Accidental cisplatin overdose in a child: Successful management with repetitive plasmapheresis and use of chemoprotective agents

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Cisplatin is one of the effective chemotherapeutic agents widely used for many tumor types in children. The most serious complications of cisplatin overdose are nephrotoxicity and ototoxicity. It may lead to life-threatening complications and even death. We report a 13-year-old female patient with osteosarcoma who received a massive cisplatin overdose mistakenly. She was given cisplatin 120 mg/m^2/day for consecutive two days, instead of one day (total 240 mg/m^2) due to a prescription error. After 12 hours, her cisplatin level was measured as 8,500 ng/ml (normal: 1,000-5,000 ng/ml). She was treated with repeated plasmapheresis combined with use of two chemoprotectants, (N-acetylcysteine and amifostine). On her follow up, renal functions and audiometric tests remained normal. According to our experience with our case, early urgent combined treatment is very important in the management of cisplatin overdose.

Key words: cisplatin overdose, plasmapheresis, chemoprotective agents, children.

Cisplatin is widely used as a valuable neoplastic agent and effective against many different tumors in children with cancer. However, it has many potential side effects such as nephrotoxicity, neurotoxicity, ototoxicity after administration of cisplatin with therapeutic doses. (90-120 mg/m^2 per one cycle of chemotherapy) High doses of cisplatin due to accidental overdose have been reported to cause severe life-threatening complications and even death[1,2].

There is limited data regarding the clinical management of patients who received overdose of cisplatin[3-7]. Herein, we present our experience and successful management of a child with cancer who accidentally received overdose of cisplatin.

Case Report

A 13-year-old female patient with mandibular osteosarcoma began chemotherapy regimen consisting of cisplatin and adriamycin after the pathological diagnosis.

During second cycle of chemotherapy, she was given cisplatin after intravenous hydration at the dose of 120 mg/m^2/day for two consecutive days, instead of one day (total 240 mg/m^2) due to a prescription error. The mistake was recognized during checking chemotherapy orders after second cisplatin administration. She received a total dose of 360 mg of cisplatin. Serum cisplatin level was measured as 8,500 ng/ml after 24 hours (normal: 1,000-5,000 ng/ml). She underwent double-exchange plasmapheresis 36 hours after the accidental administration. Fresh frozen plasma was used as a replacement fluid.

After first plasmapheresis cycle, her cisplatin level was measured as 6,440 ng/ml. She developed NCI grade III nausea and vomiting, acute renal failure as well as elevated liver enzymes. Intravenous hydration, electrolyte replacement, and antiemetic treatment were started for supportive care. In addition, NCI grade IV myelosupression and hearing loss were determined. Despite plasmapheresis, her toxic

Table I. Laboratory Findings of the Patient

	Before cisplatin overdose	After 24 hours	After 48 hours	5th day	15th day	Normal values
SGOT/SGPT(U/L)	30/21	64/45	140/125	85/50	15/15	0-35
Urea (mg/dl)	30	32	35	25	20	11-35
Creatinine (mg/dl)	0.4	0.6	0.75	2.6	0.4	0.4-1.0
White blood cell count (/mm^3)	4,700	4,000	3,200	1,200	5,800	4,000-8,900
Plasma cisplatin level (ng/ml)		8,500	6,440	1,230	110	1,000-5,000

SGOT: Serum glutamic oxaloacetic transaminase, SGPT: Serum glutamic pyruvic transaminase

symptoms gradually worsen. For this reason, N- acetylcysteine (NAC) for detoxification was initiated in order to reduce toxic effects of cisplatin. It was given at the same dosage for paracetamol intoxication (140 mg/kg first dose, followed by 70 mg/kg every 4 hour for 4 days).

Her creatinine levels gradually increased from 0.4 mg/dl to 2.6 mg/dl. Amifostine was also initiated after 72 hour after the cisplatin infusion. Amifostine dose was 740 mg/m^2/day. She underwent plasma exchange three times, one cycle per day. Her plasma cisplatin concentrations decreased from 6440 to 110 ng/ml on the 15th day (Table I).

After this combined treatment, toxicity related symptoms gradually improved and she recovered without any sequela. Audiometric tests were made at several time points. No ototoxicity was detected.

Further follow-up analyses were performed at 3, 12, and 18 months after cisplatin intoxication. All glomerular and tubular renal function was found to be within normal range.

Discussion

The data regarding the clinical management of cisplatin overdose, particularly in children, is scarce[8-10]. A possible treatment option for cisplatin overdose has been reported as to eliminate cisplatin from body fluids. After intravenous administration, most of the cisplatin in the blood is bound to proteins within a few hours. Plasmapheresis is one of the effective options for enhancing excretion of poisons among several methods such as hemodialysis, hemoperfusion[3,6]. Since cisplatin binds to plasma proteins very quickly, hemodialysis is not capable of reducing the protein-bound fraction of cisplatin. In contrast to hemodialysis, plasmapheresis removes both free and protein–bound cisplatin from the plasma compartment. Yamada et al.[8] reported that the plasma cisplatin concentration was very high after one cycle of hemodialysis while it had dramatically decreased to low levels after two cycles of plasma exchange. Similar to other published cases, our case shows that plasma exchange is useful for lowering cisplatin levels efficiently. The number of plasma exchange to decrease cisplatin to non-toxic levels is controversial. We recommend that early and repeated plasmapheresis, at least three cycles, is useful in the management of cisplatin overdose based on our observation.

Therefore, plasma exchange should be performed as soon as possible. If plasma cisplatin levels can be measured, we recommend following serial measurements of cisplatin levels.

On the other hand, plasma exchange is not enough to avoid all side effects due to cisplatin, such as hearing loss. Additional protective treatment choices are necessary to control all occurring side effects. Some thiols such as NAC and sodium thiosulfate have been studied as chemoprotectants. They could be useful for rescuing cisplatin overdose. Some reports suggested the use of NAC which is frequently used in children after paracetamol overdose[10].

N- acetylcysteine was given in order to bind reactive platinum particles and to prevent further deterioration of renal function. Amifostine, a type of thiophosphate, may protect against cisplatin-induced toxicity by providing a protective thiol group[11].

Bleyer et al.[11] reported that they used amifostine for a case who developed severe acute renal failure after cisplatin overdose. It can remove cisplatin though a covalent binding mechanism. Amifostine does not reduce chemotherapy

induced cytotoxic effect *in vitro* and may be given in cases of overdose or acute renal failure.

Our case was treated with additional chemo protective agents such as NAC, amifostine and three times plasmapheresis. She recovered completely. She had no hearing loss or renal dysfunction during the two years follow-up. It seems that chemoprotectants reverse loss of hearing.

According to our experience, adverse events due to cisplatin overdose were successfully prevented with repeated plasmapheresis, combined with use of two chemoprotectants in our case. Optimal frequency of plasma exchange in cisplatin overdose is controversial. Similar to Yamada et al.[8] We also recommend at least three cycles within the first ten days. According to our clinical experience, after three cycles, plasma platinum concentration decreased significantly.

When cisplatin overdose is realized, urgent treatment should be started as soon as possible. In addition to repeated plasma exchange, chemo protective agents may also be added to the treatment. Close follow-up of laboratory parameters including renal functions, complete blood counts, electrolytes and cisplatin levels should be determined on a daily basis. Intravenous hydration, electrolyte replacement, and antiemetic treatment are principal for the treatment success as well.

In our opinion, plasmapheresis and use of chemo protective agents should be considered in all cases when a cisplatin overdose occurs.

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