

Platinum levels in various tissues of a patient died 181 days after cisplatin overdose determined by electrospray ionization mass spectrometry

KAYOKO MINAKATA, OSAMU SUZUKI

Hamamatsu University School of Medicine, Japan

AIM: Exclusion of a drug from tissues is an important factor in pharmacology in relation to its metabolism or side effects of the metabolites. Cisplatin, cis-diamminedichloroplatinum (II), is reported to bind to DNA displaying anti-tumor activities. The tissue distribution of platinum (Pt) appears to be dependent on its dose, duration of time as well as kinds of tissues but the studies on Pt levels in tissues were limited mostly to a short test period as 10 days in experimental animals. Recently we reported Pt levels in human tissues of a patient died 44 days after cisplatin overdose. Again we encountered with the present patient died 181 days after cisplatin overdose. An appreciable retention of cisplatin was also observed in this case, suggesting possible side effects of cisplatin, although the patient's death might be ascribed to the recurrence of malignant lymphoma.

MATERIALS AND METHODS: A 45-year-old female (59.2 kg) with malignant lymphoma received an accidental overdose of cisplatin (600 mg during 4 days). Determination of Pt was performed by electrospray ionization mass spectrometry (ESI-MS) using silver (Ag) as internal standard. Patient samples were spiked with Ag at 1,000 ng/g wet weight. Tissues from reference subjects were spiked with Ag at 1,000 ng/g and Pt at either 0, 6, 20, 100, 200 or 2000 ng/g. Ethical approval was obtained for removal of samples from the patient and reference subjects. One g of sample was mixed with 1 ml of conc. HNO_3 and wet-ashed. Pt and Ag complexed with diethyldithiocarbamate (DDC) in wet-ashed solution were extracted into isoamylalcohol, and then were acidified with oxalic acid. After injecting 1μ liter of the isoamylalcohol into a TSQ 7000 LC/MS/MS instrument directly, the quantitation was performed by ESI-MS using the signals of $\text{Pt}(\text{DDC})_3^+ \text{nd Ag}(\text{DDC})_2^+$ at m/z 639 and 403, respectively.

RESULTS: Metal ions such as Pt and Ag showed clusters of peaks with their isotopes, and the shapes of the cluster proved useful for the purpose of identification. Pt levels of the patient were determined for blood, urine and 14 kinds of organs. They were, for example, 25, 28, 1,030 and 2,050 ng/g in blood, urine, kidney and liver, respectively. The distribution of Pt was specific to organ. In short periods up to 12 days, kidney showed the highest Pt level among all organs. In the previous patient died on day 44 the Pt level in kidney, 1280 ng/g, was lower than that in liver, 1680 ng/g. This tendency that Pt level in kidney is lower than that in liver is more pronounced in the present patient died on day181. The present patient received 600 mg cisplatin and the removal started on day 7 whereas previous patient received 462 mg of cisplatin and the removal started on day 3. This may be one of the reasons why the present patient showed comparable Pt levels to the previous patient, although the duration of time was much longer in the present patient than that in the previous patient. Pt levels in tissues were remained rather high even after such a long time as 181 days whereas Pt levels in blood and urine were quite low. This fact indicates that cisplatin absorbed in tissue when the concentration in blood was high, was excreted quite slowly into urine via blood circulation.

CONCLUSIONS: Pt levels of a patient died after 181 days of cisplatin overdose was determined by ESI-MS. Various metals in tissues did not interfere with the present assay. Pt levels ranged from 25 ng/ml in the blood to 2,050 ng/g wet weight in the liver.

KEYWORDS: *Cisplatin, Platinum, Electrospray ionization, Mass spectrometry, Diethyldithiocarbamate*

Corresponding author: kminakat@hama-med.ac.jp