Short report

Vidarabine encephalopathy

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SUMMARY Vidarabine (adenine arabinoside, ara-a) has been found to be useful in the treatment of various viral infections. Its adverse neurological effects include tremor and encephalopathy. Two cases of vidarabine encephalopathy are reported and the five other cases in the literature are reviewed. The clinical features of the tremor and encephalopathy are discussed.

Vidarabine (adenine arabinoside, ara-a) is an analogue of adenosine. It has been used to treat various viral infections, including herpes simplex, herpes zoster, hepatitis B and cytomegalovirus. Its most common toxic effects include nausea and vomiting, weight loss, weakness, megaloblastosis, tremor and thrombophlebitis. Although vidarabine encephalopathy has been reported in five patients,¹⁻⁴ its existence has not been well recognised in the literature. We recently treated two patients suffering from herpes zoster infections who became delirious while receiving vidarabine.⁵ We report these cases and review previous cases in the literature.

Case reports

Case 1 A 58-year-old man was admitted with the chief complaint of weakness of the right lower extremity. He had developed herpes zoster approximately five weeks previously with vesicles in the distribution of T4 on the right side. Approximately two weeks prior to admission he had developed another small crop of vesicles over the distribution of T8 on the right. Neurological examination revealed an alert, cooperative male who was oriented in all three spheres. There was slight weakness in the left lower extremity and severe weakness in the right lower extremity. Sensory examination showed that light touch, pain and temperature sensations were lost between T4 and T8 on

the right and below T4 on the left. Proprioception was absent below T4 on the right side. The ankle jerks were absent. There was a bilateral extensor plantar response. A diagnosis of herpes zoster myelitis was made. He was treated with corticosteroids but his condition continued to deteriorate. The corticosteroids were discontinued and treatment with vidarabine 15 mg/kg iv per day was started. The only other medications he received were paracetamol and flurazepam. Two days later the patient was found to be delirious. He was drowsy and when awakened appeared confused and out of touch with his environment. Laboratory investigations revealed no metabolic abnormality. The neurological examination remained unchanged except for his mental status. Treatment was stopped and the delirium resolved over the following 24 hours. Vidarabine was started again at 10 mg/kg iv per day for a further eight days, without adverse effects. The weakness began to improve about eight days after the commencement of treatment with vidarabine. He was discharged one month after admission with marked improvement. There was no evidence of renal failure or underlying malignancy.

Case 2 A 24-year-old woman was admitted with generalised cutaneous herpes zoster which had begun to develop 4-5 days prior to admission. The patient was known to have Stage III B nodular sclerosing Hodgkins disease and had been treated with 10 courses of chemotherapy. The last course was two months prior to admission. On admission the patient was alert, cooperative and oriented in all three spheres. The neurological examination was unremarkable, except for a mild peripheral neuropathy. Treatment was started with vidarabine 15 mg/kg per day and within several days the herpetic lesions began to resolve. She also continued to receive amitriptyline, diphenhydramine, pethidine, hydroxyzine and prochlorperazine. On the fifth day of treatment with vidarabine the patient was noticed to have a rapid tremor present upon action and intention. The amplitude of the tremor increased over the following four days. On the ninth day the patient developed auditory and visual hallucinations. Treatment

