Relationship between mood disturbances and free and total plasma tryptophan in postpartum women

Mild disturbances of mood occur in 50-70% of women in the postpartum period,[1] when they may begin to cry for no apparent reason. The crying may be intense and prolonged and may often, but not always, be associated with a depressed mood. The synthesis of brain 5-hydroxytryptamine (5-HT) may be decreased in depressive illness, and the precursor of central 5-HT is brain tryptophan, which is probably derived from free plasma tryptophan.[2] Lowered levels of free plasma tryptophan have been reported in depression,[3] and we have examined the relation between free plasma tryptophan levels and affective changes in the puerperium.

Patients, methods, and results

We invited 18 women in a postnatal ward to participate. During their seven or eight days in hospital they rated themselves daily from 0 to 4 for each of the following five symptoms: tearfulness (no tears to cried for more than 30 minutes); depression (no depression to very depressed); anxiety (normal anxiety to desperately anxious); appetite (normal to complete loss); insomnia (good night's sleep to very disturbed sleep). An average daily score for each symptom for every patient was calculated, and the sum of the average daily scores for each symptom provided an average daily "total affective score." Thus the maximum possible average daily score per symptom was 4, and the maximum daily total affective score was 20, which enabled the patients to be ranked in order of increasing affective disturbance.

On the sixth day postpartum a 30-ml fasting blood sample was taken from each patient, a pilot study having shown that mood disturbance is most severe then. None of the patients were receiving drugs. For comparison, groups of normal controls and depressed inpatients were also studied. Laboratory staff who were unaware of the psychiatric state of the patients at the time estimated the free plasma tryptophan and total plasma tryptophan levels in the puerperal women, normal controls, and depressed patients using the same laboratory and methods.[4] There was no correlation between age and free plasma tryptophan in any of the three groups. The table shows groups of postpartum patients in order of increasing affective disturbance together with their tryptophan levels.

Patients who appeared clinically to have severe depression (ranks 15-18) had free plasma tryptophan levels similar to those found in depressive illness. Only one of the remaining patients (rank 7) had a low free plasma tryptophan level (4·60 μmol/l (0·94 μg/ml); free:bound plasma tryptophan = 0·055), and she appeared to be clinically hypomanic. Free plasma tryptophan correlated significantly with depression ($r = -0{\cdot}60$; $P < 0{\cdot}01$) and also with the total affective score ($r = -0{\cdot}49$; $P < 0{\cdot}05$). The other symptoms showed similar trends but the correlation failed to reach statistical significance. Total plasma tryptophan did not correlate with any of the clinical data but was 33·5% higher than in the controls.

Comment

These results show a significant correlation between the severity of affective disturbances and free plasma tryptophan levels. Hence mood changes in the postpartum period may be mediated by changes in brain 5-HT and free plasma tryptophan, as may be the case with depressive illness.

Decreased 5-HT turnover has been reported in hypomania, and the one patient in our series who appeared to be hypomanic had a low free plasma tryptophan level. The reason for the high total tryptophan in the plasma of postpartum women is unknown, but this high level is consistent with what has been found in animals. Thus in a study of the brains of parturient mice on the fifth day postpartum, lowered levels of 5-HT and 5-hydroxyindoleacetic acid were found together with a raised total brain tryptophan level.[5] The biochemical mechanisms causing these alterations in tryptophan metabolism are unknown but may be related to the considerable changes in oestrogen and progesterone secretion that follow delivery.

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Treatment of childhood asthma with sodium cromoglycate and beclomethasone dipropionate aerosol singly and in combination

Inhalation of sodium cromoglycate (SCG) and beclomethasone dipropionate aerosol each reduces the frequency and severity of asthmatic symptoms in children.[1 2] A comparison of these drugs in patients previously untreated with either drug has not been reported, however, and no advantage has been shown from combining them. We have therefore compared the protective effects of these drugs and studied the possible benefits of combining them.

Patients, methods, and results

Eleven boys and three girls participated in the trial with parental consent. They suffered recurrent attacks of wheeze and dyspnoea inadequately controlled with bronchodilators but had not required oral corticosteroids. All had at least one positive skin test result. The mean age at the start of the trial was 8·9 years (range 5·2-15·0 years).

