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ORIGINAL ARTICLE

Fatality involving vinblastine overdose as a result of a complex medical error

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Abstract The purpose of the study is a presentation of a fatal case involving an 83-year-old woman, who died due to an overdose of vinblastine—a cytostatic agent of a *vinca alkaloid* employed in cancer chemotherapy. The postmortem investigation included an autopsy and histological examination, as well as a toxicological analysis of post-mortem specimens collected in the course of autopsy. The authors performed a toxicological assessment of vinblastine employing liquid chromatography-atmospheric pressure chemical ionization-tandem mass spectrometry (LC-MS-MS-APCI). The determined vinblastine concentration levels amounting to 29 ng/g in blood and 52.5 ng/g in liver were in a considerable excess of values encountered in patients on chemotherapy using the drug. The fatality was investigated in the context of medical error. In the described case, the erroneous and medically unjustified administration of vinblastine was identified by a series of unfortunate events involving as many as three acting consecutively individuals: a physician, a pharmacist and a nurse. The report may thus document the clinical course of vinblastine poisoning along with postmortem changes resulting from the drug action.

Keywords Vinblastine · Overdosage · Medical error · Liquid chromatography · Atmospheric pressure chemical ionization mass spectrometry

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Introduction

Between the end of the 19th century and the present time, problems pertaining to medical errors have been discussed by eminent European medical and legal bodies. Numerous legal treatises of a fundamental character have concentrated on this issue, while defining conditions necessary for appropriate interventions. The problem of a medical error is, thus, ever-present in the history of medicine and it seems that despite the increasingly growing level of medical knowledge and various procedures aiming at—at least—limiting erroneous activities, the issue of medical errors continues to be live [9, 19].

In this context, an opportunity for discussing the issue of medical error is offered by the present report, which provides an analysis of a fatality in consequence of vinblastine (Vinblastin, Richter-Gedeon, H) overdosage—a cytostatic agent of a *vinca alkaloid* employed in cancer chemotherapy [14, 15].

In the described case, the erroneous and medically unjustified administration of vinblastine was identified by a series of unfortunate events involving as many as three acting consecutively individuals: a physician, a pharmacist and a nurse.

In post-mortem materials collected in the course of autopsy, the authors performed a toxicological assessment of vinblastine concentration levels, employing a unique analytical procedure that included liquid chromatography-atmospheric pressure chemical ionization-tandem mass spectrometry (LC-MS-MS-APCI).

The determined blood and liver vinblastine concentration values were several times in excess of levels encountered in patients on chemotherapy using the drug.

In the analyzed case, clinical observations prior to the patient's death combined with post-mortem macro and microscopic examinations and toxicology allowed for an unmistakable determination of vinblastine overdose as the cause of death.

Case report

Case history

An 83-year-old female was hit by a car, what resulted in her right lower limb contusion. A lower leg bruising persisted for a long time; subsequently, the hematoma spontaneously perforated forming a wound that started to heal by granulation. In view of the problems with wound healing (the patient was treated for diabetes), an orthopedist suggested a therapy with a new, expensive drug, the purchase of which was delegated to the patient's daughter. In the medical records of the patient, the issued prescription and in the intramuscular injection order, the physician entered the name of the drug as ''Vinplastin''. As he testified later, he had had in mind ''Vasolastine'' manufactured by ENZYPHARM, an enzymatic preparation employed as an adjuvant agent in abnormal wound healing [20]. In the pharmacy, following initial problems with deciphering the name of the medication, the staff assumed that the physician must have meant ''Vinblastin''. The names of the medications ''Vinplastin'' and ''Vinblastin'' are sound-like, and their spelling differs in one character only (''p'' vs. ''b'').

The drug ''Vinblastin'' then was ordered from a wholesale dealer, received by the pharmacy and sold to the patient's daughter, despite the fact that in keeping with Polish regulations, it can be purchased solely by hospitals.

