Discussion

Because some patients on anticonvulsant drugs have low levels of serum folate^{1, 2, 8} and red cell folate⁹ most investigators have assumed that the macrocytosis that may develop in such patients is caused either by folate deficiency or by some interference with folate metabolism. The mechanisms that have been proposed to explain the low serum and red cell folate levels include (a) an inadequate dietary intake of folate compounds, (b) an impaired absorption of folate monoglutamate from the diet,¹⁰⁻¹² (c) an impaired absorption of dietary folate polyglutamate as a consequence of the inhibition of folate conjugase by the drug(s),¹³⁻¹⁵ (d) displacement of folate compounds from their carrier plasma proteins by the drug(s),⁸ (e) interference with the formation and function of intracellular folate coenzymes as a result of a structural similarity between folate coenzymes and anticonvulsant drugs,^{1, 16} and (f) increased utilisation of folate in the liver as a consequence of the involvement of folate coenzymes in the detoxification of anticonvulsant drugs.⁹

Nine of the treated epileptics with megaloblastic erythropoiesis studied by us (including four patients with high MCVs) gave normal results in the deoxyuridine suppression test. Therefore, neither folate deficiency nor an interference with the 5, 10-methylenetetrahydrofolate-dependent methylation of deoxyuridylate to thymidylate could be implicated in the pathogenesis of the macrocytosis and megaloblastic changes in these nine patients.

The results in cases 11 and 13 indicate that the bone marrow cells of some patients on anticonvulsant drugs do suffer from an abnormality in the methylation of deoxyuridylate. In case 13 this abnormality was partially corrected by the addition of 10 µg pteroylglutamic acid per ml of marrow culture. As this concentration of pteroylglutamic acid corrects the abnormal deoxyuridine suppressed value in folate-deficient patients,⁷ and as the bone marrow cells in case 13 gave a normal deoxyuridine suppressed value after one month on an improved diet, it is likely that the abnormality in the methylation of deoxyuridylate detected in this case was caused by a dietary folate deficiency. The addition of 10 µg pteroylglutamic acid per ml of marrow culture did not correct the abnormal deoxyuridine suppressed value in case 11, suggesting the possibility of some drug-induced interference with the methylation of deoxyuridylate. The elucidation of the mechanisms underlying the abnormal deoxyuridine suppressed values that are occasionally encountered

in patients on antiepileptic drugs will require a study of a much larger group of treated epileptics.

The two patients giving abnormal results in the deoxyuridine suppression test had low red cell folate levels. Two other patients with low red cell folate levels (cases 2 and 14), however, gave normal results in the test. This discrepancy is reminiscent of the previously reported failure of most treated epileptics with low serum folate levels to excrete abnormal amounts of formimino-glutamic acid (figlu) in their urine after a loading dose of histidine.^{1, 17} Apparently the two folate-dependent metabolic steps investigated by the deoxyuridine suppression test and the figlu excretion test are sometimes unimpaired in treated epileptics, even when their serum and red cell folate levels have fallen below normal. The explanation for this is uncertain.

The megaloblastic changes and macrocytosis in patients giving normal results in the deoxyuridine suppression test are presumably caused by a direct effect of the anticonvulsant drugs or their metabolites on some biochemical step(s) other than the conversion of deoxyuridylate to thymidylate.

We thank Dr C H Edwards and Sir Roger Bannister for permission to study patients under their care.

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Continuous positive airway pressure and mechanical ventilation by facemask in newborn infants

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Summary

During a nine-month period 24 newborn infants were treated with continuous positive airway pressure (CPAP)

or mechanical ventilation delivered through a facemask. The mask was held in place in a way that minimised trauma and distortion of the head. The median birth weight of the infants was 1096 g and their median gestational age 29 weeks. The usual reason for treatment was hyaline membrane disease or recurrent apnoea due to inadequate control of breathing. Twenty-one of the infants survived. The technique was simple to apply and complications were minimal. We suggest that it may have advantages over other methods of applying CPAP or mechanical ventilation to infants mildly affected by respiratory illnesses and that it should be useful in avoiding endotracheal intubation or reducing the length of time that infants with more serious illnesses are intubated.

