View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by Archivio istituzionale della ricerca - Università di Palermo

Australian Journal of Forensic Sciences

ISSN: 0045-0618 (Print) 1834-562X (Online) Journal homepage: http://www.tandfonline.com/loi/tajf20

An unusual fatal case of overdose of Vinblastine and review of literature

Elvira Ventura Spagnolo, Cristina Mondello, Francesca Indorato, Luigi Cardia, Cataldo Raffino, Giulio Cardia & Giovanni Bartoloni

To cite this article: Elvira Ventura Spagnolo, Cristina Mondello, Francesca Indorato, Luigi Cardia, Cataldo Raffino, Giulio Cardia & Giovanni Bartoloni (2017) An unusual fatal case of overdose of Vinblastine and review of literature, Australian Journal of Forensic Sciences, 49:6, 704-710, DOI: 10.1080/00450618.2016.1195874

To link to this article: http://dx.doi.org/10.1080/00450618.2016.1195874

Published online: 21 Jun 2016.

Submit your article to this journal

Article views: 31

View related articles

View Crossmark data

Full Terms & Conditions of access and use can be found at
http://www.tandfonline.com/action/journalInformation?journalCode=tajf20

Download by: [93.46.65.176] **Date:** 12 October 2017, At: 23:34

Australian Journal of Forensic Sciences, 2017
Vol. 49, No. 6, 704–710, https://doi.org/10.1080/00450618.2016.1195874

Taylor & Francis
Taylor & Francis Group
Check for updates

An unusual fatal case of overdose of Vinblastine and review of literature

Elvira Ventura Spagnolo[a]*, Cristina Mondello[b], Francesca Indorato[c], Luigi Cardia[d], Cataldo Raffino[e], Giulio Cardia[b] and Giovanni Bartoloni[f]

[a]*Department of Biotechnology and Legal Medicine, University of Palermo, Palermo, Italy;* [b]*Department of Biomedical Science and of Morphological and Functional Images, University of Messina, Gazzi Messina, Italy;* [c]*Department of Medical Science, Surgery and Advanced Technologies, "G. F. Ingrassia" – Section of Legal Medicine, University of Catania;* [d]*Department of Neurosciences, University of Messina, Gazzi, Italy;* [e]*Legal Medicine Centre of INAIL, Enna, Italy;* [f]*Department GB 'Ingrassia', University of Catania, Catania, Italy*

(*Received 12 February 2016; accepted 23 May 2016*)

The pharmacological treatment of neoplasia is based on the use of chemotherapeutic substances. Chemotherapeutic agents can cause acute and chronic toxicity even at therapeutic doses. For this reason their overdose puts a patient's life at severe risk. This work presents an unusual fatal case of overdose subsequent to an accidental massive administration of Vinblastine (90 mg instead of 9 mg), slow bolus (five minutes), to a 33-year-old woman who suffered from Hodgkin's Lymphoma. The administration of the massive dose was due to a transcription error of the therapeutic treatment plan and miscommunication between the health professionals which caused the use of the wrong dose. The forensic investigation showed the systemic macroscopic and histological changes due to the toxic effect of Vinblastine on the body, by offering a realistic example of the microscopic tissue changes caused by the antineoplastic agent to different organs. Such evidence shows the importance of being very accurate when writing the therapeutic treatment plans and of counting on adequately-trained health care staff.

Keywords: Vinblastine; overdose; intoxication; death; medical malpractice

Downloaded by [93.46.65.176] at 23:34 12 October 2017

1. Introduction

Vinblastine (VBL) is a vinca alkaloid whose antineoplastic effect consists of stopping cancer cell division by inhibiting the formation of microtubules in the mitotic spindle.

VBL is a chemotherapeutic agent commonly used in combination with other drugs when treating some pathologies such as Hodgkin's Lymphoma, lymphocytic and histiocytic lymphoma, testicle carcinoma and Kaposi's Sarcoma.

The most common side effects are nausea, vomiting, myelosuppression and consequently leucopenia, anaemia and thrombocytopenia.

Vinblastine used in combination with substances such as cisplatin, interferon, itraconazole and methotrexate can produce an accentuation of the cytotoxic effect especially on the myocardium and on the nervous system. In addition, the VBL used in association with mitomycin C can determine pulmonary toxicity and acute respiratory distress.

