Vincristine toxicity unrelated to dose

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O'Callaghan, M. J., and Ekert, H. (1976). *Archives of Disease in Childhood*, 51, 289. **Vincristine toxicity unrelated to dose.** Four children with vincristine toxicity unrelated to dose are described. Fever, haematological toxicity, and abdominal distension occurred 2-7 days after vincristine was given. Convulsions occurred 6-8 days after vincristine in all 4. Inappropriate secretion of antidiuretic hormone was thought to have occurred in 3 patients. 2 patients died during the acute toxicity phase. Necropsy findings did not show neuronal changes which could be directly ascribed to vincristine.

The vinca alkaloid vincristine is widely used in the treatment of leukaemia and solid tumours in childhood. Neurotoxicity is a common toxic manifestation and often limits the dose of the drug that can be given. This neurotoxicity has been well detailed in recent review articles (Weiss, Walker, and Wiernik, 1974; Rosenthal and Kaufman, 1974). Severe neurotoxicity can also occur after quite small doses of vincristine, and convulsions and coma have been reported where no other factors (e.g. infection, tumour invasion) seemed to be operating (Johnson *et al.*, 1973; Martin and Mainwaring, 1973; Whittaker *et al.*, 1973). Hyponatraemia, occasionally associated with convulsions, has also been described and attributed to inappropriate antidiuretic hormone (ADH) secretion (Fine, Clarke, and Shore, 1966; Slater, Wainer, and Serpick, 1969). Some of these patients had raised ADH levels (Suskind, Brusilow, and Zehr, 1972; Robertson, Bhoopalani, and Zerkowicz, 1973; Stuart *et al.*, 1975). Recovery from the acute toxic effects of the drug occurred in all the reported cases, except in that of Weiden and Wright (1972) where the patient died of bronchopneumonia after vincristine-induced paraplegia.

We report 4 cases of nondose-related vincristine toxicity. 2 patients died during the phase of vincristine toxicity and necropsy findings are described.

Case reports

Case 1. A girl presented at the age of 21 months with a stage 1 right Wilms's tumour. Chemotherapy

according to a protocol using vincristine (1.5 mg/m²) on days 1, 8, 15, and 22, and actinomycin D (0.5 mg/m²) on days 1, 3, 5, and 8 was begun. Nephrectomy was performed on day 3 and irradiation begun on day 23 (2295 rads in 18 doses). Subsequent courses of chemotherapy identical to the first were planned for 10 weeks after the start of treatment, and then 3-monthly for 5 courses. After the initial courses of vincristine and actinomycin D, thrombocytopenia and neutropenia developed on day 12, and on day 19 signs of intestinal obstruction led to resection of a jejunojejunal intussusception.

The child then improved and irradiation was begun. 3 weeks after completing radiation therapy the first dose of vincristine and actinomycin D of her secondary course was administered. Several hours after administration of these drugs she started vomiting and 48 hours later was admitted to hospital seriously ill. Apart from fever, mouth ulcers, and mild dehydration the clinical examination was normal. The peripheral blood film showed Hb 11g/dl, total white cell count 2100/mm³, and platelets 20 000/mm³. Neutropenia and thrombocytopenia became more marked and persisted for the remainder of the illness. Blood cultures were taken and intravenous gentamicin and cephaloridine given. Blood cultures showed no bacterial growth.

The abdomen became markedly distended 3 days after vincristine injection. Electrolytes taken at this time showed a serum sodium 123 mEq/l, potassium 4.3 mEq/l, and urea 24 mg/100ml, while the urine osmolality was 745 mOsm/kg. Unfortunately it was impossible to obtain a blood specimen for estimation of serum osmolality. Over the next 2 days on a regimen of fluid restriction electrolytes returned to normal, abdominal distension diminished, and fever abated. On the evening of day 6 after administration of chemotherapy she was noted to be drowsy. Examination was normal apart from crepitations in both lower lungs. Over the next few hours she was more alert but later that evening she suddenly convulsed and became

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comatose. There were no localizing neurological signs. Investigation showed normal electrolytes, blood sugar, and a mild metabolic acidosis with normal PCO_2 . CSF showed no cells, protein 20 mg/100ml, sugar 45 mg/100ml. Chest x-ray showed patchy consolidation of right lower and middle lobes. Over the next 4 hours, during which time twitching of the right arm was observed, she again improved but later that night a sudden cardiorespiratory arrest occurred and she died.

