Original articles**Vitamin E treatment of haemolytic uraemic syndrome**

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SUMMARY Because low plasma vitamin E concentrations have been reported in patients with haemolytic uraemic syndrome and there is accumulating evidence of lipid peroxidation in this disease, treatment with the antioxidant vitamin E was undertaken in 16 consecutive children with the syndrome. Twelve children had features at presentation suggesting a poor prognosis for recovery but despite this all 16 patients survived and are well three months later. Fifteen children now have normal values for serum creatinine, blood pressure, and urinalysis for protein but one has slight renal impairment. Although this is not a report of a controlled trial, it seems that patients treated with vitamin E have fared considerably better than our previously treated patients with haemolytic uraemic syndrome, even in the presence of early, adverse prognostic features. We suggest that vitamin E alters the natural history of the disease, and in view of the absence of any observed side effects further experience with this treatment is being sought.

Haemolytic uraemic syndrome is a disease of unknown aetiology and substantial mortality and morbidity.^{1 2} Many different forms of treatment have been suggested including heparin,³ streptokinase,⁴ antithrombotic agents,^{4 5} plasma,⁶ and measures to induce prostacyclin formation⁷ but none have proved beneficial. Adequate controlled studies of any of these treatments are lacking and would be difficult to carry out because of the small numbers of patients and large differences in outcome in different centres. Any new treatment, therefore, would need to produce a substantial improvement in outcome compared with previous results to be generally accepted as effective. We describe another approach to the treatment of haemolytic uraemic syndrome directed at offsetting the effects of lipid peroxidation in this disease. The early results are encouraging.

A defect in prostacyclin (epoprostenol) production has been proposed as a pathogenetic mechanism in haemolytic uraemic syndrome.^{6 7} The observation that, unlike normal plasma, plasma from patients with haemolytic uraemic syndrome failed to stimulate prostacyclin production from exhausted rat aortic rings⁶ suggested a deficiency of a factor which normally stimulates this. Such an abnormality in the plasma of patients with haemolytic uraemic syndrome has recently been ascribed,

however, to the presence of an inhibitor of the vessel wall enzyme, prostacyclin synthetase.⁸ Certain lipid peroxides inhibit this enzyme^{9 10} and although these very unstable compounds have not yet been conclusively shown in the plasma of patients with this syndrome, phospholipid changes suggestive of peroxidative damage have been described in red blood cells¹¹ and the inhibitor in the plasma of patients with haemolytic uraemic syndrome has biochemical characteristics of peroxides of polyunsaturated fatty acids.⁸

Vitamin E (alpha tocopherol) is a biological antioxidant that inhibits lipid peroxidation¹² and low plasma concentrations of vitamin E have been found in some patients with haemolytic uraemic syndrome.¹¹ We report the results of a pilot study of vitamin E treatment in children with haemolytic uraemic syndrome in Australia and the United Kingdom.

Patients and methods

Sixteen children suffering from haemolytic uraemic syndrome were treated with vitamin E at the Royal Children's Hospital, Melbourne, the Children's Hospital, Birmingham, and the Royal Children's Hospital, Brisbane. All had a typical acute illness with preceding diarrhoea, microangiopathic

Table 1 Findings at presentation in 16 children with haemolytic uraemic syndrome

Case no	Age (yrs)	Sex	Blood pressure (mm/Hg)	Haemoglobin (g/dl)	Platelet count ($\times 10^9/l$)	Blood urea (mmol/l)	Serum creatinine (mmol/l)	Plasma vitamin E ($\mu\text{mol/l}$)
1	6.4	M	115/60	6.4	70	49.7	0.73	46
2	1.7	M	100/70	5.9	15	24.0	0.11	56
3	5.9	F	125/65	4.8	20	47.0	0.80	51
4	0.6	F	90/40	4.6	20	33.0	0.73	48
5	2.0	M	130/80	6.3	6	31.8	0.52	—
6	7.2	F	140/85	8.2	89	65.4	1.12	26
7	1.9	F	120/80	6.9	66	64.8	0.56	—
8	7.8	M	130/90	3.0	69	53.6	1.19	17
9	2.3	F	130/110	5.9	62	31.9	0.67	—
10	5.5	M	110/80	6.7	68	69.0	1.13	17
11	1.7	F	100/60	9.6	84	23.0	0.47	—
12	11.8	F	110/80	7.9	64	32.0	0.20	—
13	1.2	M	110/70	6.6	91	11.4	0.07	—
14	1.7	M	115/85	4.5	70	64.0	0.92	16
15	0.8	F	120/95	5.9	50	63.0	0.94	9
16	1.9	F	140/90	6.8	71	39.8	0.62	46

