The death of an infant after the unfortunate intrathecal injection of vincristine

Objective: This study presented the infants born with twin pregnancy who were suffering from congenital leukemia. One of them, 9 weeks old boy, was accidentally administrated intrathecal injection of vincristine. The mistake was noticed immediately. The cerebrospinal fluid was removed with the given medications. Next lavage of spinal cord by Solutio Ringeri Lactate with FFP, were included and the intravenous cytoprotective treatment was used.

Neurologic symptoms appeared after 5 days. The patient died after 115 days of hospitalization. The causes of fateful mistake was analysed, found the recommendations and changed interdisciplinary working procedures in the hospital.

Conclusions: Intrathecal injection of vincristine, led to death of the infant, despite the inclusion of multiple treatment.

Keywords: vincristine, intrathecal injection, child

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Introduction

Vincristine is *Vinca* alkaloid used during oncological therapy. It is a cytostatic drug which inhibits the formation of spindles and stops mitosis by combining with tubulin in the cells. It is used intravenously only. In the literature, there are several dozens of described cases of pediatric and adult patients who suffered from cancer foci in the central nervous system. They were unintentionally given vincristine intrathecally during diagnostic and therapeutic lumbar punctures. Most patients died within a few weeks. Few who survived, thanks to immediately performed lavage of the spinal cord, had serious neurological deficits [1,2].

In my article, I describe a case of unintentional intrathecal administration of vincristine and therapy of one of the twins. Both of them suffered from congenital leukemia.

Case report

Five-week-old twins were hospitalized in a Pediatric Intensive Care Unit. The boys were preterm, born in the 36th week of gestation. The parents said that erythematous rash of the skin appeared, appetite decreased and the circumference of the abdomen increased in the 4th week of life. Both the twins had persistent fever, general oedema, exacerbated dyspnoea, tachypnoe (90 breaths per minute), high respiratory effort (III grade Silver score), tachycardia (175 beats per minute); blood pressure was normal.

Both the infants had hepatomegaly and splenomegaly (both organs reached the symphysis pubis) as well as haematuria and gastrointestinal haemorrhage caused by coagulopathy and thrombocytopaenia. Additionally, both the boys had carbon dioxide retention and hypoxaemia. The first twin had white blood cells of 52 × 103/µl, the second – 12 × 103/µl. Both had anaemia, haematocrit was 25% and 24%, haemoglobin: 8.8 and 8.7 g/dl, and thrombocytopenia 57 × 103/µl and 60 × 103/µl respectively. The levels of C reactive protein were very high 110 mg/l and 239 mg/l respectively. The levels of procalcitonin (PCT) were 7.12 ng/ml and 13.18 ng/ml respectively. The levels of antibodies to Epstein-Barr nuclear antigen and to viral capsid antigen were raised. Blood cultures were negative. There was suspicion of haemophagocytic lymphohistiocytosis (HLH).

The patients were intubated due to respiratory failure. High parameters of mechanical ventilation were used. Packed red blood cells, fresh frozen plasma, antithrombin III and human albumin were transfused before the bone marrow puncture and lumbar puncture were performed. Blasts were also present in CSF. Congenital leucaemia was diagnosed in both the boys. Acute renal failure, hydropericardium and increasing ascites were treated with furosemide and dopexamine. Cardiocirculatory failure was treated with catecholamines (initially dobutamine and dopamine, subsequently

norepinephrine). Ventricular tachycardia, which occurred in the first twin, was treated with lidocaine. Total parenteral nutrition was used because both the infants had enteral feeding intolerance.

Because of the serious general state, leukemia was initially treated with steroid (methylprednisolone). After obtaining relative clinical stability, one boy was treated in accordance with the Interfant 6 protocol. The treatment was interrupted or deferred due to the severe general status of the infants. Hypocalcaemia, increased urea and creatinine in the course of renal failure, pancytopenia, cholestasis, bleeding from the stomach, convulsions, sepsis of the *Aspergillus* sp. aetiology occurred during treatment.

Owing to the very serious general state of the infants, the multiorgan failure and hospitalization in the PICU, all diagnostic and therapeutic lumbar punctures were performed by an anaesthetist doctor working in that unit at the request of treating oncologists. On the 27th day of treatment, intrathecal administration of vincristine was inadvertently performed with methotrexate and steroids in the first twin.

The mistake was immediately recognised. First, 3.5 ml of spinal fluid with drugs was removed during next lumbar puncture. The therapy was introduced immediately as advised by Al Ferayan, Michelagnoli, Walter in their articles [3-5].

