma ammonia level.

Three major alternatives are considered: the reduction of nitrogen intake, the increase of excretion of ammonia and the decrease of the ammonia production[1,9]. To reduce the nitrogen intake, a low protein diet is required, including essential amino acids supplementation only. Energy must be provided by administration of

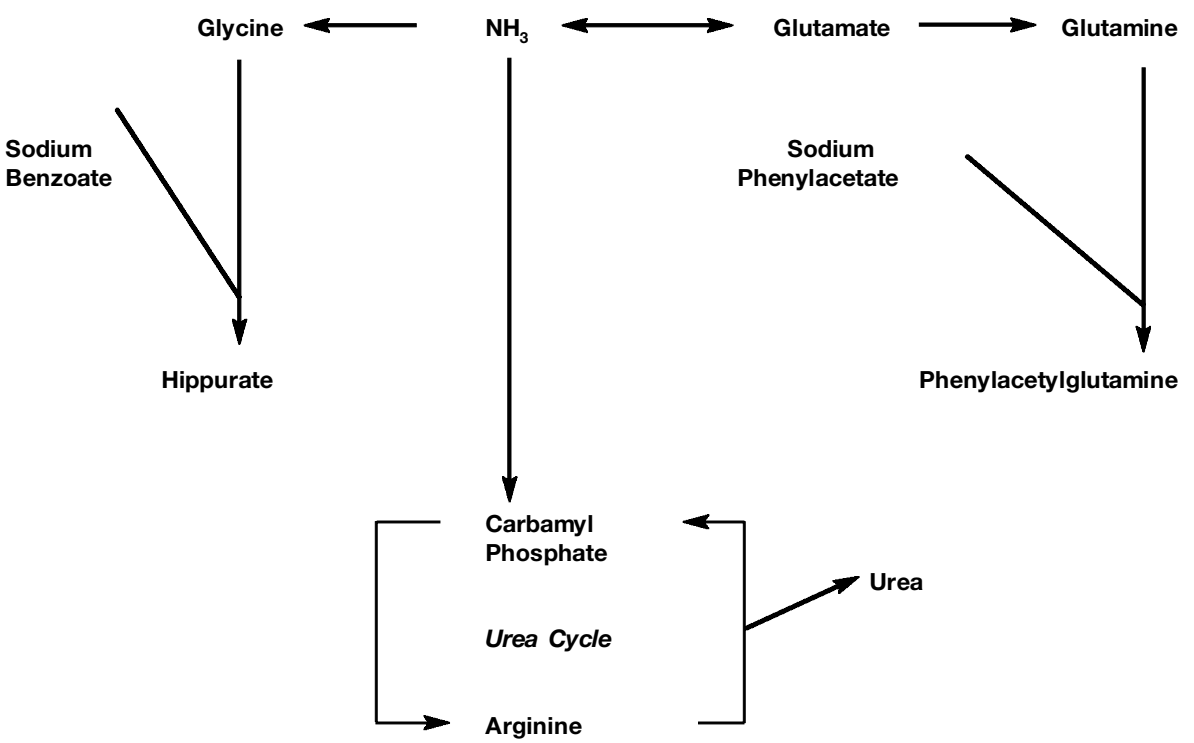

Figure 2. Ammonia-trapping therapy mechanism.

concentrated glucose and lipids to minimize endogenous protein catabolism.

To increase the excretion of ammonia, dialysis is possible, but the effect is only transient. The suppression of ammonia precursors, such an urea and some amino acids, is a way to decrease ammonia production. Neomycin and lactulose, induce the reduction of ammonia production in the digestive tract and suppress intestinal ureolysis, due to digestive bacteria[10,11]. Indeed, neomycin and lactulose allow the decontamination of the digestive tract and the acceleration of digestive transit respectively.

Another solution is ammonia-trapping therapy (Figure 2), including sodium benzoate and sodium phenylacetate, that decrease ammonia production by diverting and eliminating some nitrogenous amino acids. Sodium benzoate and sodium phenylacetate react respectively with glycine and glutamine, to form hippurate and phenylacetylglutamine which are then excreted in the urine without further metabolism.

For treatment of urea cycle disorders, sodium phenylbutyrate can be used [12]. However, for this patient it would have been inappropriate. For its action, phenylbutyrate requires glutamine. Due to the action of asparaginase competing with glutamine synthetase activity, the endogenous stock of glutamine of our patient was depleted, and hence this treatment would have been ineffective.

When arginine is given as a rapid infusion, the excessive ammonia is cleared more efficiently because urea synthesis is promoted. These methods of treatment can be prescribed separately or in combination, whatever the etiology of the hyperammonaemia.