Conversion—SI to traditional units: blood urea 1 mmol/l (≈ 6.0 mg/100 ml); serum creatinine 1 mmol/l (≈ 0.88 mg/100 ml); plasma vitamin E 1 $\mu\text{mol/l}$ (≈ 0.04 mg/100 ml).

haemolytic anaemia, thrombocytopenia, and acute renal failure (Table 1). Six children were aged over 4 years and 14 were oliguric. Eleven required dialysis, 10 being oliguric for one week or more. Plasma vitamin E concentrations were measured by the fluorometric method of Hansen and Warrick¹³ in 10 patients at presentation, the lower limit of the normal range being 11 $\mu\text{mol/l}$.

As this was a pilot study all patients received vitamin E from presentation and no attempt was made to control other forms of treatment, which were determined by the individual physicians. Six children were given heparin for two weeks but none were given streptokinase, aspirin, dipyridamole, or plasma exchange transfusion. Vitamin E was given orally in a dose of 1000 mg/m²/day and continued for at least one week.

To assess the results of vitamin E treatment of haemolytic uraemic syndrome, a comparison was made with the outcome in patients treated at the Royal Children's Hospital, Melbourne in the 20 years before 1981 when vitamin E began to be used. Over this time heparin, streptokinase, aspirin, dipyridamole,⁴ and intravenous fat emulsion,⁷ have been used alone or in various combinations.

Results

Plasma vitamin E concentrations at presentation were within the normal range in 9 of the 10 children tested (Table 1). After one week of treatment concentrations of 48 to 79 $\mu\text{mol/l}$ were recorded.

All patients survived and are well three months after presentation. All but one patient have normal values for serum creatinine, blood pressure, and urinalysis for protein and blood. The course of the illness is shown in Table 2. The one patient (case 16)

Table 2 Course of haemolytic uraemic syndrome in 16 children given vitamin E

Case no	Duration of oliguria (days)	Status 3 months after presentation		
		Serum creatinine (mmol/l)	Blood pressure (mm Hg)	Proteinuria (Albustix)
1	1	0.05	110/70	Neg
2	0	0.03	90/60	Neg
3	7	0.04	115/75	Neg
4	12	0.04	80/50	Neg
5	6	0.04	90/65	Neg
6	7	0.07	100/60	Neg
7	7	0.04	95/60	Neg
8	7	0.06	110/70	Neg
9	2	0.04	90/55	Neg
10	30	0.05	120/80	Neg
11	7	0.06	90/60	Neg
12	5	0.06	105/60	Neg
13	0	0.04	90/60	Neg
14	7	0.04	85/50	Neg
15	8	0.06	110/70	Neg
16	12	0.10	105/80	+++

with proteinuria and a slightly raised serum creatinine concentration had an area of tissue infarction which was found at renal biopsy performed soon after presentation, indicating the likelihood of permanent impairment of renal function. This patient's serum creatinine concentration (0.10 mmol/l) three months later compares with the upper limit of normal of 0.06 mmol/l for her age.

Comparison of the results of treatment with vitamin E with those of other forms of treatment (Table 3) shows that patients treated with vitamin E have a substantially better outcome. Statistical comparison of treatment groups is not justified, however, as we are comparing current results with those obtained from a retrospective study over many years.

Table 3 Comparison of vitamin E treatment with results of other treatment regimens for haemolytic uraemic syndrome at Royal Children's Hospital Melbourne

Treatment*	Total no of cases	Deaths during acute illness	Renal impairment failure at follow up	Normal at follow up
Symptomatic only	22	9	5	8
Heparin	44	11	11	22
Streptokinase and either dipyridamole or aspirin, or both	12	2	4	6
Intralipid	10	2	3	5
Vitamin E	16	0	1	15

*All patients were given blood transfusion, dialysis, and antihypertensive treatment as required.