Drains were inserted. The proximal cannula was put into the ventricle of the brain and the distal one – into the lumbar part of the spinal canal by laminectomy. The lavage was started. The Solutio Ringeri and fresh frozen plasma were used (10 ml per hour). We did not obtain fluid from the lower drain. We performed MRI which showed that the location of the drains was correct. A neurosurgeon believed that the failure to obtain fluid was connected with the loss of cerebrospinal fluid while installing the drains or the presence of synechiae in the spinal canal caused by the previous injections of cytostatics. Therefore, the lavage was performed solely with the proximal drain. The treatment was finished after three days. Calcium folinate and vitamin B6 were administered intravenously.

The first neurological symptoms appeared after five days. They occurred gradually. There was paresis of the anal sphincter, tetraplegia, atrophy of spontaneous breath, unconsciousness and coma. Additionally, hydrocephalus appeared and thus Rickham's reservoir was implanted. The baby died on the 115th day of hospitalization. The direct cause of death was sepsis. The second twin survived.

Discussion

Interdisciplinary treatment is connected with an increased risk of medical mistakes. Intrathecal injection of vincristine leads to the death of a majority of patients. When the error is quickly noticed treatment is introduced immediately, patients can have a chance of survival. Unfortunately, patients who survived suffer from serious neurological damage, such as paresis associated with radiculomyeloencephalopathy. That is caused by irreversible demyelination of nerve fibres [6-9].

Reasons for committing this tragic mistake were complex. The direct reason for the administration of the drug to the subarachnoid space was the shift of the syringe from the intravenous drug package into the syringe package for the administration at the lumbar puncture in one box during transport, bad communication among doctors working in the PICU and oncology department, and the lack of any procedures in the hospital. Such procedures would have prevented that kind of mistakes. The decision on the administration of oncological therapy with vincristine and other cytostatics, in spite of the serious general status and the age of the infant, was made by oncologists. The second twin was treated with steroids at the time.

The immediate treatment of our patient did not prevent his death. I think that the doses of drugs, the intrathecal injection of vincristine as the first drug, the small weight and young age of the baby, the lack of the flow of Solutio Ringeri and fresh frozen plasma in the spinal canal, and the lack of communication between the proximal and distal drains were the cause of the therapy failure.

The WHO report was published in 2007. Other medical agencies from particular countries have also published their reports (National Patient Safety Agency, UK, BC Cancer Agency, Canada, Institute for Safe Medication Practices, USA, Commission on Accreditation of Healthcare, USA, NSW Safety Work Practice, Australia). They draw attention to procedures which prevent the commission of

this terrible mistake. Both they and the authors of published articles formulate the following recommendations:

1. Training courses for all medical staff who have contact with vincristine should be definitely performed [10,11].

2. Vincristine should be contained in mini-bags and the short continuous intravenous infusion should be performed. Statistically, this way of infusion does not increase the risk of extravasation of the drug (0.31% – bolus infusion, 0.4% short continuous infusion) [11-14].

3. The alternative to mini-bags is the preparation of the drug in big, 50 ml syringes in small patient's therapy, too. The use of 20 ml syringes only decreases the rate of this complication but does not eliminate this mistake [2,9,11-14].

4. Special needles for lumbar puncture should be used. These needles are not compatible with the "luer" syringes which are used for standard intravenous injections.

5. Vincristine must not ever be stored in the room where the lumbar puncture is performed [10].

6. Vincristine must not ever be transported in the same box with other drugs prepared for injection during lumbar puncture. Vincristine should be transported in a special box with an inscription "For intravenous use only – fatal if given by other routes" [17].

7. Changes in therapeutic protocols should be performed if it is possible. A diagnostic or therapeutic lumbar puncture should not be carried out on the same day as an intravenous injection of vincristine [10].

9. Oncological drugs must be administered only by oncological staff.

10. Each syringe should be carefully labelled: the drug name, dose, method of administration, and the name of the patient.

Compliance with these recommendations allows eliminating the risk of this tragic mistake.

Since that time the principles of cooperation between oncologists and doctors of other specialties have changed. Therapeutic intrathecal injections are performed only by oncologists. These doctors are present during intravenous injections of oncological drugs, irrespective of the unit or department where the patient is hospitalized.

One hundred ninety-three patients received an intrathecal injection of methotrexate and cytarabine hydrochloride contaminated with vincristine in China in 2007, which caused neurological symptoms in the patients [9,15].

WHO and the authors of medical studies state that a lot of intrathecal injections of vincristine can be unnoticed because the symptoms appear after a few days. Then the neurological symptoms are associated with the progress of cancer in the central nervous system or with viral encephalitis in these patients. The results of testing the cerebrospinal fluid are normal after the administration of the drug. The suspicion of the improper administration of the drug can be confirmed only by histopathology of the central nervous system [7,8,16,17].

Despite numerous recommendations aimed at increasing the safety of patients, inadvertent intrathecal injections of vincristine and their fatal complications still occur.

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