More recently Barr reported the use of a mixture of helium:oxygen (80:20), to treat moderate increases of ammonia with an animal model [13]. However, further studies are warranted to evaluate its application in the treatment of patients suffering from hyperammonaemia.

The management of our patient's hyperammonaemia included a low protein diet and sodium benzoate. The recommended dose of sodium benzoate is 250 mg/kg/day, given orally or intravenously[9]. Following recent guidelines for acute neonatal hyperammonaemic coma, a loading dose of 250 mg/kg each of sodium benzoate and sodium phenylacetate in 25 to 35 mL/kg of 10% dextrose solution given over a 90 minute period is recommended[14]. In our case, 206 mg/kg/day was prescribed in order to make drug administration easier. As there is no paediatric oral solution commercially available in France, the IV form was given orally.

The sodium benzoate was discontinued after two days of treatment for three reasons:

- the patient was asymptomatic,
- the ammonia serum concentration was decreasing,
- the half-life of asparaginase (8 to 30 hours) suggested that after two to three days of treatment, most of the drug was excreted.

No data were found regarding the optimal duration of treatment. Nevertheless, we observed that after readministration of asparaginase (half dose until the end of the regimen), plasma ammonia concentrations kept on decreasing and were back to normal 18 days after the overdose.

A case of acute encephalopathy and hyperammonaemia complicating treatment of acute lymphoblastic leukaemia has been reported for a 4 year boy, who had received a dose of asparaginase of 4,200 IU[15]. The maximum ammonia level measured for this patient, 26 hours after the asparaginase infusion, was 675 µmol/L which is approximately twice that of our patient.

Regarding the latter, the highest ammonia level, *i.e.* 319 µmol/L, was recorded about 15 hours after the overdose, reflecting the erratic half-life of the drug. Asparaginase's plasma half-life after intravenous injection has been shown to vary from 8 to 30 hours[4], with an average of 20 ± 6 hours [6]. This could be related to the enzymatic activity differences between patients. The possible physiologic depletion of the substrate (*i.e* asparagine and glutamine) subsequent to the excessive asparaginase's quantity is likely to limit the ammonia formation.

In the case of hyperammonaemic encephalopathy reported above, sodium benzoate (260 mg/kg, 4 hours infusion and then 200 mg/kg) and arginine intravenously (two infusions, each of 300 mg/kg) were given in order to reduce the plasma ammonia concentration[15]. This treatment had little effect and the patient died. Although, the patient developed hyperammonaemia plus cerebal haemorrhage and oedema, the authors concluded that it was due to the lack of efficacy of the cytotoxic therapy. In our case the response was clearly apparent: plasma ammonia levels decreased from 319 to 226 µmol/L.

Nine other hyperammonaemic encephalopathies have been reported after chemotherapy including other cytotoxics apart from asparaginase[16]. Similar

treatment was used (sodium benzoate and phenylacetate) to treat patients with hyperammonaemia. Seven patients died in relation to the hyperammonaemia, one from its leukaemia and one was in complete remission. The authors outlined that hyperammonaemia is often observed during high-dose chemotherapy and that the etiology is unknown.

Del Rosario suggests that early treatment before the ammonia level reaches 350 µmol/L may improve the outcome of the patient[16]. Idiopathic hyperammonaemia after high-dose chemotherapy (in adults) has been described[16]. It shows again that hyperammonaemia could lead to death and that sodium benzoate and sodium phenylacetate (which was actually replaced by phenylbutyrate) are typically used to treat hyperammonaemia.

No serious side effects are reported when sodium benzoate and sodium phenylacetate are used according to their recommended doses. Sometimes, digestive troubles, such as nausea and vomiting were observed, but owing to the disease it was difficult to establish whether it was related or not to the medication. Three cases of overdoses of intravenous sodium benzoate and sodium phenylacetate were reported by Praphanphoj[17]. Patients presented, at first, with confusion, then biochemical disorders, with metabolic acidosis and increase of anion gap, and at the end, sometimes with cerebral oedema, hypotension and cardiovascular collapse.

Finally, a few past protocols have used high doses of asparaginase *i.e* 50,000 IU/m^2 in the treatment of childhood non-T-cell acute lymphoblastic leukaemia[18]. Apparently, it seems that adverse effects were not apparent, but this dose was less than half the dose given to our case.

Conclusion

In our case, critical consequences after overdose were limited except for hyperammonaemia; no clinical symptoms related to hyperammonaemia were observed.

