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Case Report

Fatal overdosage with cisplatin by accidental substitution for carboplatin: a case report

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Abstract: *Purpose:* We presented a case of stage II ovarian yolk sac tumor who was treated with accidental overdose of cisplatin. To avoid the accuracy of the same case, a guideline was edited. *Findings:* A 1-year-old girl with stage II ovarian yolk sac tumor had been treated with neo-adjuvant chemotherapy for 2 cycles (PVB: carboplatin 100 mg/m^2 d1-5, bleomycin 10 mg/m^2 d1 and d7, vincristine 1.5 mg/m^2 d1 and d7). On the day 1 of the third cycle, she received the usual dose of bleomycin and vincristine, but this time received 45 mg (100 mg/m^2) cisplatin instead of carboplatin from day 1 to 5. On day 7, she was noted diminishing vision and anuria. Then she was admitted to our hospital on day 7. On admission, her blood pressure was 80/62 mmHg. She had severe deficits of hearing and vision and drowsiness. The serum potassium level was 6.1 mmol/L; blood urea nitrogen (BUN), 33 mmol/L; creatinine (Cr), 340 mmol/L; creatinineas 6.1 mmol/L; blood pressure was 80/62 mmHg. She had severe deficits of hearing and vision and drowsiness. 83 IU/l; bilirubin, 1.1 mg/dL; leukocyte count, 3.4×10^9/L; hematocrit, 32.1%; and platelet count, 167×10^9/L. She was treated with glucose and bicarbonate to control hyperkalemia. Supportive treatment was started immediately. And hemodialysis, imipenem, granulocyte colony-stimulating factor (G-CSF) and interleukin-11 (IL-11) therapy were performed. Coma occurred at day 25, followed with sudden cardiac arrest, and died although actively rescue was performed. *Conclusions:* Cisplatin is one of the most widely used antineoplastic agents in the treatment of solid tumor and hematological malignancies. Accidental overdose of cisplatin may occur despite all precautions. Our study helped to carry out general accepted guidelines for the treatment of such cases.

Keywords: Cisplatin, carboplatin, plasmapheresis, hemodialysis

Introduction

Cisplatin is one of the most widely used antineoplastic agents in the treatment of solid tumor and hematological malignancies, including cancers of the testes, ovary, bladder, head and neck, esophagus, stomach and lung, as well as lymphoma and osteosarcoma [1]. Cisplatin is frequently associated with renal toxicity. Despite vigorous intravenous hydration and mannitol treatment, acute nephrotoxicity and chronic renal damage may occur after the administration of therapeutic doses. These toxicities are dose-dependent and dose- and therapy-limiting. The maximum tolerated single dose of cisplatin is considered to be 100 to 120 mg/m^2 per cycle and should be administered with adequate pre- and post-hydration [2, 3]. However, accidental overdose of cisplatin may occur despite all precautions. To date, no general accepted guidelines for the treatment of such cases are available, nor the published guidelines for managing cisplatin overdose. There is no specific antidote for cisplatin. There are only few reports, however, on the clinical management of patients after accidental overexposure to cisplatin. In particular, no general therapeutic strategies are available in the case of cisplatin poisoning in children. This article reported a 1-year-old girl who received a massive cisplatin overdose of 500 mg/m^2 as an accidental substitution for carboplatin.

Case presentation

A 1-year-old girl with stage II ovarian yolk sac tumor had been treated with neo-adjuvant che-