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Table Summary of cases

Case	Infection	Vidarabine dose	Renal failure	Symptoms	Age	Underlying cause	EEG	Reference
1	Herpes zoster myelitis	15 mg/kg/day	Absent	Delirium Confusion Disorientation	58	None	Not done	5
2	Generalised cutaneous herpes zoster	15 mg/kg/day	Absent	Tremor Hallucinations Confusion Delirium	24	Hodgkins disease	Diffuse Slowing	—
3	Herpes simplex encephalitis	15 mg/kg/day	Absent	Tremor Confusion Aphasia	33	None	Focal Slowing	1
4	Chronic hepatitis B infection	Not stated	Present	Tremor, Ataxia Disorientation Myoclonus, Fits Respiratory arrest	56	Hepatitis B	Diffuse Slowing	2
5	Generalised cutaneous herpes zoster	20 mg/kg/day	Absent	Aphasia Ataxia Disorientation	52	Hodgkins disease	Diffuse Slowing	3
6	Generalised cutaneous herpes zoster	20 mg/kg/day	Absent	Disorientation Tremor Aphasia	53	Squamous CA of larynx and Hodgkins disease	Diffuse slowing	3
7	Unspecified herpes infection	20 mg/kg/day	Not stated	Tremor Confusion	?	Not stated	Duffuse slowing	4

was discontinued on the tenth day when the patient became uncooperative, confused, delirious and severely tremulous. The neurological examination remained unchanged except for her mental status and the appearance of the tremor. Laboratory investigations revealed no metabolic abnormality. A computed tomographic scan and lumbar puncture done at the time revealed no abnormalities. An electroencephalogram (EEG) revealed "a moderately severe, diffuse disturbance of cerebral electrical activity". After discontinuation of vidarabine the patient's improved steadily and she was discharged within one week without neurological impairment.

Review of literature

We could find only five accounts in the literature of vidarabine encephalopathy (table). Nadel¹ reported the case of a 33 year-old woman (case 3) hospitalised for herpes simplex encephalitis. She received vidarabine at a dosage of 15 mg/kg/day. On the sixth day of administration, when she was receiving only vidarabine, she developed a movement disorder characterised by intermittent swaying of the body and slow, rhythmic, 3–4 HZ rotatory movements of the arms and legs. On the seventh day the movements increased and the patient developed a fixed stare and became aphasic. The electrolytes were within normal limits. An EEG showed pre-existing right temporal slowing. Vidarabine administration was stopped and within 24 hours the patient became talkative and more alert. Within one week the movement disorder had completely disappeared.

Sacks *et al*² reported the case of a 56-year-old patient (case 4) treated with vidarabine for chronic hepatitis B infection. The dosage was not stated.

The patient developed a tremor and ataxia and the treatment was stopped. Prerenal azotaemia had developed secondary to dehydration and despite cessation of vidarabine administration the patient suffered progression to disorientation, hallucinations, generalised myoclonus, major motor convulsions, and, eventually, recurrent respiratory arrests with respirator dependence. These symptoms were out of proportion to the patient's metabolic derangements. An EEG showed diffuse slowing. The patient recovered fully over four to six months.

Lauter *et al*³ described two cases. The first was a 52-year-old woman (case 5) with Stage IV B Hodgkins disease, who was hospitalised for generalised cutaneous herpes zoster. She was given vidarabine 20 mg/kg/day. On the eighth day of administration she developed difficulty speaking and seemed less aware of her surroundings. By the next morning, she was unable to answer even simple questions but could still respond to directions with movement of her eyes. On examination she was ataxic. An EEG showed a generalised dysrhythmia. Vidarabine treatment was discontinued and within 48 hours the patient was more alert. During the next six days the aphasia and ataxia disappeared. Their second case was a 53-year-old man (case 6) with squamous cell carcinoma of the larynx and Stage IV B Hodgkins disease. He was hospitalised with generalised cutaneous herpes zoster, and treated with vidarabine 20 mg/kg/day. On the tenth day of treatment he was less alert. By the eleventh day he was unaware of his immediate surroundings, had semi-rhythmic bilateral tremors of all extremities, and had become aphasic. His EEG showed generalised

disorganisation in the low-voltage theta range. Treatment with vidarabine was discontinued and the patient gradually became more alert and recovered fully.

Ross *et al*⁴ described the case of a patient (case 7) who developed an essential tremor between the fifth and seventh days of vidarabine therapy. The patient had an unspecified herpes virus infection and was treated with vidarabine at a dose of 20 mg/kg/day. The patient went on to become confused. An EEG showed diffuse slowing. The patient recovered spontaneously after discontinuation of vidarabine therapy.