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Introduction

Continuous positive airway pressure (CPAP)¹ and mechanical ventilation are widely used for newborn infants with serious respiratory difficulties, particularly hyaline membrane disease and apnoea due to inadequate control of breathing. Infants with severe pulmonary illnesses usually require endotracheal intubation, but this has its dangers, such as trauma to the upper airway and problems with the removal of secretions. It is therefore important to dispense with the tube when possible. Various methods of applying CPAP include pressurised head-boxes,^{1,2} plastic bags over the head,³ nasal cannulae,⁴⁻⁶ and facemasks.⁷ Mechanical ventilation has also been applied through facemasks,^{8,9} and negative-pressure tanks have been used both for maintaining lung inflation during spontaneous breathing^{10,11} and for mechanical ventilation.^{10,12,13}

All these techniques have disadvantages. Head-boxes, plastic bags, and negative-pressure tanks make access to the infant difficult, and unless special care is taken the neck seal may obstruct cerebral venous return.¹⁴ Nasal cannulae are, in our experience, difficult to fix, and distortion of the nose and septal ulceration may occur.^{4,6} Facemasks may cause oedema of the face, and the strap used to hold them on may cause serious moulding of the head and cerebellar haemorrhage.^{8,9,15} Our method of holding a mask in place and applying CPAP and mechanical ventilation through it avoids these hazards. Because the method is simple and seems to be virtually without complications we here report our experience with it over nine months.

Methods

The facemask used was the Bennett infant mask, Nos 1-4, as used by Swyer *et al.*⁹ Usually a size was selected that fitted round the chin and upper part of the nose without pressing on the eyes. Occasionally a good fit could not be obtained in this way and a larger mask was applied round the forehead and chin. The mask was held in place with a piece of tubular elastic netting 8-10 cm long (Netelast C or D, depending on the size of the head) stretched over the whole head (see fig). The edge of the mask was lifted periodically so that the pharynx could be cleared of secretions.

When CPAP was used a continuous flow of warmed humidified gas was passed through the mask at 4-8 l/min to a water manometer, expiratory resistance being provided by a 500-ml anaesthetic bag with a screw clamp on its outlet for varying the CPAP.¹ The pressure was 5-7 cm H₂O initially for hyaline membrane disease, and it was subsequently varied to maintain an arterial oxygen tension (Pao₂) of about 8-6 kPa (65 mm Hg). Pressures above 10 cm H₂O were not used.

Mask CPAP being applied to infant weighing 734 g at 29 weeks of gestation. A No 1 Bennett infant facemask and Netelast tubular elastic netting were used. Tape coming from under mask was for fixing feeding tube.

For apnoea due to inadequate control of breathing a pressure of 3-4 cm H₂O was selected.⁶ When mechanical ventilation was required a Bennett PR2 or Drager Spiromat 661 ventilator was employed, the initial settings being usually as follows: peak airway pressure 12-15 cm H₂O, end-expiratory pressure 0-2 cm H₂O, respiratory frequency 30-40/min, and inspiration:expiration ratio 1:2. These settings were altered as necessary to regulate Pao₂ and Paco₂. When gastric distension developed, an open-ended 5F feeding tube was passed.

Infants

Twenty-four infants (13 boys and 11 girls) were treated between 1 November 1974 and 31 July 1975. Twenty received mask CPAP, and 11 mask ventilation. Their median birth weight was 1096 g (range 638-2440 g) and their median gestational age 29 weeks (range 26-36 weeks). Nineteen were suffering from hyaline membrane disease, 10 from apnoea due to inadequate control of breathing, and two were hydropic from rhesus haemolytic disease.

The indication for starting mask CPAP in 10 infants with deteriorating hyaline membrane disease was a Pao₂ less than 8-0 kPa (60 mm Hg) while the infant was breathing a fractional inspired oxygen (FIO₂) greater than 0-6. Five infants recovering from this illness who had been intubated for CPAP or mechanical ventilation were extubated and mask CPAP was substituted when their Pao₂ was above 8-0 kPa with an FIO₂ of 0-6-0-8 and relatively low inflating pressures (CPAP ≤7 cm H₂O; ventilator settings: peak airway pressure ≤20 cm H₂O, end-expiratory pressure ≤3 cm H₂O, inspiration:expiration ratio ≤1:1.) Six infants with apnoea due to inadequate control of breathing were treated with mask CPAP because they needed peripheral stimulation about five times an hour to prevent apnoea.

Mask ventilation was employed in 11 infants with normal or recovering lungs who could not sustain adequate spontaneous ventilation. Five of these infants were weaned from mask ventilation with mask CPAP.

Results

Details of treatment were entered, at the time they were obtained, into a PDP 11/45 computer by means of a keyboard in the neonatal unit. These details were processed by the computer, and values for the age when treatment was started and stopped are given in the table.