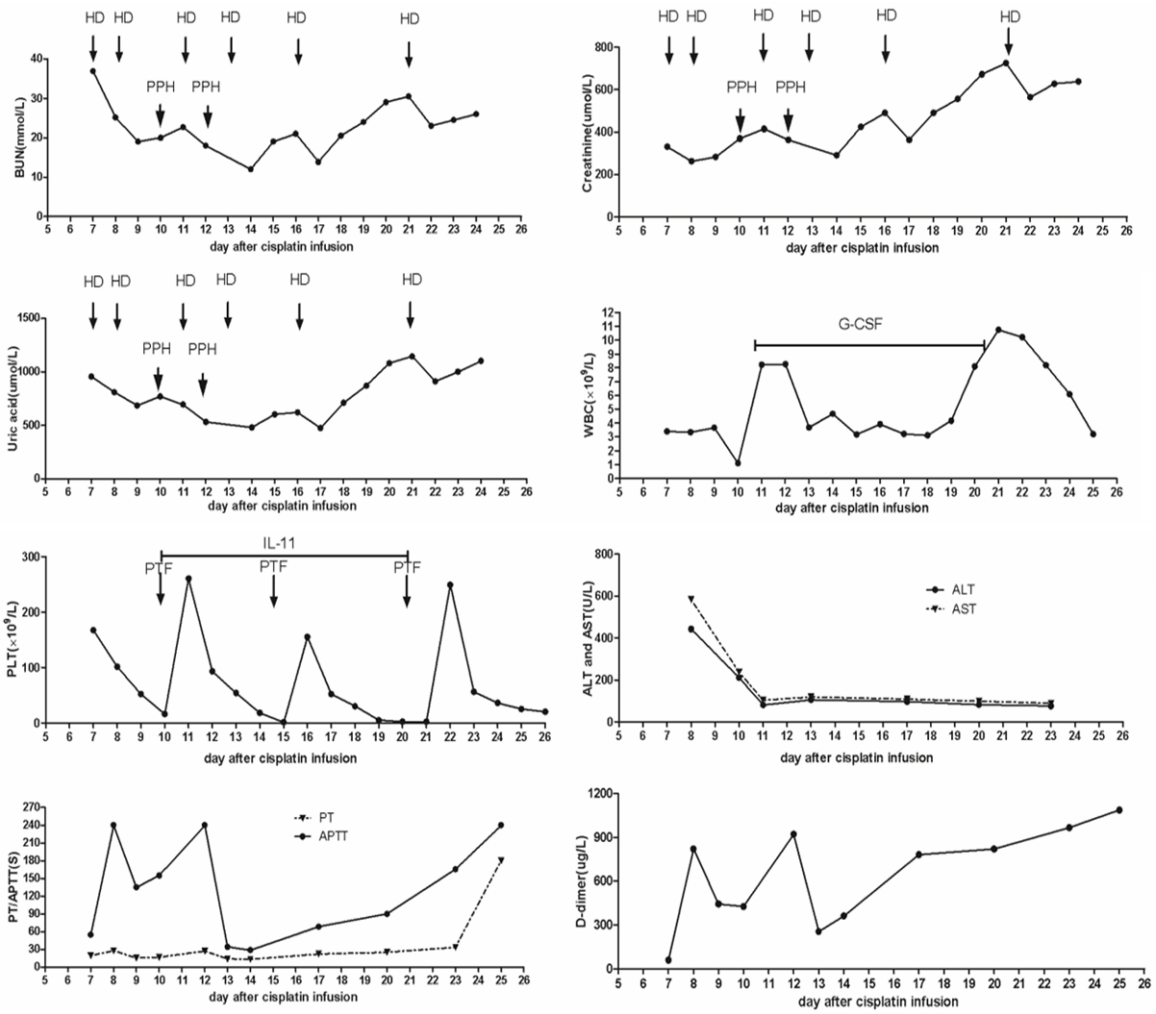

Figure 1. The toxic-related parameters of the patient. HD: hemodialysis; STS: sodium thiosulfate; PPH: plasmapheresis; PTF: platelet transfusions; G-CSF: granulocyte colony stimulating factor; IL-11: interleukin-11; ALT: glutamic pyruvic transaminase; AST: glutamic oxaloacetic transaminase; PT: prothrombin time; APTT: activated partial thromboplastin time.

motherapy for 2 cycles (PVB: carboplatin 100 mg/m^2 d1-5, bleomycin 10 mg/m^2 d1 and d7, vincristine 1.5 mg/m^2 d1 and d7). On the day 1 of the third cycle, she received the usual dose of bleomycin and vincristine, but this time received 45 mg (100 mg/m^2) cisplatin instead of carboplatin from day 1 to 5. On day 3, she began to experience severe nausea and vomiting. On day 4, she was noted the onset of hearing loss that progressed to total deafness by day 6. On day 7, she was noted diminishing vision and anuria. Then she was admitted to our hospital on day 7. On admission, her blood pressure was 80/62 mmHg. She had severe deficits of hearing and vision and drowsiness. There were repeated single movements of her head turn to the right with simultaneous flinging movements of her right arm. The serum potassium level was 6.1 mmol/L; blood urea nitrogen (BUN), 33 mmol/L; creatinine (Cr), 340 mmol/L; creatininepital on day 7. On admission, her blood pressure was 80/62 mmHg. She had severe deficits of hearing and vision and drowsiness; serum glutamic oxaloacetic transaminase, 583 IU/L; bilirubin, 1.1 mg/dL; leukocyte count, 3.4×10^9/L; hematocrit, 32.1%; and platelet count, 167×10^9/L. She was treated with glucose and bicarbonate to control the hyperkalemia. Supportive treatment including vigorous hydration, electrolyte replacement and antiemetic therapy was started immediately and hemodialysis was conducted the