Clinical problems of a case

The therapeutic agent was administered—as per the prescription, which, however, ordered the administration of ''Vasolastine'' in keeping with the physician's intent—as intramuscular injections given daily by a nurse. However, the nurse did not notice that the injection order provided for ''Vasolastine'', while the medication she received to be injected was in ampoules labeled as ''Vinblastine''. In consequence, the patient received one 5 mg ampoule of vinblastine per day. Moreover, the daughter also failed to notice that her mother was administered a medication different from the drug prescribed by the physician and assumed the deterioration in the mother was ascribable to her taking ''Vasolastine''. After the sixth dose, the daughter brought the patient for a follow-up examination in an Outpatient Orthopedic Clinic, reporting weakness observed in the female. The physician seeing outpatients on that day advised discontinuation of the drug, being of the opinion that the female did not tolerate ''Vasolastine'', so he recommended contacting the doctor who had originally prescribed the medication. In view of further progressive deterioration of the patient's health, the daughter called an ambulance the following morning and the woman was taken to hospital.

Upon admission, the daughter produced medications her mother had been taking. She expressed her conviction that deteriorated health was most likely associated with the administered drug. It was then concluded that the mother received without good reason a very high dose of the anti-cancer medication ''Vinblastin''.

On admission, the patient complained of malaise, intensifying myalgia, melalgia and pain involving oral cavity mucous membranes. Lab tests performed on the day of admission showed WBC of 3.2 G/l and platelet count of 71 G/l. The employed treatment was identical with the therapeutic protocol employed in sepsis concomitant with drug-induced bone marrow aplasia. The patient was isolated and administered three antibiotics (cefotaxime, metronidazole and amikacin), a granulocyte growth-inducing agent (filgrastim) and an antifungal medication (nystatin). Over several subsequent days, the patient further deteriorated, her leukocyte count dropped to 0.7 G/l on day 8 and to 0.3 G/l on day 9 following the first dose administration. On the same day, the patient developed fever, pneumonia and bloody vomiting, her blood pH decreased to 6.94. In the afternoon, her arterial blood pressure dropped to 80/40 mm Hg, the patient developed oliguria and fungal-bloody coating in the oral cavity and throat. Despite intramuscular infusions of dextran, dopamine and norepinephrine, her blood pressure failed to rise above 100 mm Hg. The patient developed cardiac arrest, was resuscitated, but she continued to be in a deep coma and several hours later died.

Postmortem examination

The autopsy showed uterine, tubal and ovarian hemorrhages, petechiae in the intestinal mucosa and pulmonary edema. Preexisting diseases included atherosclerosis and status post right coronary artery angioplasty. In addition, histopathology demonstrated bone marrow emboli in isolated pulmonary vessels and profoundly hypoplastic bone marrow displaying signs

of hemopoietic function damage: interstitial edema, distended vessels and scattered macrophages with foamy cytoplasm.

Materials and methods

Biological materials

Postmortem specimens were collected at autopsy of the victim, which was performed at the Institute of Forensic Medicine, Collegium Medicum, Jagiellonian University in Kraków within 24 h of death. The samples were as follows:

(a) Sample of femoral blood and liver.
(b) Control autopsy blood and liver samples (''blank'' sample)—free from any xenobiotics taken from a non-poisoned subject.

Chemicals and reagents

All chemicals and solvents were of analytical grade. Standards of vinblastine and vincristine (used as an internal standard) were purchased from Richter-Gedeon Ltd (Hungary), acetonitrile—HPLC grade (Merck, Germany), formic acid (Rediel, Germany), methanol, chloroform (POCh, Poland).

Extraction—blood and liver samples

The autopsy blood sample was subjected to liquid/liquid extraction, then 1 ml of a sample was aliquoted into a clean 40 ml tube. The autopsy liver sample was 1 g of a tissue which was homogenized for 3 min and subjected to liquid-liquid extraction. To the blood and liver samples was added vicristine as an internal standard at concentration 10 ng/ml (blood) and at concentration 50 ng/g (liver), then 2 ml of phosphate buffer (pH 3), 10 ml of chloroform and 2 ml of 2-propanol were added to each sample. The mixtures were shaken for 10 min and afterwards, the samples were centrifuged for 10 min at 3,000 rpm. The organic layers were separated and evaporated to dryness at 40°C under a stream of nitrogen. The residues were reconstituted with 100 μl of methanol and finally 10 μl of the extract was injected into LC-MS system.