*Corresponding author. Email: elvira.ventura@unipa.it

This article was originally published with errors. This version has been corrected. Please see Corrigendum (http://dx.doi.org/10.1080/00450618.2016.1255300).

© 2016 Australian Academy of Forensic Sciences

The overdose of VBL causes the worsening of side effects above all leucopenia, and in some cases neurotoxicity with paraesthesia; therefore, since there is no antidote, it is important that the symptomatic and support treatment are started as early.

In the literature there are only few cases of VBL[1–4] overdose described and just one fatal event[5]; thus, below we report a case of fatal VBL poisoning that occurred after the administration of a massive dose.

2. Case report

A 33-year-old woman suffering from nodular sclerosis Hodgkin's lymphoma went to the hospital to undergo the second chemotherapy treatment. According to the therapeutic treatment plan there was expected to be an infusion of 37 mg of Doxorubicin, 15 IU of Bleomycin, 555 ng of Deticene and 9 mg of Vinblastine. Due to a transcription error on the therapeutic treatment plan, 90 mg of Vinblastine were slow bolus (five minutes) administered into the vein. Four hours later the medical staff, after having realised the error, called the woman back to the hospital and hospitalised her. The patient showed copious diarrhoea, vomiting and abdominal colic; a symptomatic and support treatment was set up with granulocyte-colony stimulating factor, detoxicants, anti-emetics and antibiotics. Four days later the patient developed mucositis, arthralgia, fever and severe pancytopenia. After 11 days the patient showed clear skin manifestations such as facial erythema, bullous erythrodysesthesia to the hands and purpura. Two weeks later the amount of white blood cells was 0.26 $\times 10^3/\mu L$, the body temperature was 41°C and the patient manifested clear neurotoxic effects such as hallucinations, delirium and epileptic seizures. A thorax CT scan showed an intralobular septal thickening, ground-glass opacity of lungs, pleuric and pericardial effusion. 16 days later a brain CT scan showed the presence of a cerebral oedema that was getting progressively worse to cause, 22 days later, the patient's death. Therefore an autopsy was arranged.

2.1. Post-mortem and histological results

The autopsy showed some desquamated lesions in the oral cavity and at perioral level with some scabby areas, areas of limb bullous erythrodysesthesia, areas of desquamation on the trunk and areas of necrosis on fingers. The encephalon showed a severe oedema and vascular congestion. The heart showed several petechiae in the area of the left ventricle wall, above all at papillary muscles level. Both lungs showed congestion and multiple whitish dot-like lumps. The stomach showed some areas of mucosa erosion. The remaining abdominal organs were congested.

During the autopsy some cutis, organs and spinal nerves were sampled to further perform the histological examination by means of the usual technique (Haematoxylin and Eosin staining). The encephalon showed congestion, intravascular coagulation micro-centres of infection and perivascular micro-haemorrhages (Figure 1). The spinal nerves showed an axonal degeneration (Figure 2). The lungs examination showed an intra-alveolar oedema alternating with areas of massive exudation of granulocytes, pneumocytes and hyaline pseudomembranes and areas of intra-alveolar haemorrhage; purulent bronchitis and red-hepatizing bronchopneumonial foci (Figure 3). The heart showed multiple areas of intravascular coagulation with coagulative necrosis foci associated with interstitial lymphohistiocytic inflammation (Figure 4). The gastric and duodenal mucosa showed some areas of erosive inflammation. The liver showed a widespread hepatic necrosis with marked lipidosis and bile stagnation (Figure 5).

Downloaded by [93.46.65.176] at 23:34 12 October 2017

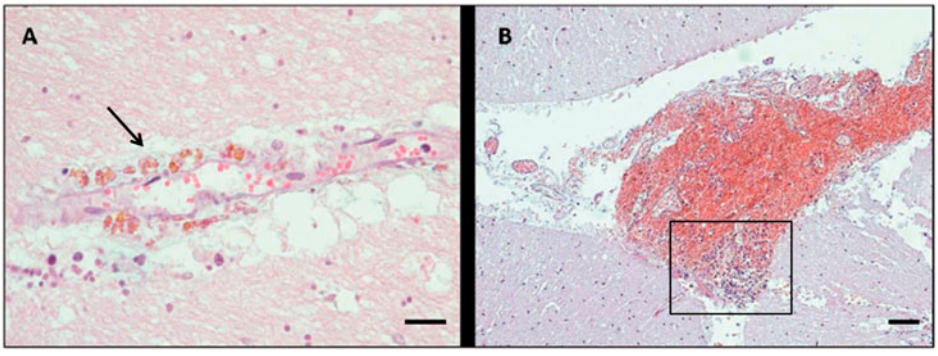

Figure 1. Brain: perivascular micro-haemorrhages (a) (arrow; H&E stain 100× magnification; scale bar, 50 μm); (b) congestion, intravascular coagulation and septic microfoci (insert) (H&E stain 50× magnification; scale bar, 100 μm).