The study was double-blind. All patients were given placebo SCG and placebo beclomethasone aerosol for the first two weeks to ensure that the parents could complete diary cards correctly and that the children were using their inhalers satisfactorily. Thereafter each patient had 12 weeks on each of the three treatment regimens (see table) in random order. Separate records were kept by the parents of the severity (scale 1-4) of diurnal and nocturnal wheezing during every 24-hour period. At four-week intervals the patients were reviewed by one of us. Inhaler technique was checked, the chest was examined, diary cards were scrutinised, and the forced expiratory

Mean plasma tryptophan levels in the 18 postpartum patients ranked in order of increasing severity of affective disturbances. Levels in 16 normal women controls and 50 women with endogenous depression are given for comparison. All figures are expressed ± SE

		Mean total affective score	Mean age (years)	Free plasma tryptophan (μmol/l)	Free:bound plasma tryptophan	Total plasma tryptophan (μmol/l)
Postpartum patients (rank Nos)	1–5	0·75 ± 0·10	27·6 ± 2·7	7·00 ± 0·93	0·094 ± 0·012	82·3 ± 4·1
	6–10	1·79 ± 0·09	29·6 ± 3·0	6·51 ± 0·54	0·084 ± 0·010	86·7 ± 4·2
	11–14	2·31 ± 0·14	25·8 ± 0·6	6·76 ± 0·59	0·082 ± 0·003	89·1 ± 5·5
	15–18	5·10 ± 0·90	25·0 ± 1·7	4·36* ± 0·49	0·058** ± 0·007	80·8** ± 5·3
	1–14	1·57 ± 0·19	27·8 ± 1·5	6·76† ± 0·39	0·087†† ± 0·010	85·7 ± 2·5
	1–18	2·35 ± 0·42	27·4 ± 1·2	6·22 ± 0·39	0·080** ± 0·005	84·7** ± 2·3
Normal women controls			25·6 ± 0·8	5·93 ± 0·34	0·118 ± 0·010	56·3 ± 1·6
Women with endogenous depression			55·2 ± 1·9	4·06 ± 0·20	0·075 ± 0·003	59·7 ± 1·5

Difference from controls: *P < 0·05; **P < 0·001. Difference from ranks 15–18: †P < 0·02; ††P < 0·05.
Conversion: SI to traditional units—Plasma tryptophan: 1 μmol/l ≈ 0·2 μg/ml.

volume in one second (FEV_1) was recorded. A supply of trial capsules and inhalers was issued at each visit.

All patients completed the trial and none required oral corticosteroids. The mean FEV_1 at the start of the trial was 1·54 (range 0·4-2·8 l). In each case the mean scores for diurnal and nocturnal wheezing were calculated for every treatment period. The three treatments were then ranked 1-3 (1 = fewest symptoms) in order of efficacy for each patient in relation to the severity of diurnal and nocturnal wheezing. The totals of ranks for severity of symptoms on each treatment were then compared (see table). No statistically significant difference was shown between the totals for either of the treatments used alone or for the combined treatment. There were also no significant differences between the mean FEV_1 values recorded in the three treatment periods, though these recordings were, of course, made only at monthly intervals. Six patients were virtually without symptoms during the nine months of the study. The others continued to have symptoms, and separate analysis again failed to show any statistically significant differences between the three treatment regimens.

Symptom ranking and treatment given

Treatment regimen*	Total of ranks for wheeze		Mean FEV_1 (l)
	Diurnal	Nocturnal	
SCG + placebo beclomethasone	29·5	34·5	1·80
Beclomethasone + placebo SCG	27·5	25·5	1·84
SCG + beclomethasone	27·0	24·0	1·76

*Doses (all four times daily): SCG 20 mg; beclomethasone 50 μg if aged less than 13 years, 100 μg if 13 years or over.

Comment

This small study showed no difference in efficacy between the two drugs or between either drug and the two drugs in combination. These results agree with those of Hiller and Milner.[3] Our results are disappointing since SCG and corticosteroids, with their different modes of action, might have been expected to produce additive therapeutic effects when used in combination. Although such effects were not observed, the number of patients in this study and in Hiller and Milner's study may have been too small for a statistically significant advantage to be shown. It is notably difficult to find large numbers of patients suitable for this type of trial, for if the results are to be unbiased only patients who have not previously been treated with SCG or a corticosteroid aerosol—and this includes many asthmatic children—can be accepted. There may therefore be a case for mounting a large-scale study, possibly on a multicentre basis, before concluding that a combination of the two drugs is not more effective than either given alone.

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Desensitisation in a patient with chronic renal disease and severe allergy to allopurinol

Allergy complicates treatment in 15% of patients with renal disease given allopurinol. In such cases the risk of toxidermia requires immediate interruption of the treatment.[1] We tried to desensitise an allergic patient with gout because we thought that inhibiting uric acid synthesis might arrest the progression of renal failure. This approach was beneficial to the patient.