Necropsy findings. There was evidence of haemorrhagic pneumonia from which *Staphylococcus aureus* was cultured. The brain was macroscopically normal with no evidence of subarachnoid haemorrhage or infiltration. Light microscope sections of medulla, cerebellum, thalamus, basal ganglia, and frontal cortex showed only moderate vascular congestion. In the pons the periaqueductal grey matter showed mild vacuolation and some neurons showed infolding of the nuclear membrane resulting in a notched appearance. The sections taken for electron microscopy were technically unsatisfactory and could not be interpreted.

Case 2. This child presented at the age of 3½ years with acute lymphocytic leukaemia. Apart from prolonged neutropenia the induction with vincristine (2 mg/m²) and prednisolone was uncomplicated. 6 months later she was given craniospinal radiotherapy (3000 rads) because of leukaemic involvement of the central nervous system. 9 months after initial presentation she relapsed and reinduction with vincristine (2 mg/m²) and prednisolone was started. 4 days after the first dose of vincristine she was admitted to hospital with fever, vomiting, headache, and bone pain. Full blood examination showed Hb 11.4 mg/dl, total white cell count 400/mm³, and platelets 10 000/mm³. She was treated with intravenous antibiotics though all cultures were subsequently sterile. Melaena occurred that same evening and the following day a grand mal convulsion. Electrolytes taken at that time showed serum sodium 122 mEq/l, potassium 3.4 mEq/l, and urea 15 mg/100ml. Plasma and urine osmolalities were not performed as the significance of this syndrome was not appreciated.

She was treated with 0.5 mol/l saline and dextrose replacement but this resulted in considerable fluid overload. The abdomen remained distended and she passed frequent loose motions. A second injection of vincristine was given one week after the first but she remained leucopenic, gradually deteriorated, and died 14 days after the first injection of vincristine.

Necropsy findings. The brain was macroscopically normal with no signs of leukaemia or haemorrhage. Microscopically the brain showed mild gliosis in the medulla and pons with neurons in the frontal cortex, thalamus, and hypothalamus showing chromatolysis, shrinkage, and pyknosis. Mild cirrhosis of the liver

was present. The bowel was distended and 20 cm of ileum was gangrenous. Lymphoid tissue was depleted, though the marrow was well populated with microscopically normal cells.

Case 3. A boy presented with a thoracic neuroblastoma with no evidence of distant metastases at the age of 11 months. After partial laminectomy chemotherapy with a single dose of intravenous vincristine (1.5 mg/m²), vinblastine (6.5/m²), and cyclophosphamide (350 mg/m²) was started.

Six days after beginning chemotherapy the fever suddenly exacerbated and blood examination showed Hb 10.3 g/dl, total white cell count 900/mm³, with 90 neutrophils/mm³, and platelets 480 000/mm³. Blood cultures were taken (subsequently sterile) and antibiotic therapy with gentamicin and cephaloridine was begun. Abdominal distension became marked over the next 12 hours and a plain x-ray of the abdomen confirmed the diagnosis of paralytic ileus. 8 days after chemotherapy three grand mal convulsions occurred followed by a respiratory arrest from which he was resuscitated. Blood chemistry at this stage showed serum sodium 118 mEq/l, calcium 8 mg/100ml, urea 26 mg/100ml, glucose 171 mg/100ml, with normal liver function tests. Initial correction of the hyponatraemia with hypertonic saline (3%) was attempted but the child became hypertensive while remaining oliguric. The subsequent course was one of steady improvement. No further chemotherapy has been given and the child remains well and free of tumour after irradiation.

Case 4. A boy presented at the age of 10 years with an embryonal rhabdomyosarcoma of the nasopharynx with brain stem involvement. He was treated with irradiation and chemotherapy, using intermittent courses of vincristine (2 mg/m²) on days 1 and 8, actinomycin D (0.5 mg/m²) on days 1, 3, 5, and 8, with cyclophosphamide (10 mg/kg twice weekly) between courses. With this therapy his cranial nerve signs resolved and there was no clinical or biopsy evidence of remaining tumour.

Four days after completion of the seventh course of chemotherapy (21 months after starting treatment) he was admitted to hospital with headache, low grade fever, abdominal pain, and vomiting. Clinical examination was normal apart from mouth ulceration and mild abdominal distension. Blood examination showed Hb 13.2 g/dl, total white cell count 1800/mm³ with 216 neutrophils/mm³, and a normal platelet count. Initially the clinical state improved and he became afebrile. On day 8 after chemotherapy he became drowsy and several hours later convulsed. Electrolytes were normal and blood cultures sterile. CSF was normal and the electroencephalogram findings were suggestive of diffuse encephalopathy. After this convulsion he steadily improved and was eventually discharged. Subsequently he tolerated further courses of chemotherapy at a dose of vincristine of 1.5 mg/m².