Calibration curves and quantitation

Calibration curves were constructed by the analysis of drug-free blood 1 ml containing known amount of vinblastine. To prepare these standards, blood samples were spiked with vinblastine to the following concentrations: 1.0; 2.0; 5.0; 10.0; 20.0 ng/ml. Vicristine at the concentration of 10.0 ng/ml was used as the internal standard.

Calibration curves for the liver were generated by the analysis of drug-free 1 g of liver homogenate containing a known amount of vinblastine. To prepare these standards, liver samples were spiked with vinblastine to the following concentrations: 10.0; 20.0; 50.0; 100.0 ng/g and internal standard—vincristine at the concentration of 50.0 ng/g.

The samples were extracted according to the procedure described above and the calibration curves were constructed. Results of the validation procedure for blood are presented in Table 1.

Analytical method

The LC-MS system consisted of liquid chromatograph equipped with a gradient pump TSP 4000, an autosampler TSP 3000 and a mass spectrometer—ion trap LCQ series with an atmospheric pressure chemical ionization inlet-APCI (Finnigan MAT, San Jose, USA).

The chromatographic separation was performed with a LiChroCART colum 125 × 3 mm I.D., 5 μm particle size, filled with Purospher RP 18 and a LiChroCART precolumn 4 × 4 mm I.D., particle size 5 μm filled with LiChrospher 60 RP—select B (Merck, Germany).

The liquid chromatograph was operated in the gradient composition mode of 0.1% formic acid in water [A] and acetonitrile [B] phases. The gradient program was as follows: 95% [A] for 2 min, followed by a linear

Table 1 Validation data concerning vinblastine

	LOD (ng/ml)	LOQ (ng/ml)	Linearity (ng/ml)	Intraday precision (n = 5, % RSD)			Interday precision (n = 5, % RSD)			Recovery (n = 5, %)		
				1 ng/ml	10 ng/ml	20 ng/ml	1 ng/ml	10 ng/ml	20 ng/ml	1 ng/ml	10 ng/ml	20 ng/ml
Vinblastine in blood	0.5	1.0	1–20	15.8	13.3	9.1	18.7	15.9	14.3	63.2	71.8	79.4

change to 5% [A] in 8 min, 5% [A] was held for 2 min, then changed to 95% [A] in 8 min, and then 95 % [A] was held for 5 min. The constant flow rate was 400 µl/min and the injection volume was 10 µl. The total run time for one injection was 25 min.

The mass spectrometer was operated in the MS-MS mode. Ions were monitored as follows: *m*/*z* 811 (molecular ion) and *m*/*z* 793, *m*/*z* 751 (fragments ions) for vinblastine; *m*/*z* 825 (molecular ion) and *m*/*z* 807, *m*/*z* 765 (fragments ions) for vicristine. Desacethylvinblastine was identified in full scan mode. The monitored ion was *m*/*z* 769.

Relatve collision energy in MS-MS mode was 30%. The APCI inlet parameters were as follows: sheath gas (nitrogen) pressure 70 arb., vaporizer temperature 400°C, capillary temperature 150°C, capillary voltage 5 kV, discharge current 5 μA.

Results

The employed by the present authors unique analytical procedure using LC-MS-MS-APCI proved to be an appropriate and optimal method for determining the levels of xenobiotics belonging to the *vinca alkaloid* group. As a similar option, it is also recommended by other investigators [16] for this group of drugs. The validation procedure for vinblastine performed in the biological material (see the detailed results in Table 1) indicated a possibility of performing quantitative determinations at low concentration levels.