Discussion

Use of vitamin E in the treatment of haemolytic uraemic syndrome was suggested by the report of low vitamin E concentrations in some patients with this disease and was supported by the finding of evidence of lipid peroxidation in the red cell membranes of patients with haemolytic uraemic syndrome.¹¹ Vitamin E deficiency impairs prostacyclin production in rats¹⁴ and in man,¹⁵ and the Schwartzman reaction, an animal model of thrombotic microangiopathy, can be induced in vitamin E deficient rats fed oxidised lipid.¹⁶

Perico *et al* suggested that plasma from patients with thrombotic microangiopathy may have reduced antioxidant potential favouring selective inhibition of prostacyclin synthetase.¹⁷ Probably because of their chemical similarity to the cyclic endoperoxides of arachidonic acid, the linear peroxides, 15-hydroperoxyarachidonic acid and 13-hydroperoxylinoic acid, are potent inhibitors of prostacyclin synthetase.^{9, 10} We have recently identified substances with the gas chromatographic characteristics of these two lipid peroxides in the red cell membranes of two patients with haemolytic uraemic syndrome. If confirmed, the presence of these substances would help explain the proposed deficiency of prostacyclin⁶ and the finding of an inhibitor of prostacyclin production⁸ in this disease.

The reason for lipid peroxidation in haemolytic uraemic syndrome remains unknown as vitamin E deficiency would seem unlikely in most cases. Lack of other antioxidants such as selenium and glutathione or reduced activity of the enzymes superoxide dismutase or peroxidase may be important. There is good evidence that vitamin E is an effective antioxidant, stabilising unsaturated lipids against autooxidation and this protective action occurs *in vivo*. Therefore, although vitamin E plasma concentrations are not always low in haemolytic uraemic syndrome, it seems reasonable to attempt to reduce lipid peroxidation by giving vitamin E in large doses to children with this syndrome.

It has also been suggested that vitamin E by interacting with phospholipids in membranes may facilitate molecular packing and thus maintain the stability of biological membranes and increase resistance to haemolysis.¹⁸ Treatment with vitamin E, however, seems to have no noticeable effect on the early course of haemolytic uraemic syndrome and the duration of haemolysis, oliguria, and thrombocytopenia was not reduced in the treated patients. This may be attributable to the slow rise in plasma vitamin E concentrations after oral administration.¹²

Tune *et al*¹⁹ stressed the regional differences in mortality and morbidity rates of the haemolytic uraemic syndrome and the consequent difficulties in comparing results from different centres and in mounting large controlled trials. For this reason we have compared outcome in patients treated with vitamin E with outcome in patients treated by other means at the Royal Children's Hospital, Melbourne, though the validity of such a retrospective comparison is limited. The facts that no patients treated with vitamin E died and that evidence of renal damage at three months follow up was rare are very encouraging. The biopsy evidence of glomerular necrosis in the one patient who still has a slightly raised serum creatinine concentration suggests that irreversible tissue damage may have occurred before treatment was started.

Those patients who are older than 4 years at presentation or are oliguric for 7 or more days have a worse outcome than other patients with haemolytic uraemic syndrome.^{2, 20} As 12 of the patients treated with vitamin E had these adverse prognostic features the results in this group in particular suggest that treatment altered the natural history of the disease.

At present the results of treatment with oral vitamin E (1 g/m²/day) seem substantially better than those of other treatments and in view of the absence of any observed side effects it seems reasonable to use this treatment to determine if the initial good results are confirmed with wider experience. Because of the difficulty in mounting

controlled trials in haemolytic uraemic syndrome the true efficacy of vitamin E will be hard to assess but studies of prostacyclin generation and lipid peroxidation during treatment may well produce evidence supporting the use of vitamin E in this disease.

The authors thank Dr R H R White and Dr M Winterborn of Birmingham for permission to study their patients.

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Received 23 January 1984