Age when CPAP or mechanical ventilation (MV) by facemask was started and stopped and total duration of treatment. Each infant received between 1 and 26 (median 1) episodes of treatment with CPAP and MV

	CPAP (n = 20)	MV (n = 11)
Mean age at start (range)	91 h (3 h-14 d)	8 d (8 h-37 d)
Mean duration of treatment (range)	96 h (4 h-20 d)	42 h (1 h-156 h)
Mean age at finish (range)	11 d (13 h-51 d)	15 d (49 h-51 d)

The following mean values (weighted when indicated) were obtained for other variables. During mask CPAP the inflating pressure was 3-7 cm H₂O, FIO₂ 0-52, Pao₂ 10-4 kPa (78-1 mm Hg), and Paco₂ 9-0 kPa (67-8 mm Hg). During mask ventilation the peak airway pressure was 12-4 cm H₂O, end-expiratory pressure 0-3 cm H₂O, respiratory frequency 43-8 cycles/min, inspiration:expiration ratio 0-8:1, FIO₂ 0-57, Pao₂ 10-5 kPa (79-2 mm Hg), and Paco₂ 9-6 kPa (72-5 mm Hg). The Pao₂ was easy to control, and though hypercapnia was common, it was usually not progressive, so that intubation could be avoided.

Three of the infants died, two from intraventricular haemorrhage and one (whom we were unable to wean from an endotracheal tube) from airway obstruction after tracheostomy for laryngeal oedema. Complications during treatment were few. One infant with hyaline membrane disease developed bilateral pneumothoraces while receiving a CPAP of 5 cm H₂O. Ten infants developed slight gastric distension, usually when they were being ventilated with a peak airway pressure above 12 cm H₂O or when a CPAP or more than 5 cm H₂O was being used. Partly because of this distension and partly because we did not wish to overload the stomachs of very pre-term infants being weaned from ventilatory aids, nine infants were fed parenterally¹⁶ and their oral feeding was stopped or curtailed. None of the infants had any evidence of adverse pulmonary sequelae at follow-up.

Discussion

The method of holding the facemask on was simple and the mask could be quickly placed in position or removed. It was easy to change from mask CPAP to mask ventilation. The problems previously encountered with the fixation of masks⁹⁻¹⁵ seemed to have been avoided. No facial oedema necessitating repositioning of the mask or distortion of the head occurred, presumably because the pressure holding the mask against the face was evenly distributed around the head. Complications of the technique were minimal. Gastric distension was never severe, but we suspect that it might have been had higher lung-inflating pressures been used. Undetected vomiting and aspiration is a theoretical risk, but so far as we are aware it never occurred. We suggest that this technique may have advantages over other methods of applying CPAP or mechanical ventilation to infants mildly affected by respiratory illnesses and that it should be useful in avoiding endotracheal intubation or reducing the length of time that infants with more serious illnesses have to be intubated.

We are grateful to the staff of the neonatal unit for their devoted care of the infants, and to Mr C A N Evans for the photograph.

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Effects of "natural oestrogen" replacement therapy on menopausal symptoms and blood clotting

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Summary

In a double-blind study on the value of equine ("natural") oestrogens 30 patients presenting with menopausal symptoms in a group practice were monitored for possible adverse effects on blood clotting, weight, and blood pressure. The women were randomly allocated to two groups and given either three months' hormone treatment followed by three months' placebo or vice versa.

An appreciable amelioration of all symptoms on placebo made it difficult to assess the genuine value of oestrogen treatment during the period of study. Both groups made a dramatic clinical improvement during the first three months. Nevertheless, the symptoms of the 15 women who received oestrogen first returned after the cross-over to placebo without any suggestion of a placebo response. In contrast, the other group who took placebo first did not deteriorate after changing to oestrogen.

The menopausal index and the karyopyknotic index were not reliable guides to the need for oestrogen treatment. Hot flushes, however, were proportionately reduced on oestrogen and they seemed to be more readily

eliminated in individual cases by oestrogen. The results of blood clotting studies indicated that natural oestrogen administration raised the levels of the extrinsic clotting factors VII and X and accelerated the prothrombin time. The findings were similar to those observed after three months' synthetic oestrogen administration with oral contraception.

Long-term studies and epidemiological surveys of the clinical incidence of thrombotic and other sequelae are needed before large-scale oestrogen replacement treatment can be recommended.

Introduction

So-called "natural" oestrogens have been widely used in the treatment of menopausal symptoms, and long-term treatment is recommended by many workers.¹⁻² It is, however, important to decide whether this treatment is both effective and safe. The use of the term "natural" for oestrogens prepared from equine urine is questionable but we have used the term because the product is customarily described in this way.

Many adverse effects occur in women taking synthetic oestrogens. We have shown that oral contraceptive preparations containing synthetic oestrogen accelerate blood clotting and platelet aggregation,³⁻⁴ which may cause the increased risk of thromboembolism. It has been suggested that natural oestrogens may be less harmful than synthetic preparations because they have less effect on the electrophoretic mobility of platelets.⁵ Claims have also been made that natural oestrogens do not accelerate blood clotting but these require confirmation by laboratory studies.

Our double-blind cross-over study in women given natural oestrogens and placebo alternately was designed to discover whether menopausal symptoms respond to oestrogens. Objective assessment of changes in weight, blood pressure, blood clotting, and platelet aggregation were performed during the study.

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