In the course of the comprehensive toxicological analysis based on the developed analytical procedure, vinblastine and desacethylvinblastine were identified in postmortem blood and liver. The results are illustrated in Table 2.

The xenobiotics were determined in the analyzed biological extracts based on chromatographic and mass spectrometric parameters. The analytical documentation for the selected blood sample is presented in Fig. 1a, b.

Table 2 illustrates the results of quantitative analysis of vinblastine levels in blood and liver employing the developed method; blood vinblastine levels were high, reaching the values possibly encountered in acute fatal poisoning.

Table 2 Toxicological findings in fatality concerning of a vinblastine overdose

	Concentration (ng/ml, ng/g)	
	Vinblastine	Desacetylvinblastine
Bood	29.1	[+]
Liver	52.5	[+]

Discussion

Vinblastine, a *vinca alkaloid*, is derived from a common flowering herb, the periwinkle plant *Vinca rosea Linn*. As cytostatic drugs, the *vinca alkaloids* exert their antimitotic effect by binding to tubulin, a protein, which polymerizes to form intracellular microtubules. The resulting disruption of microtubule assembly interferes with the formation of the mitotic spindle, resulting in mitotic arrest [13]. Interference with the assembly of other cytoskeletal microtubules results in the disruption of cellular structure and movement [18].

Generally, the *vinca alkaloids* are poorly absorbed after oral administration and, therefore, are not administered by this route. Rapid intravenous administration results in a triphasic serum decay pattern with a rapid initial half-life for vinblastine of less than 5 min, and longer terminal half-life of 25 h [12].

After intravenous administration, vinblastine is metabolized to desacethylvinblastine, which is active. This pattern is consistent with extensive but reversible tissue biding; vinblastine penetrates poorly into the cerebrospinal fluid. The primary route of elimination is by hepatic metabolism and biliary excretion. Renal elimination accounts for less than 20% of the administered drug [18]. About 14% of a radioactively labeled dose is excreted in the urine within 72 h and 10% is eliminated in the feces in the same period of time [10].

Vinblastine is employed both as a component of combined therapy or in monotherapy of various types of cancers, including Hodgkin's disease, non-Hodgkin's lymphomas, testicular and breast carcinomas, acute monocytic leukemia and others. The drug is usually administered at the dose of 4–6 mg/m^2 every 2–4 weeks, depending on the therapeutic protocol employed in a given carcinoma type [5, 11, 14, 15].

In the analyzed case, the dosage of vinblastine was evidently exceeded. Daily administration of the drug over 6 days at the dose of 5 mg per day resulted in increasing the level of the xenobiotic due to its accumulation in the body of the patient and additionally in augmenting its cytostatic activity. Vinblastine levels detected in the blood of the deceased patient significantly exceeded therapeutic concentration values. In individuals on vinblastine therapy, the range of concentration values determined by Links et al. [10] based on their observation of 16 patients was 2.7–7.1 ug/L. None of the warnings on the possibility of adverse effects occurring in consequence of the drug adminis-