Case report

A 51-year-old man had suffered from gouty joint attacks since 1954. In 1962 tophi of multiple joints appeared and became unusually large. Several episodes of renal colic occurred. Renal failure (blood urea 13·3 mmol/l (80 mg/100 ml)) was detected in 1964 and progressed, with increasing blood pressure levels. In 1971 an intravenous pyelogram disclosed bilateral renal atrophy. Treatment with alkalinisation, colchicine, and benziodarone were unsuccessful. In 1971 treatment with allopurinol was started but had to be interrupted within a month because of severe rash. The same was observed with thiopurinol.

The patient was referred to us in 1974. Clinical examination showed disseminated tumoral tophi and severe hypertension (200/140 mm Hg). Gouty attacks were practically continuous and were poorly influenced by colchicine. Blood urea was 13·3 mmol/l (80 mg/100 ml) and serum creatinine 239 to 283 μmol/l (2·7 to 3·2 mg/100 ml). Serum urate levels fluctuated between 0·54 and 0·71 mmol/l (9·1 and 12 mg/100 ml) with a 24-hour excretion of 5·4 mmol (900 mg). A third trial of allopurinol treatment was followed within 48 hours by a severe rash with spiking fever and had to be interrupted at once.

We then thought that without the use of a uric acid synthesis inhibitor the continuous renal tissue load with urate salts would lead to increasing kidney damage. The following treatment schedule was therefore started on 5 March 1975: 40 mg of allopurinol was dissolved in 500 ml of 14% sodium bicarbonate and for the next month the treatment was conducted as shown in the table.

There was no adverse reaction. Serum urate was measured every month. Levels were 0·71 mmol/l (12 mg/100 ml) at the beginning of the treatment with allopurinol and 0·4 mmol/l (6·9 mg/100 ml) one month later. From then on they stabilised at 0·32 mmol/l (5·4 mg/100 ml). Gouty attacks disappeared, and in February 1976 the tophi had diminished by about half their initial volume. Serum creatinine concentration was 212 μmol/l (2·4 mg/100 ml) and blood pressure was controlled (120/80 mm Hg) with pindolol and hydralazine.

Treatment regimen

Day	Dose		Day	Dose	
	Solution	Equivalent to		Solution	Equivalent to
1	0·1 ml	8 μg	16	12·0 ml	0·96 mg
2	0·2 ml	16 μg	17	14·0 ml	1·12 mg
3	0·3 ml	24 μg	18	16·0 ml	1·28 mg
4	0·4 ml	32 μg	19	20·0 ml	1.60 mg
5	0·5 ml	40 μg	20	25·0 ml	2·00 mg
6	0·6 ml	48 μg	21	32·0 ml	2·56 mg
7	0·7 ml	56 μg	22	64·0 ml	5·12 mg
8	0·8 ml	64 μg	23	128·0 ml	10·24 mg
9	0·9 ml	72 μg	24	250·0 ml	20·00 mg
10	1·0 ml	80 μg	25	¼ tablet	50·00 mg
11	2·0 ml	160 μg	26	¾ tablet	75·00 mg
12	4·0 ml	320 μg	27	1 tablet	100·00 mg
13	6·0 ml	480 μg	28	1½ tablets	150·00 mg
14	8·0 ml	640 μg	29	2 tablets	200·00 mg
15	10·0 ml	800 μg	30	3 tablets	300·00 mg

Comment

Gouty nephritis is due to urate deposits in the renal interstitium and tubules. Alkalinisation of the urine prevents the formation of urate stones in the urinary tract but not of urate tophi in the renal tissue. As renal insufficiency progresses it increases the urate pooling and creates a vicious circle leading to destruction of the kidneys.[2] The xanthine oxydase inhibitor allopurinol can break this chain of events. Allergies to this drug are not uncommon and may lead to severe and sometimes lethal epidermolysis.[3 4] In the present case, a very gradual increase enabled us to reach a dose of allopurinol that had induced reactions during three previous attempts. From then on the patient's clinical condition clearly improved. The rationale of this method of desensitisation is based on the probable formation of blocking antibodies. It has been successfully applied to patients with severe allergic reactions to penicillin.[5]

The schedule described here might be useful when xanthine oxydase inhibition is thought to be absolutely necessary in spite of an allergy to allopurinol.

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