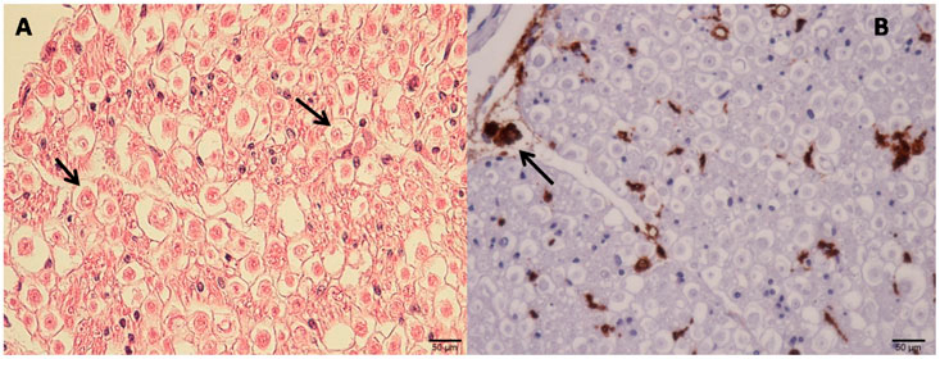

Figure 2. Axonal degeneration of the spinal nerves: (a) detail of reduced myelin thickness, onion bulb formations and various stages of myelin degeneration/debris (arrows) (H&E stain at 400× magnification; scale bar, 50 μm); (b) the same microscopic field showing positive immunophenotype for activated CD68 microglia (arrow) (PAP method 40× magnification; scale bar, 50 μm).

The skin takings showed an acute and subacute dermatitis with some bullous and erosive signs and widespread hypoderm haemorrhages (Figure 6).

3. Discussion

The post-mortem diagnosis of systemic toxicity due to a massive dose of Vinblastine (ten times higher than the one prescribed in this specific case) was based on the medical history, on laboratory findings, especially the severe pancytopenia, and on the post-mortem and histological results. Such results showed an evident case of tissue damage due to the toxic effects of VBL at cutis level[6,7] and at parenchyma level, such as encephalon, spinal marrow, lungs, heart, gastric mucose and liver.

The error in managing the chemotherapeutic drugs produces specific hazards linked both to the restricted therapeutic index of such drugs, and to the toxicity that they manifest also at therapeutic doses[8].

Downloaded by [93.46.65.176] at 23:34 12 October 2017

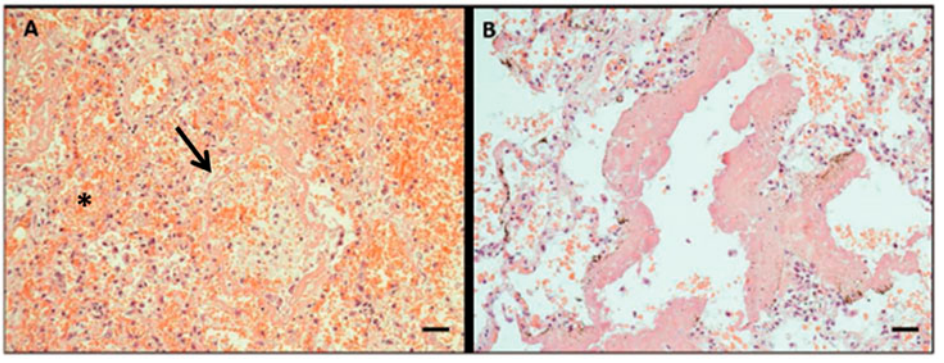

Figure 3. (a) Microphotograph of intra-alveolar haemorrhage (asterisk) (H&E stain 100× magnification; scale bar, 50 μm); (b) intra-alveolar oedema alternated with areas of massive granulocytes exudation, pneumocytes and hyaline pseudomembranes (arrow) (H&E stain at 100× magnification; scale bar, 50 μm).