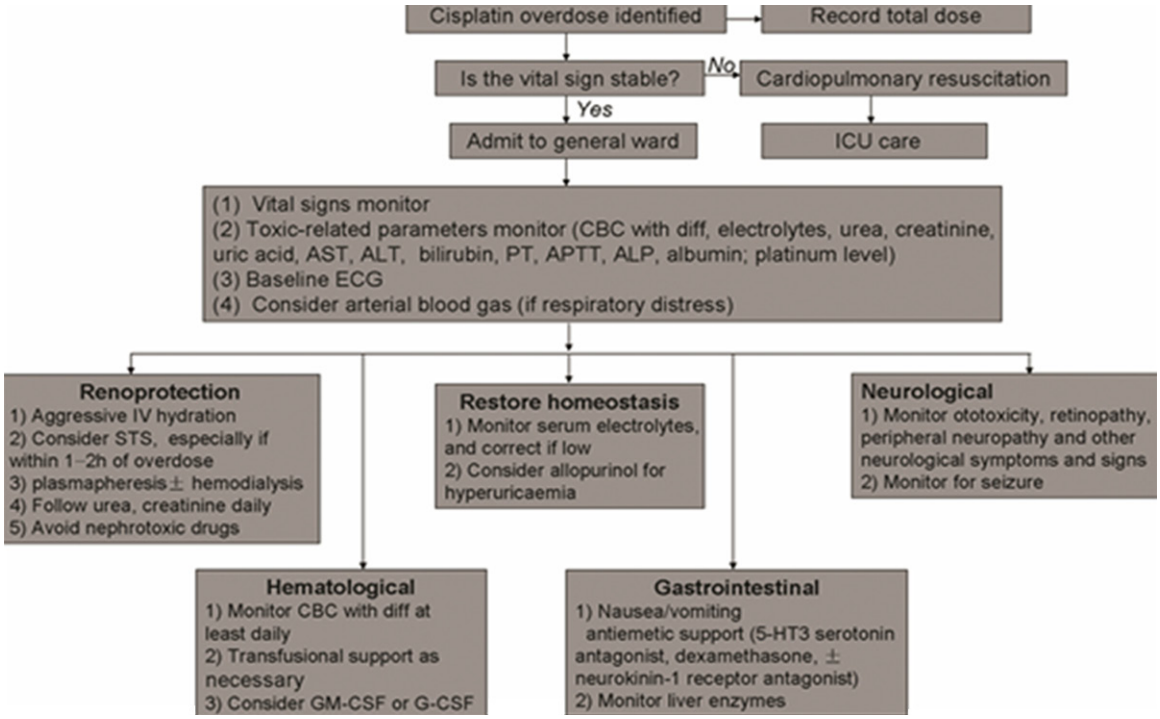

Figure 2. Suggested algorithmic approach for the initial management of a patient with a cisplatin over-dose. ICU: intensive care unit; CBC with diff: complete blood count with differential; ALT: glutamic pyruvic transaminase; AST: glutamic oxaloacetic transaminase; ALP: alkaline phosphatase; G-CSF: granulocyte colony stimulating factor; GM-CSF: granulocyte macrophage colony stimulating factor; ECG: electrocardiograph; IV: intravenous; STS: sodium thiosulfate.