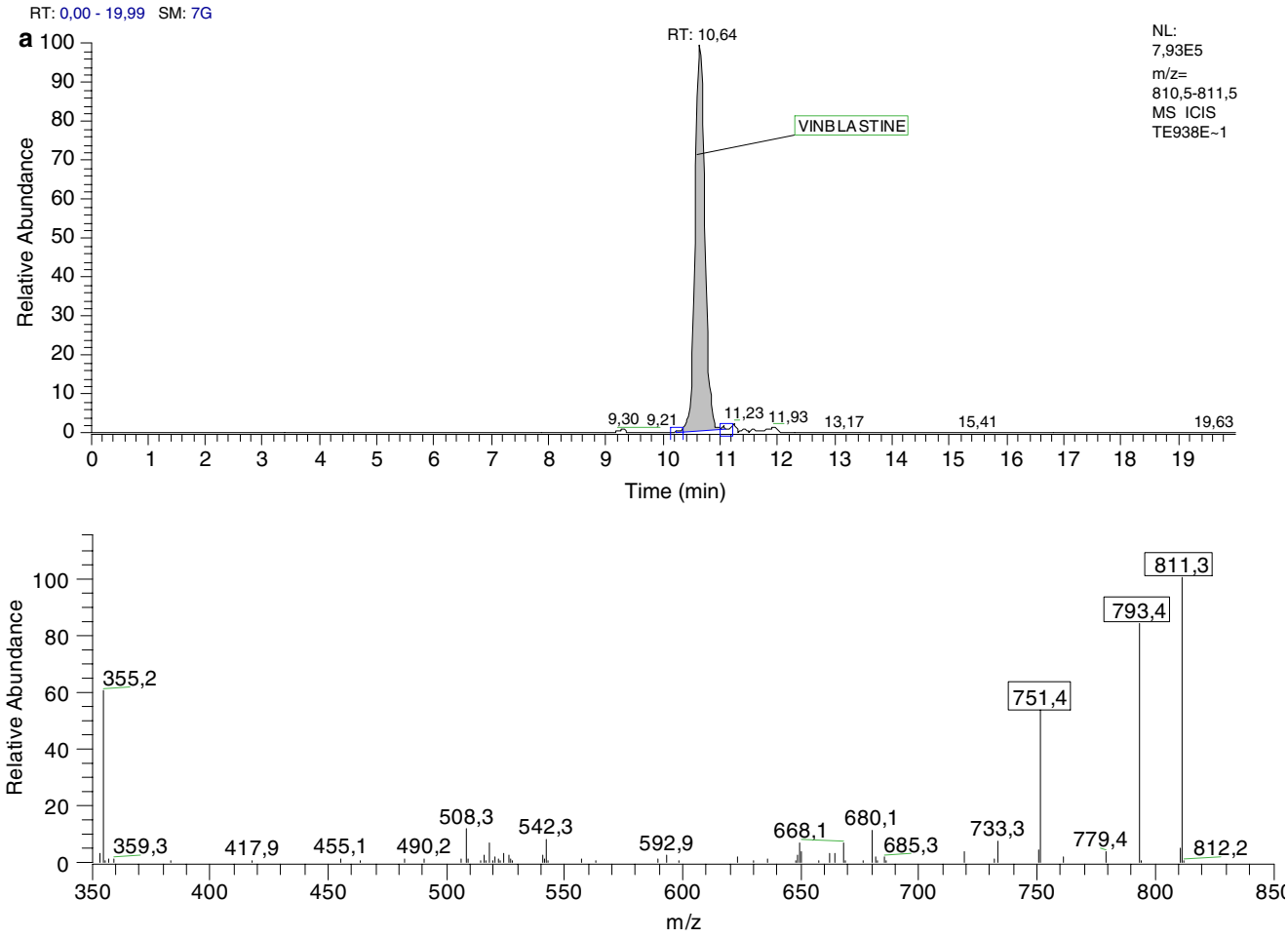

Fig. 1 **a** Mass chromatogram and mass spectrum of xenobiotics determined in blood sample of the deceased for vinblastine (monitored ions *m*/*z* 811, 793, 753). **b** Mass chromatogram and mass spectrum of xenobiotics determined in blood sample of the deceased for desacethylvinblastine (monitored ion *m*/*z* 769)

tration could have been taken into consideration in the presented case, since neither the patient, nor the individuals involving in her care were aware she was taking a drug that was different from the medication the physician had originally in mind.

The employment of cytostatics in neoplastic diseases [5, 14] is based on the fact that cancer cells are reproduced much faster than the majority of normal cells. Cytostatics destroy cells that are in the phase of cell division, but do not affect these that are in the resting state. Thus, in neoplastic diseases, chemotherapy does not affect the majority of tissues, but damages the systems that require intensive formation of new cells. The latter are predominantly represented by the epithelium, the reproductive and hemopoietic system. Even when employed at therapeutic doses, cytostatics destroy cancer cells, but also inflict damage to normally functioning systems. This results in numerous serious adverse effects encountered when this group of drugs is employed. Epithelial damage is mostly manifested as atrophic lesions, predominantly involving the gastrointestinal tract, erosions, inflammatory lesions and bleeding. In males, the production of sperm cells is inhibited, what leads to infertility. Damage to hair bulb cells triggers hair loss. Damage to bone marrow results in anemia and thrombocytopenia; the latter leads to hemorrhagic diathesis. The most serious adverse symptom of cytostatic agent administration is the destruction of white blood cells resulting in weakening the immune system.