Discussion

Vidarabine has been used increasingly in recent years to treat herpes zoster infections in immunocompromised hosts and to treat herpes simplex encephalitis. Reports of adverse experiences have been infrequent. Gastrointestinal side-effects are the most frequent, and appear to be dose-related. Tremor is the most commonly reported neurological side-effect. In most cases the tremor is indistinguishable clinically from benign essential tremor, being accentuated by action or intention and disappearing during sleep. The EEG in patients with vidarabine-induced tremor often reveals increased slow-wave activity. Vidarabine encephalopathy usually, but not invariably, occurs in patients already exhibiting tremor. Patients receiving beta-adrenergic blocking drugs for other reasons may fail to exhibit tremor during vidarabine toxicity. Since the EEG shows the same changes in patients with tremor, but normal levels of consciousness, as it does in vidarabine encephalopathy, one could argue that tremor is an early sign of vidarabine encephalopathy. This accords well with the fact that most patients who develop encephalopathy first develop tremor.

The encephalopathy consists of sub-acute onset over 24 to 48 hours of confusion, delirium and disorientation. It can be accompanied by hallucinations, both auditory and visual, aphasia, resembling a form of akinetic mutism, and ataxia. In patients with impaired renal function it can progress to include myoclonus, generalised tonic-clonic convulsions and respiratory arrest. Its incidence can be estimated to be between 3%⁴ and 22%,³ when doses of up to 20 mg/kg/day are employed. However, the effect appears to be dose-related and encephalopathy is much less common when doses of 15 mg/kg/day are administered. It has not been reported at 10 mg/kg/day and, in fact, our first patient (case 1), who developed encephalopathy on 15 mg/kg/day, did not subsequently show any

neurological toxicity on 10 mg/kg/day.

In patients who are receiving vidarabine and who develop impaired consciousness the differential diagnosis between vidarabine encephalopathy and neurological manifestations of the underlying illness may be difficult, especially in herpes simplex encephalitis.⁶ The presence of tremor should suggest the possibility of vidarabine encephalopathy. One obvious method of differentiation is discontinuation of vidarabine administration. In the absence of renal impairment, vidarabine encephalopathy begins to resolve quickly after cessation of vidarabine infusion. Lumbar puncture and electroencephalography are both of value. No abnormalities of the cerebrospinal fluid have been reported in vidarabine encephalopathy, therefore a normal lumbar puncture suggests the presence of vidarabine encephalopathy rather than an infection. The EEG shows diffuse slowing and is consistent with toxic or metabolic encephalopathy. It is important that every patient with suspected vidarabine encephalopathy be screened for electrolyte abnormalities. Since vidarabine is relatively insoluble in aqueous solution, it must be diluted in a large volume of fluid before infusion. The administration of large quantities of fluid intravenously may cause haemodilution with resulting hyponatraemia. This is not an uncommon cause of changing mental status in patients receiving vidarabine and is easily correctable.

The method by which vidarabine produces neurological effects is as yet unknown. The existence of adenosine pre-synaptic receptors in the central nervous system, which inhibit norepinephrine release, has recently been shown.⁷ Theophylline has been shown to block the pre-synaptic effects of adenosine. Since the neurotoxicity of vidarabine is very similar to that of theophylline and since vidarabine closely resembles adenosine in molecular structure, it might be reasonable to hypothesise that vidarabine in toxic doses acts as an adenosine antagonist at pre-synaptic receptors in the nervous system.

Because of the risk of developing encephalopathy, patients receiving vidarabine should be watched closely for the development of tremor, decreased level of consciousness or renal impairment. If these develop, the dose should be reduced or administration should be discontinued. Physicians prescribing vidarabine should be cognisant of the existence of a specific encephalopathy, lest they assume incorrectly that deterioration in their patients' mental state is due to underlying disease.

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