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Short communication

Accidental actinomycin D overdosage in man, a case report

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Summary. Although actinomycin D is a relatively old cytotoxic agent, relatively little is known about its toxicity in man in comparison with some of the newer cytotoxic agents that have been extensively investigated. We wish to describe a case where an overdose of actinomycin D was inadvertently administered.

Case report

The patient is a 17-year-old Caucasian male who initially presented at the age of 14 with a left ophthalmoplegia. This was found to be due to an orbitobasal pleomorphic rhabdomyosarcoma. Treatment was carried out with chemotherapy and radiotherapy, and although he has considerable neurological weakness (left hemiparesis, blindness in the left eye, bilateral ptosis), he is of normal intelligence. His chemotherapy consisted of vincristine and cyclophosphamide every 4 weeks with alternating actinomycin D and doxorubicin (IRS III 36 regimen). He also receives phenobarbitone (45 mg twice daily), amitryptiline (25 mg twice daily) and folic acid (5 mg) daily. He was admitted for week 92 of his chemotherapy and received vincristine (1 mg), actinomycin D (2.5 mg) and cyclophosphamide (440 mg) with prophylactic mesna on the day of admission. He was given a further 1 mg dose of vincristine and 2.5 mg of actinomycin D 24 h later. Fortunately, the mistake was realised shortly after administration and all further chemotherapy (two further doses of cyclophosphamide) was discontinued. His weight and surface area at this time were 50.7 kg and 1.5 m^2, respectively, and he therefore received a total dose of 0.1 mg/kg (3.3 mg/m^2) of actinomycin D. The error was explained in full to the patient and his parents, and the following problems were encountered subsequent to the administration of the actinomycin D.

The patient had a generalised convulsion which responded to intravenous diazepam 48 h after the second dose of actinomycin D. Plasma biochemistry at this stage showed hyponatraemia, hypokalaemia, hypocalcaemia and hypomagnesaemia (128, 2.7, 1.83 and 0.44 mmol/l, respectively). No further convulsions occurred and the electrolytes were replaced by intravenous supplementation. The course of the plasma biochemistry is shown in Table 1. Excessive urinary magnesium loss was documented (magnesium:creatinine ratio, 3.88 and 1.25 on days 5 and 9, respectively; upper limit of normal 0.43) [3].

The patient developed considerable generalised oedema of all four limbs and the trunk. This was initially associated with an intense erythema (radiation recall) which then developed into superficial peeling and associated ulceration of the gastrointestinal tract. Several bullae developed in particular on the left arm, which was the most oedematous and tender limb. Over several days the erythema changed to a purpuric rash in association with his profound thrombocytopenia. He received platelet transfusions from days 4–16. His platelet count did not exceed 100×10^9/l until 6 weeks after the actinomycin D.

Table 1. Blood count and plasma biochemistry

Day	Hb g/dl	Neut $\times 10^9$/l	Platelets $\times 10^9$/l	Na mmol/l	K mmol/l	Ca mmol/l	Mg mmol/l	ALT IU/l	Prot g/l
0	14.2	3.9	130	137	3.3	–	–	66	71
2	13.6	4.0	103	128	2.7	1.83	0.44	58	66
4	12.2	4.9	40	131	2.8	2.02	0.67	47	60
6	9.9	4.9	15	133	3.3	2.01	0.75	82	61
8	14.4*	5.9	15	132	3.5	2.24	0.64	111	61
10	14.0	1.6	17	134	3.0	2.15	0.62	–	–
12	12.2	0.14	20	138	3.1	1.89	0.81	150	65
14	12.4	0.03	57	140	2.9	2.01	0.63	91	62
16	12.6	0.2	51	143	2.3	1.92	0.53	–	–
18	13.7	1.1	45	134	4.0	2.02	0.43	–	–
21	14.6	4.4	40	137	3.3	2.31	0.53	–	–

* Transfusion of packed red blood cells

Severe oral mucositis and profuse diarrhoea (day 9 to day 21) resulted in the need for parenteral nutrition. Associated with the neutropenia, the patient became febrile 3 days after the administration of the second dose of actinomycin D and was commenced on intravenous antibiotics. His full blood count and plasma biochemistry are shown in Table 1. He was discharged after a total of 3 weeks in hospital and has since remained well, having completed his chemotherapy without mishap.

Discussion

The myelosuppression of actinomycin D has been well documented in both children and adults [1, 2]. The major dose-limiting toxicity is mucositis primarily confined to the oral mucosa and severe dermatitis, often exacerbated by irradiation [1]. These effects were more marked in adult patients at 2.5 mg/m^2 than at 2.0 mg/m^2. Gastrointestinal symptoms (diarrhoea, nausea and vomiting) are all common during actinomycin D therapy. Hepatic dysfunction has been reported in a child following actinomycin D and irradiation but is relatively uncommon [4, 7].

Electrolyte abnormalities in man have not previously been reported with actinomycin D. They have, however, been extensively studied in animals, and falling plasma concentrations of sodium, potassium, calcium and chloride have all been documented [5, 8]. The mechanism involved is not fully understood but is thought to be due to a direct effect on DNA-dependent synthesis of RNA by aldosterone [6]. Plasma magnesium concentrations do not appear to have been studied in animals, but as the plasma magnesium is related to the calcium, one can anticipate the problem of hypomagnesaemia.

In conclusion, the problems encountered by this patient were: (a) bone marrow suppression, (b) diarrhoea, (c) mucositis, (d) oedema, (e) generalised rash and radiation recall, (f) electrolyte abnormalities, and (g) hepatic dysfunction.

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