

URINARY MELATONIN IN DEPRESSION

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SUMMARY

This report is based on a study of 12 cases of depression (8 endogenous, 4 neurotic) with a view to explore the possible association between urinary melatonin and the illness prior to and following treatment. While cases of endogenous depression had low 24 hour as well as nocturnal urinary melatonin levels, the neurotic depressives showed higher than normal levels. A rise in the 24 hour melatonin levels occurred in all cases of endogenous depression though this did not apply to the nocturnal levels. An association between melatonin levels with suicide behaviour, insomnia, psychomotor retardation and diurnal variation is discussed.

Pineal gland has now been proved to exercise endocrine function in humans (Reiter, 1978). Its important hormones thus far studied include, melatonin, other methoxyindoles, and peptides. "The most intense investigations with respect to human pathology has been in the field of psychiatric medicine" (Arendt, 1981). The cyclic and seasonal nature of depressive illness, diurnal variation in symptomatology, a pattern of sleep disturbance and a reported correlation between hospital admission for depression and suicide behaviour and the rhythmic nature of melatonin secretion have all contributed to the study of pineal gland function in depression (Eastwood and Peacocke, 1976). Normally the urinary levels of melatonin are higher by night than day but this pattern is reversed in depression (Lewy *et al.*, 1979; Mendelwicz *et al.*, 1980). Melatonin secretion is generally low in depression (Smith *et al.*, 1979; Wetterberg *et al.*, 1982; Lewy, 1981). It tends to rise with the setting in of remission and excessively so with the occurrence of mania.

Manic depressive patients tend to be supersensitive to light suppression of their

night time melatonin (Lewy, 1981). A subtype of depression characterized by hypofunction of pineal gland has been postulated by Wetterberg (1981). Measurement of urinary melatonin has been suggested as an index of human pineal function (Fellenberg *et al.*, 1980). Absolute quantity of melatonin excreted each day may vary several fold from person to person and causes of such variations are not yet clear (Lynch *et al.*, 1979; Wurtman, 1979). Body weight has no correlation with melatonin levels (Arendt *et al.*, 1982). In our other study melatonin excretion ranged from 10 micrograms to 35 microgram/24 hours with nocturnal levels always exceeding the day level in the healthy human volunteers (unpublished data). In a study of Fellenberg *et al.* (1980) the normal 24 hours excretion of melatonin was found to be around 30 microgram/24 hours. The content of melatonin in urine appears to be a function of kidney (Dadambaew, 1980).

AIMS

The principal aim of the study was to study the pineal function in depression as reflected in the levels of the urinary

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melatonin. The study was directed:

1. To estimate the urinary melatonin in depression cases both before and after treatment.
2. To note the relationship, if any, between certain features of depression like insomnia, psychomotor retardation, diurnal variation and suicide behaviour and urinary melatonin levels.

MATERIAL AND METHODOLOGY

Twelve (6 M : 6 F) subjects sufferings from depression (8 endogenous and 4 non endogenous type) in the age range of 30-75 years who attended the out-patient department of the Institute of Psychiatry, Madurai Medical College and Government Rajaji Hospital, Madurai formed the material for study. They were all investigated and treated as in-patients. Besides a standard psychiatric examination, they were rated on Hamilton Rating Scale for Depression (HRSD). The pretreatment 24 hour urine quantity was collected (morning volume from 7 AM to 7 PM and night volume from 7 PM to 7 AM), in polythene containers without any preservative being added. The collection was made within 48 hours of admission. Melatonin was extracted from urine samples and was estimated spectrophotofluorometrically by the method of Dreux (1969) using Hitachi's MPF-4 Fluorescence Spectrophotometer. All patients received tricyclic antidepressants and some chlorpromazine and electroconvulsive therapy as well. None of the patients switched over to manic episode following the treatment. After two weeks of treatment psychiatric assessment and administration of HRSD were repeated. The estimations of melatonin were repeated by the same technique. Prior to admission none of the subjects received any psychotropic agents or other drugs. The renal function status (as estimated by the urinary volume and specific gravity and serum creatinine) was within normal limits in all of them.

DATA AND OBSERVATIONS

Table I provides the details of Hamilton Score, day-night and 24 hours urinary melatonin excretion of the patients both at index evaluation and two weeks following antidepressant therapy.

In six cases the pretreatment 24 hour excretion of melatonin was below normal, the lowest being 8.5 microgram/24 hours. In two others the values were around normal. In the remaining four the levels exceeded the normal and varied from 50 to 71. In the pretreatment phase, the night levels were lower than the day levels in 8 cases, while it was reversed in four other cases. Following improvement from treatment (judged clinically and by HRSD) a marked elevation of 24 hour melatonin excretion was observed in all the six whose levels in the pretreatment phase were lower and also in the two where the pretreatment levels were normal. The elevation was however highest i.e. 80 in a patient whose pretreatment level was higher than the average i.e. 55 microgram. On the other hand there were three in whom a fall in the level was registered following the treatment but who had higher than normal levels prior to treatment. It is interesting to note that an elevation of nocturnal levels over the day levels occurred in three cases only, thereby indicating a reversal to normal pattern of melatonin excretion.

