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

Elvira Ventura Spagnolo*a, Cristina Mondellob, Francesca Indoratoc, Luigi Cardia, Cataldo Raffinoe, Giulio Cardiab and Giovanni Bartoloni

*Department of Biotechnology and Legal Medicine, University of Palermo, Palermo, Italy; bDepartment of Biomedical Science and of Morphological and Functional Images, University of Messina, Gazzi Messina, Italy; cDepartment of Medical Science, Surgery and Advanced Technologies, “G. F. Ingrassia” – Section of Legal Medicine, University of Catania; dDepartment of Neurosciences, University of Messina, Gazzi, Italy; eLegal Medicine Centre of INAIL, Enna, Italy; fDepartment GB ‘Ingrassia’, University of Catania, Catania, Italy

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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

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 consequentely 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

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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 overdose described and just one fatal event; 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 $0.26 \times 10^3/\mu\text{L}$, the body temperature was $41^\circ\text{C}$ 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 bronchopneumonal 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).
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 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.
The most severe side effects of VBL at a standard therapeutic dose, 4-6 mg/m², affect the bone marrow, the mucosae, the kidneys, and the gastrointestinal apparatus, and in some cases also the central and peripheral nervous system.

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 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 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,
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.

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