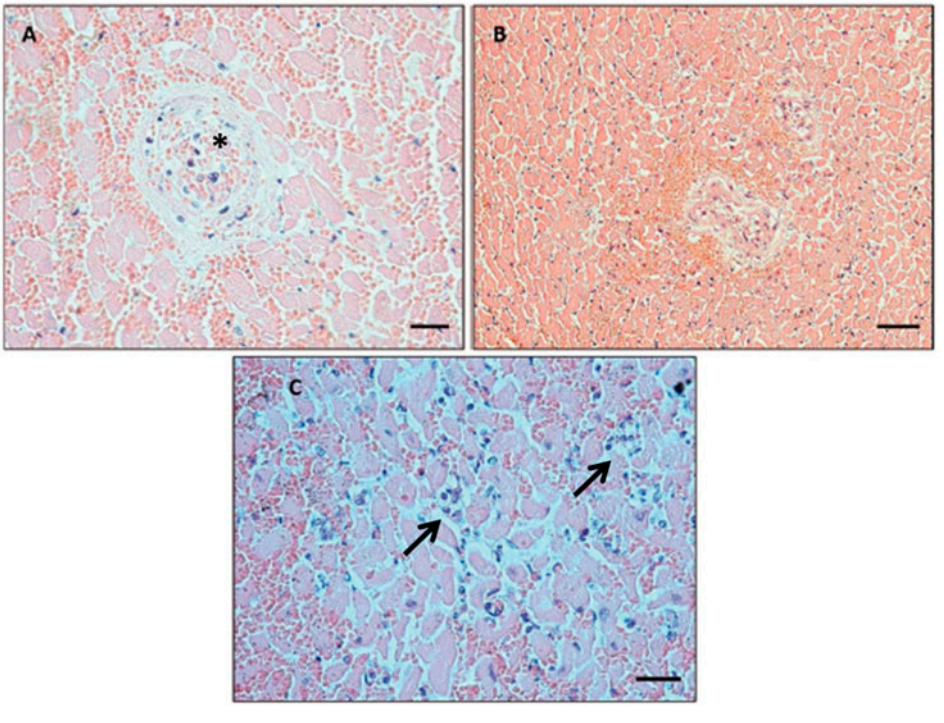

Figure 4. Myocardial samples: (a) intravascular coagulation (asterisk) (H&E stain 200× magnification; scale bar, 50 μm); (b) coagulative necrosis foci (H&E stain at 50× magnification; scale bar, 100 μm); (c) mixed inflammatory cellular infiltration of myocardial interstitium (arrows) (H&E stain at 100× magnification; scale bar, 50 μm).

The most severe side effects of VBL at a standard therapeutic dose, 4-6 mg/m^2, affect the bone marrow, the mucosae, the kidneys, and the gastrointestinal apparatus, and in some cases also the central and peripheral nervous system.

Downloaded by [93.46.65.176] at 23:34 12 October 2017

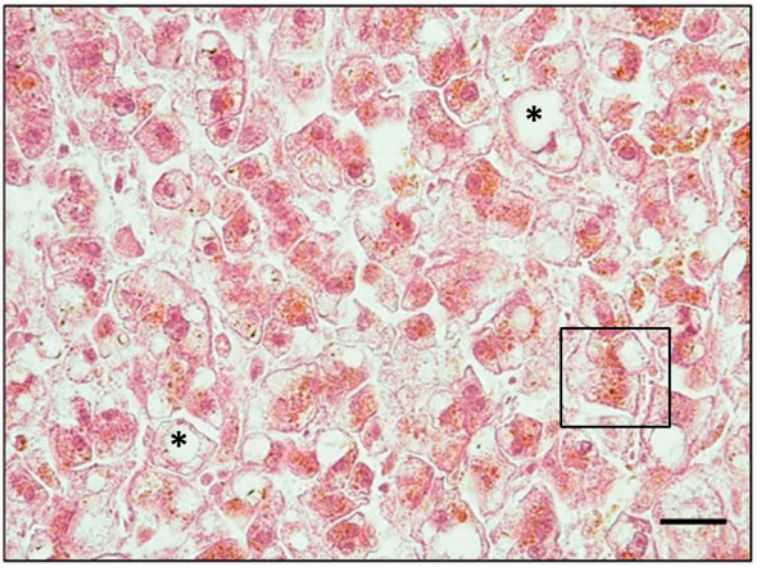

Figure 5. Microscopic liver panlobular collapse (400× magnification) showing hepatocellular necrosis, marked lipidosis (asterisks) and bile concentration (insert) (H&E stain; scale bar, 50 μm).