All the above damages are, however, reversible. When the drug concentration level is decreased, the function of the damaged tissues is restored, including new hair growth and regained fertility. Therefore, cytostatic drugs are administered in short cycles with long intervals to allow for regeneration of damaged organs in the body of the patient.

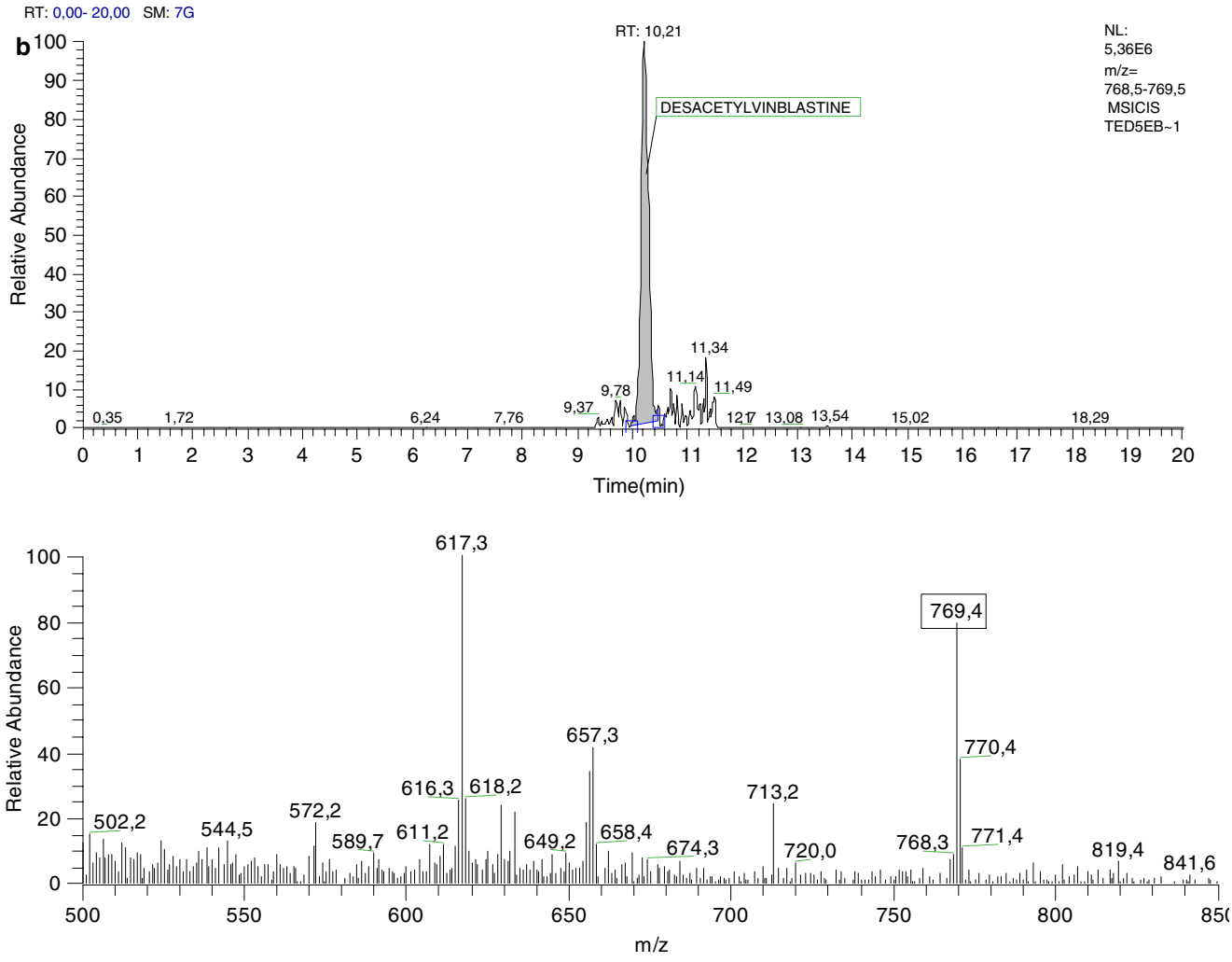

Fig. 1 continued

In the presented case, vinblastine, which should have been administered as a single dose per 2 weeks at the maximum in justified cases of its therapeutic employment, was given to the woman in question daily over a period of 6 days. The total dose administered amounted to 6×5 mg = 30 mg. Such a way of vinblastine administration most likely resulted in a complete inhibition of cell reproduction. In some blood systems, with blood cells characterized by a longer life, the drop in their number was relatively low. The level of red cells, with their lifespan of approximately 120 days, decreased from the normal value of 3.5 to 2.89 T/l, while the platelet (lifespan of 9–10 days) count dropped from 150 to 30 G/l. On the other hand, the number of white blood cells, with their life amounting to 4–5 days, decreased tenfold, from approximately 4.0 (lower normal limit) to 0.4 G/l. This resulted in a practically complete inhibition of the immune system function and fulminant sepsis that caused death. In spite of the fact that no microorganism was determined that had caused sepsis (it might have been a virus, bacteria or a fungus), septic shock was diagnosed based on the course of the disease and the clinical presentation.

The v*inca alkaloids* are an important component of many multidrug chemotherapeutic regiments for the treatment of a wide range of malignant diseases. Their structural similarity is in contrast to their distinct biological and toxicological properties. Great care should be taken in the preparation and administration of these agents [13]. Thus, the administration of cytostatic drugs, in view of their considerable toxicity, is subject to numerous regulations. Most likely, for this reason poisoning with these drugs is relatively rare. However, if such cases of poisoning do occur, the instances of overdosing may provide useful information on the causes of the mistakes, on drug-induced toxic effects and on the possible salvage therapy.