Treatment that must be considered is sodium benzoate (dose 250 mg/kg per day up to 500 mg/kg per day, orally or intravenously over 90 minutes) associated with a low protein diet, plus arginine (300 mg/kg per day, orally or intravenously), if a deficiency in this amino acid is identified.

In France, a "special" sodium benzoate solution manufactured by the Pharmacie Centrale des Hôpitaux (recently renamed AGEPS = Agence Générale des Equipements et Produits de Santé) is available. This injectable preparation contains 1g of sodium benzoate in 10 mL of sterile water for injection. Prior to IV administration in particular, caution must be taken as the solution is hypertonic (Osmolarity-1300 mOsm/L).

The duration of the treatment is not clear, because the half-life of the enzyme varies a lot. Monitoring plasma levels of ammonia and amino acids could be good indicators to assess both the efficacy of the treatment, and the optimal duration of the treatment.

This paper has been written in order to inform the pharmacist and the physician about the outcome of an overdose of asparaginase. If this kind of information had been more readily available, this would have facilitated the appropriate treatment.

This paper again highlights that tenfold errors still happen in paediatric patients and that further efforts are needed to reduce them as summarized by the Paediatric Pharmacy Advocacy Group of the Institute for Safe Medications Practices[19].

References

1. Mathias RS, Kostiner D, Packman S. Hyperammonemia in urea cycle disorders: role of nephrologist. Am J Kidney Dis 2001; 37: 1069–1080.
2. Koren G, Barzilay Z, Greenwald M. Tenfold errors in administration of drug doses: a neglected iatrogenic disease in pediatrics. Pediatrics 1986; 77: 848–849.
3. Koren G, Haslam RH. Pediatric medication errors: predicting and preventing tenfold disasters. J Clin Pharmacol 1994; 34: 1043–1045.
4. The Complete Drug Reference. In: Parfitt K, editor. Martindale. 32th ed. London: The Pharmaceutical Press; 1999.
5. Broome JD. Evidence that the L-asparaginase activity of guinea pig serum is responsible for antilymphoma effects. Nature 1961; 191: 1114–1115.
6. Médicaments utilisés en cancérologie. In: Dossier du CNHIM. 4th ed. Paris: Latour. JF: 2001.p. 105.
7. Holle L M. Pegasparase: an alternative? Ann Pharmacother 1997; 31: 616–624.
8. Haskell CM, Canellos G P, Leventhal BG, *et al.* L-asparaginase: therapeutic and toxic effects in patients with neoplasic disease. N Engl J Med 1969; 281: 1028–1034.
9. Feillet F, Leonard JV. Alternative pathway therapy for urea cycle disorders. J Inher Metab Disp 1998; 21: 101–111.
10. Frere P, Canivet JL, Gennigens C, *et al.* Hyperammonemia after high-dose chemotherapy and stem cell transplantation. Bone Marrow Transplant 2000; 26: 343–345.
11. Winter SS, Rose E, Katz R. Hyperammonemia after chemotherapy in an adolescent with hepatocellular carcinoma. J Pediatr Gastr Nutr 1997; 25: 537–540.
12. Stevenard M, Lamonier M. Asparagine. Rev Fr Etud Clin Biol 1968: 13: 229–235.

13. Barr J, Eshel G, Chen-Levy Z, Lahat E. Heliox use in the treatment of acute hyperammonemia. J Child Neurol 2001; 16: 456–457.
14. The urea cycle disorders conference group. Consensus statement from a conference for the management of patients with urea cycle disorders. J Pediatr Gastr Nutr 2001; 138: S1–S5.
15. Leonard JV, Kay JDS. Acute encephalopathy and hyperammonemia complicating treatment of acute lymphoblastic leukaemia with asparaginase. Lancet 1986; 18: 162–163.
16. Rosario MD, Werlin SL, Lauer SJ. Hyperammonemic encephalopathy after chemotherapy. J clin Gastroenterol 1997; 25: 682–684
17. Praphanphoj V, Boyadjev SA, Waber LJ, Brusilow SW, Geraghty MT. Three cases of intravenous sodium benzoate and sodium phenyacetate toxicity occurring in the treatment of acute hyperammonemia. J Inher Metab Dis 2000; 23: 129–136.
18. Sallan SE, Hitchcock-Bryan S, Gelber R, *et al.* Influence of intensive asparaginase in the treatment of childhood non-T-cell acute lymphoblastic leukaemia. Cancer Res 1983; 43: 5601–5607.
19. Cohen R, Blanchard N, Frederico F, *et al*. Draft guidelines for preventing medication errors in paediatrics. J Ped Pharm Practice 1998; 3: 189–202.