The VBL overdose causes a worsening of side effects with an intensification of the myelosuppression and a higher degree of probability of neurotoxicity. Therefore, as for any other pharmacological substance, above all the antineoplastic drugs, the side-effect worsening and the probability of systemic toxicity are directly proportional to the quantity of administered VBL. In fact, the bigger the dose of administered VBL, the greater the toxic effect on the body and the lower the chances of survival.

Such data are clearly documented by the presented case in which the massive dose of VBL caused the systemic toxic effects, refractory to support therapy, that brought about the woman's death. In particular the 90 mg of VBL caused the anatomo-functional damage to the encephalon, to the peripheral nervous system, to lungs, liver, cutis, mucosae and to the hematopoietic system pointed out by the clinical course, by the laboratory examinations, by the post-mortem and histological examination results.

The case at issue demonstrates the serious inherent risk of using VBL and, in general, of all antineoplastic drugs. Unfortunately, this is the class of substances, together with antibiotics, which is more susceptible of errors.

It has been estimated that the errors linked to chemotherapeutic treatment represent 15.6% of therapeutic errors, 21% of which are due to a wrong transcription of the therapeutic treatment plan while 38% to the administration of wrong doses[9–11].

The cases of overdose of the most signalled chemotherapeutic drugs concern methotrexate, cisplatin, oxaliplatin, imatinib, and vincristine[12–18]. Although fatal events are rare, the systemic toxic effects documented by the presented case highlight the fact that the activities of the health care staff involved in the chemotherapeutic treatment are burdened by potentially lethal risks for patients.

The management of the chemotherapeutic agents is very important in the ordering, preparation and administration phases. Moreover, in order to avoid such adverse events,

Downloaded by [93.46.65.176] at 23:34 12 October 2017

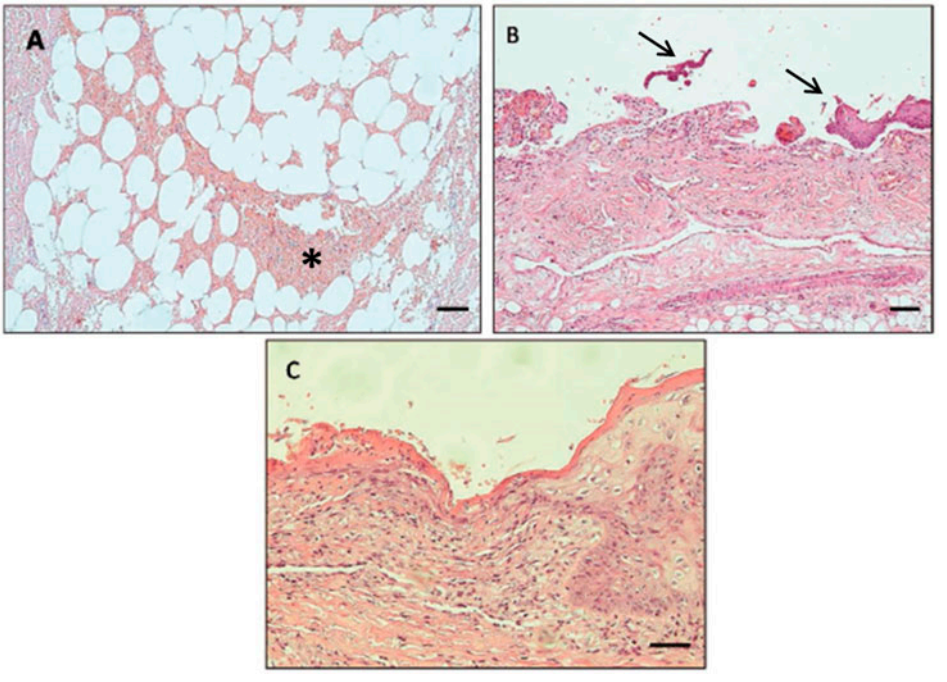

Figure 6. Histological skin lesions: (a) widespread hypoderm haemorrhages (asterisk) (H&E stain 20× magnification; scale bar, 100 μm); (b) horny layer erosions of the epidermis (arrows) (H&E stain at 50× magnification; scale bar, 100 μm); (c) thickening of the epidermis (H&E stain at 100× magnification; scale bar, 50 μm).

the importance of communication among the staff members and the accurate set up of the therapeutic treatment plan, as well as the adequate training of nurses who check the dose of drugs and administer them should be emphasised.