Conter et al. [2] reported a case of vinblastine overdose in a 18-month-old child affected by Langerhans' cell histiocytosis, Hand Schuller-Christian syndrome according to the previous classification of histiocytosis X. The authors suggested that the dosage the child had been administered, which was 1.5 mg/kg instead of 0.15 mg/kg, was probably the highest dose of the drug ever given to a patient. The child was successfully treated with steroids and citrovorum factor. Ultimately, the major adverse effects were neurological toxicity (seizures, coma) and bone marrow aplasia, which improved and gradually resolved beginning on day 12.

To our knowledge, no previous reports exist in the toxicological literature on death after the administration of massive doses of vinblastine. In this context, it appears interesting that a much greater number of reports concentrate on an erroneous administration of another medication belonging to the *vinca alkaloids* group, namely vincristine [1, 3, 4, 6, 7, 8, 17].

The described case is, on the one hand, an interesting study on medical error, but on the other hand, it prompts a search for more universal solutions to be introduced to the system of prescribing and selling medications, especially those with strong adverse or toxic effects. In the presented situation, three separate safety zones protecting the patient against adverse effects of the drug were infringed. An erroneous notation of the name of the drug on the prescription gave origin to a series of unfortunate events, while the lack of literal approach by a pharmacist to the order contained in the prescription, the interpretation of an erroneously entered name of the medication, and the sale of a drug that is designed to be employed in inpatient setting only resulted in a danger that practically could not have been averted. The entire situation provides an example of a tragic accumulation of transgressions from objective, independent professional guidelines at their most basic level. The probability of such a series of behaviors ever occurring strengthens our belief that the case is worthy of presentation as a specific kind of a warning signal.

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