same day. The BUN and Cr were decreased to 25 mmol/L and 262 on day 8 (**Figure 1**), hemodialysis was performed again. By day 10, her leukocyte count was 1.1×10^9/L, the platelet count was 16×10^9/L; BUN, 20 mmol/L; Cr, 369 μmol/L (**Figure 1**); activated partial thromboplastin time (APTT), 155 seconds; and her temperature spiked to 39°C, blood cultures were obtained, Imipenem was started immediately. At the same time, granulocyte colony-stimulating factor (G-CSF) and interleukin-11 (IL-11) therapy was also started. Due to the severity of these side effects, the medical records of the patient were reviewed and revealed that cisplatin, instead of carboplatin, had been administered on day 1 to 5, therefore, plasmapheresis was initiated in an effort to remove platinum from the patient at day 12, and hemodialysis was performed on day 11, platelet transfusions was also given. On day 12, the clotting times were elevated obviously with prothrombin time of 27 seconds and APTT of over 240 seconds, and she presented as epistaxis, hematuresis and melena. Ecchymosis was also found in the left antecubital and perineum area, fresh-frozen plasma therapy was given. On day 15, blood cultures showed growth of an organism that proved to be enterococcus faecium, and the diagnosis of septicemia was confirmed. Due to the potential hepatic and renal function damage, vancomycin was not administrated according to her parents APTT of over 240 seconds, and she presented as epistaxis, hematuresis and melento the elevated BUN and Cr. However, due to the low economic status, the parents decided not to receive hemodialysis on day 20, day 23 and day 24, although the BUN and Cr were elevated over 22 mmol/L and 600 μmol/L, respectively. Coma occurred at day 25, followed with sudden cardiac arrest, and died although actively rescue was performed. The toxic-related parameters were showed in **Figure 1**.

Discussion

Toxicities of cisplatin include emesis, nephrotoxicity, neurotoxicity, hearing loss, visual impairment, cholestasis, gastrointestinal disturbances, and bone marrow suppression. The

Table 1. Dosis, treatment, and outcome of selected literatures

Age	Sex	Dosis	Treatment	Outcome	Author
14	Female	360 mg/m^2	STS	Alive, hearing loss	Erdlenbruch et al.
33	Female	400 mg/m^2	PPH, HD	Dead	Jurek T et al.
36	Male	480 mg/m^2	HD	Alive, CRF, hearing loss	Schiller et al.
38	Female	Total 640 mg	NAC	Dead	Sheik-Hamad et al.
41	Female	200 mg/m^2	HD	Alive, n.s	Brivet et al.
46	Female	225 mg/m^2	PPH	Alive, n.s	Hofmann G
48	Male	400 mg/m^2	PPH, HD	Alive, n.s	Choi et al.
54	Female	205 mg/m^2	HD	Alive, n.a	Lagrange et al.
59	Male	300 mg/m^2	PPH	Alive,	Jung et al.
62	Male	240 mg/m^2	STS, HD	Alive, n.a.	Delanian et al.
63	Male	Total 750 mg	HD, NAC, PPH	Dead	Charlier et al.
66	Male	400 mg/m^2	HD	Alive, CRF	Pourrat X
67	Male	240 mg/m^2	STS, HD, PPH	Alive, n.s.	Yasuhiro Yamada et al.
68	Female	280 mg/m^2	PPH, HD	Alive, CRF, hearing loss	Chu et al.
1	Female	500 mg/m^2	PPH, HD	Dead	Our patient

HD: hemodialysis; STS: sodium thiosulfate; PPH: plasmapheresis ; NAC: N-acetylcysteine; n.s.: no sequelae; n.a.: not applicable; CRF: chronic renal failure.

most serious complication is nephrotoxicity, which may result in irreversible renal failure. Key management strategies for a cisplatin overdose involve renal protection and enhancing drug elimination, with aggressive intravenous hydration with or without the use of an osmotic diuretic, and consideration of sodium thiosulfate and plasmapheresis. Close monitoring of the patient, with aggressive institution of supportive therapies for expectant toxicities and avoidance of nephrotoxic medications, is paramount [1]. A suggested algorithmic approach for the initial management of a patient with a cisplatin over-dose is presented in **Figure 2**.

To our knowledge, patients inadvertently receiving less than 300 mg/m^2 of cisplatin reportedly often recover, whereas overdoses exceeding 400 mg/m^2 frequently result in death [4-17] (**Table 1**). To our knowledge, our case is the youngest one who received a high dose of cisplatin (500 mg/m^2) in the absence of intravenous hydration, and nephrotoxicity result in renal failure, hearing loss, visual impairment, severe myelosuppression complicated by life-threatening sepsis were presented in this patient. Although vigorous therapies were given, including hemodialysis, plasmapheresis, cytokines like G-CSF or GM-CSF and antibiotic, the patient decreased.