Disclosure statement

No potential conflict of interest was reported by the authors.

References

1. Spiller M, Marson P, Perilongo G, Farina M, Carli M, Bisogno G. A case of vinblastine overdose managed with plasma exchange. Pediatric Blood & Cancer. 2005;45:344–346.
2. Winter SC, Arbus GS. Syndrome of inappropriate secretion of antidiuretic hormon secondary to vinblastine overdose. Can. Med. Assoc. J. 1977;117(10):1134.
3. Conter V, Rabbone ML, Jankovic M, Fraschini D, Corbetta A, Pacheco C, D'Angelo P, Masera G. Overdose of vinblastine in a child with langerhans' cell histiocytosis: toxicity and salvage therapy. J Pediatr Hematol Oncol. 1991;8(2):165–169.
4. Aversa SM, Zanon S, Marino D, Canova F, Chiarion-Sileni V, Jirillo A. Overdose of Vinblastine in place of Vinorelbine during IGEV chemotherapy. Immunopharmacol Immunotoxicol. 2012;34(5):879–880.
5. Kłys M, Konopka T, Scisłowski M, Kowalski P. Fatality involving vinblastine overdose as a result of a complex medical error. Cancer Chemother. Pharmacol. 2007;59(1):89–95.
6. Gilbar P. Palmar-plantar erythrodysestesia. J Oncol Pharm Pract. 2003;9:137–150.

Downloaded by [93.46.65.176] at 23:34 12 October 2017

7. Childress J, Lokich J. Cutaneous hand and foot toxicity associated with cancer chemotherapy. J Clin Oncol. 2003;26:435–436.
8. Muller T. Typical medication errors in oncology: analysis and prevention strategies. Onkologie. 2003;26:539–544.
9. Lustig A. Medication error prevention by pharmacists – an Israeli solution. Pharm. World Sci. 2000;22:21–25.
10. Ford CD, Killebrew J, Fugitt P, Jacobsen J, Prystas EM. Study of medication errors on a community hospital oncology ward. J. Oncol. Pract. 2006;2:149–154.
11. Schwappach DLB, Wernli M. Medication errors in chemotherapy: incidence, types and involvement of patients in prevention. A review of the literature. Eur. J. Cancer Care. 2010;19:285–292.
12. Tsang RY, Al-Fayea T, Au HJ. Cisplatin overdose: toxicities and management. Drug Saf. 2009;32(12):1109–1122.
13. Soloni P, Compostella A, Carli M, Bisogno G. A case of oxaliplatin overdose. Pediatr. Blood Cancer. 2009;52(7):902–903.
14. Dehours E, Riu B, Valle B, Chatelut E, Recher C, Fourcade O, Huguet F. Overdose with 16,000 mg of imatinib mesylate. Leuk. Res. 2010;34(10):e286–e287.
15. Kosmidis HV, Bouhoutsou DO, Varvoutsi MC, Papadatos J, Stefanidis CG, Vlachos P, Scardoutsou A, Kostakis A. Vincristine overdose: experience with 3 patients. Pediatr. Hematol. Oncol. 1991;8(2):171–178.
16. Moisa A, Fritz P, Benz D, Wehner HD. Iatrogenically-related, fatal methotrexate intoxication: a series of four cases. Forensic Sci. Int. 2006;156(2-3):154–157.
17. Jurek T, Rorat M, Dys P, Swiatek B. Fatal cisplatin overdose in the treatment of mediastinal lymphoma with the ESHAP regimen - analysis of the causes of the adverse drug event. Onkologie. 2013;36(1-2):49–52.
18. Charlier C, Kintz P, Dubois N, Plomteux G. Fatal Overdosage with Cisplatin. J. Anal. Toxicol. 2004;28(2):138–140.

Downloaded by [93.46.65.176] at 23:34 12 October 2017