Discussion

The clinical features in these 4 patients represent a recognizable pattern of bone marrow toxicity followed by abdominal distension, hyponatraemia, and convulsions. This combination of neural and bone marrow toxicity is characteristic of vincristine (Slater *et al.*, 1969). In one patient actinomycin D was associated with a similar spectrum of side effects but vincristine was administered concurrently. This spectrum of side effects was not associated with any of the other chemotherapeutic agents administered to our patients. Infection was presumed to be present in all cases, though only in Case 1 was there any evidence to substantiate its presence. Inexplicable neurological complications of tumours, though well documented in adults (Posner, 1971) seldom occur in children. There was no clinical evidence of tumour invasion of the central nervous system in any patient and likewise the necropsy findings in 2 patients did not show tumour in the central nervous system.

The detection of haematological toxicity depends largely on the timing of a blood examination. Neutropenia and thrombocytopenia were present by day 4 in 3 patients, and 48 hours after vincristine plus actinomycin D in Case 1. Blood examinations were not performed daily and it is possible that haematological manifestations of toxicity may have been evident before 4 days in all the patients. Abdominal distension with symptoms and signs of paralytic ileus occurred between days 4 and 7. Vincristine therapy is frequently complicated by abdominal pain, though paralytic ileus only occasionally occurs (Sandler, Tobin, and Henderson, 1969). The ileus present in 3 of our 4 patients seems to represent one aspect of a generalized neurotoxic reaction to vincristine.

Hyponatraemia was present in 3 patients. The high urine osmolality in Case 1, the absence of clinical evidence for a reduced extracellular fluid volume, and the clinical response of Cases 2 and 3 to a saline load suggest an inappropriate secretion of ADH and this has been shown to occur with repeated vincristine injections in some patients (Stuart *et al.*, 1975). Convulsions occurred between days 6 and 8 in all patients. This and coma have been the cardinal signs of nondose-related vincristine neurotoxicity in other reports. Hyponatraemia was present at the time of the convulsion in Cases 2 and 3. In 4 patients described by Johnson *et al.*, (1973) and in 2 described by Whittaker *et al.* (1973), central nervous system manifestations occurred in the absence of hyponatraemia. Hyponatraemia was not present in Case 4 at the time of convulsion though the electroencephalogram suggested that

a diffuse encephalopathy was present. Cardio-respiratory arrest followed convulsions in Cases 1 and 3, proving fatal in Case 1.

An explanation for this widespread idiosyncratic neurotoxic reaction to vincristine encompassing paralytic ileus, inappropriate ADH secretion, and convulsions is suggested by Shelanski and Wisniewski (1969), who showed interference by the drug with the neurotubular system of the axon with proliferation of neurofilaments. This disruption of axonal flow caused an initial physiological disturbance of the axon followed by axonal degeneration, and finally an axonal reaction occurred in the nucleus. The time taken for this axonal reaction to occur varied, but with severe injury initial light microscope changes were present by 48 hours, and maximal changes were present by 12 days. 2 of our patients died 6 and 14 days after injection of vincristine and actinomycin D and of vincristine alone. Death was directly due to bronchopneumonia in Case 1 and haemorrhage and infection due to gangrenous bowel in Case 2. The necropsy changes in the brain of Case 1 showed no evidence of proliferation of neurofilaments or axonal degeneration as described by Shelanski and Wisniewski (1969). This suggests that at least in this patient the toxic effects of therapeutic doses of vincristine on the brain were subtle and not associated with histological evidence of neuronal damage at the time that the clinical symptoms were apparent. Neuronal changes were present in Case 2, but there was no light microscope evidence of neurofibril proliferation, and the pattern of the changes was similar to that caused by anoxia. The lack of histological damage to the brain is consistent with the clinical experience that this syndrome is usually reversible and does not recur with subsequent administration of vincristine.

Although severe nondose-related vincristine toxicity is rare, it is necessary to be aware of the constellation of symptoms, signs, and laboratory findings. It is wise to anticipate inappropriate ADH secretion and convulsions when haematological side effects and marked abdominal distension develop after administration of a usually nontoxic dose of vincristine.

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