As the toxicity of cisplatin is dose-dependent, early elimination of the drug from plasma should be critical in the management. Most of the platinum in the blood plasma is bound to proteins within a few hours after intravenous administration. The binding of cisplatin to proteins reduces urinary excretion of platinum and causes deposition of platinum in tissues. Binding of cisplatin to proteins and enzymes is generally believed to be the cause of its side effects, especially ototoxicity and nephrotoxicity. Renoprotection including hydration，sodium thiosulfate, plasmapheresis and hemodialysis. Plasmapheresis has been attributed to the removal of cisplatin-bound plasma proteins, and should nonetheless be strongly considered, regardless of time elapsed, in order to potentially reduce not only renal toxicities but also other systemic toxicities such as transaminitis [16]. In the previous case reports utilizing plasmapheresis, most patients had a fall in blood platinum concentrations and were associated with better clinical improvement. Only one patient received a fatal overdose of cisplatin 750 mg instead of 170 mg, plasmapheresis did not appear to be beneficial. In our case, although plasmapheresis was adapted once the diagnosis of cisplatin overdose was confirmed, it did not appear to be effective due to the delay, which emphasizes the importance of early elimination of the drug.

Hemodialysis, as opposed to plasmapheresis, is ineffective in removing or clearing cisplatin

from the body in an overdose setting due to the highly protein-bound nature of the drug [17]. However, hemodialysis is likely to be a beneficial adjunct in the support of acute renal failure, it was be recommended with or without hemodialysis support in nephrology and/or intensive care unit.

Sodium thiosulfate appears to be an effective agent, although the studies on the overdose setting are limited. The mechanism of action of sodium thiosulfate relates to the binding of free platinum, which results in an increase in the total clearance of inactive metabolites [18], thereby limiting renal tubular cell necrosis. A pediatric case report by Erdlenbruch highlighted the reversal of acute renal failure at 4 weeks after a cisplatin overdose when sodium thiosulfate was administered shortly after the overdose was identified [4]. However, due to the delay of confirming cisplatin overdose and being admitted to our hospital, sodium thiosulfate was not administered in our patient. Based on the limited evidence, use of sodium thiosulfate should be considered, especially if it can be administered within 1-2 hours after a cisplatin overdose, although further studies are warranted to investigate its potential role.

Myelosuppression may persist for weeks after the overdosage and despite treatment with G-CSF/GM-CSF, CBC with differential should be monitored on a daily basis. However, it is controversial as to whether the administration of G-CSF should be implemented as soon as cisplatin overdose is revealed [9]. It is possible that stimulating hematopoietic cells to proliferate in the presence of toxic agents results in more substantial damage of such cells. Another reason we withheld the use of G-CSF in our case was that the patient had sufficient numbers of granulocytes and no signs of infections, thereby G-CSF was started on day 10, when the patient had developed substantial leucopenia.

A recent prospective cohort study at a major US cancer center found a potential adverse drug event rate of 3% involving chemotherapy use [19], strategies for avoiding chemotherapy overdoses (including cisplatin) or preventing future errors are of utmost importance. These include being cognizant of medication errors through staff education, avoiding medication abbreviations, utilizing computerized prescriber chemotherapy ordering and double checking of chemotherapy orders by pharmacy and nursing staff. In some institution, standard operating procedures was established and reevaluated at regular intervals, however, even such complex procedures are not able to completely prevent such mistakes as published [13]. Therefore, physicians and pharmacists should be aware of this problem and strictly follow appropriate guidelines in order to give the best care possible to patients.

Upon cisplatin overdose, the attempt of immediate, continuous, and sufficient removal of the drug is an important factor for the management of the overdose. Although there is no specific antidote for cisplatin, important therapeutic strategies include aggressive intravenous hydration with or without the use of an osmotic diuretic, avoidance of nephrotoxic medications, and consideration of sodium thiosulfate and plasmapheresis, with or without haemodialysis support. However, the best strategy still remains to be the prevention of such errors. In order to prevent the recurrence of such an accident, we recommended evaluating, establishing and implementing the best possible and accurate control mechanisms on the different levels for prescription, preparation and administration of chemotherapy agents.

Disclosure of conflict of interest

None.

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