DISCUSSION

Urine Melatonin levels in pre and post treatment phase: The present study indicates that the decreased night levels of melatonin and 24 hour melatonin excretion and the latter's elevation following the treatment tended to occur in those cases diagnosed as "endogenous depression". The other four with pretreatment levels of 24 hour melatonin ranging from normal to higher than normal were diagnosed as neurotic depression with increased restlessness, anxiety and anxiety pat-

TABLE I

Sl. No.	Diagnosis	Melatonin Excretion						HRSD Total Score	
		Before treatment			After treatment			Before treatment	After treatment
		Day 12 hrs mc. g	Night 12 hrs mc. g	Total 24 hrs mc. g	Day 12 hrs mc. g	Night 12 hrs mc. g	Total 24 hrs mc. g		
1.	E	11.0	9.0	20.0	27.0	25.0	52.0	32	15
2.	E	21.0	9.0	30.0	28.0	8.0	36.0	44	20
3.	E	9.0	6.0	15.0	10.0	11.0	21.0	32	15
4.	E	18.0	6.0	24.0	20.0	16.0	36.0	38	14
5.	E	25.0	10.0	35.0	45.0	20.0	65.0	32	7
6.	E	25.0	40.0	35.0	34.0	26.0	60.0	15	6
7.	N	36.0	30.0	66.0	15.0	22.0	37.0	25	11
8.	N	33.0	38.0	71.0	25.0	19.0	44.0	21	8
9.	N	25.0	30.0	55.0	40.0	40.0	80.0	36	13
10.	N	20.0	30.0	50.0	13.0	12.0	25.0	36	5
11.	E	12.5	9.0	21.5	9.0	20.0	29.0	25	5
12.	E	7.0	1.5	8.5	4.6	6.7	11.3	25	8

E : Endogenous depression

N : Neurotic depression

tern of insomnia. This confirms in general the observations of Lewy et al (1979), Mendelwicz et al (1980) and Lewy (1981), Smith et al (1979). It also supports the hypothesis of Wetterberg (1981) suggesting a subtype of depression wherein there is a hypofunction of the pineal gland. It is not possible to state whether the urinary melatonin rose as a result of an improved clinical status or from the antidepressant administration. Imipramine was shown to be without effect on urinary melatonin in normal healthy human volunteers (Arendt, 1981). However, experimental animal data have revealed an increased pineal gland activity following imipramine (Parfitt and Klein, 1977 and Parvathi Devi et al, 1980). Hence the increased melatonin in the subjects is likely to be due to stimulatory

action of imipramine on the pineal gland. Although none in the series received lithium, we have observed an increase in plasma and urinary melatonin in normal healthy human volunteers and also in the manic depressive patients following lithium administration (unpublished data). Similarly experimental animal studies have shown a hyperactivity of pineal gland induced by lithium (Parvathi Devi et al 1972; 1973; 1976; 1978; 1982). It is a distinct possibility that antidepressant action of imipramine and lithium are pineal mediated.

Symptomatology and urine melatonin levels : The relationship between urinary melatonin and certain symptoms are discussed below :

The Table II offers the details of suicide attempt, insomnia, diurnal varia-

TABLE II

Sl. No.	Diagnosis	Total Melatonin Excretion (24 hrs)		Suicide		HRSD Scores on						Total HRSD Score	
		Pre	Post	Pre	Post	Insomnia		Diurnal Variation		Psycho Motor retard.		Pre	Post
1.	E	20	52	1	0	3	2	1	0	1	1	32	15
2.	E	30	36	4	0	5	3	1	1	2	1	44	20
3.	E	15	21	2	1	3	1	1	1	1	0	32	15
4.	E	24	36	4	0	6	1	1	0	1	1	38	14
5.	E	35	65	2	0	5	1	1	0	3	1	32	7
6.	E	35	60	3	0	3	1	0	0	0	0	15	6
7.	N	66	37	2	0	5	2	0	0	1	0	25	11
8.	N	71	44	4	0	6	3	0	0	0	0	21	8
9.	N	55	80	2	1	5	1	1	0	1	1	36	13
10.	N	50	25	2	0	4	1	1	0	2	0	36	3
11.	E	21.5	29	4	0	3	1	1	1	2	0	25	5
12.	E	8.5	11.3	2	0	5	0	2	0	2	0	25	8

Pre : Pre treatment
Post : Post treatment

E : Endogenous depression
N : Neurotic depression

tion in the symptomatology and psychomotor retardation with scores on HRSD in pre and post treatment phase and the corresponding melatonin estimations.

Suicide Behaviour : Wetterberg (1981) reported in a longitudinal study of MDP patients an association between suicide behaviour and diminished melatonin levels. In the present series suicide attempts were made by 5 cases and in 3 of them the 24 hour melatonin level was lower than normal. In one the level was about normal. All these four were cases of endogenous depression. In the fifth case one of neurotic depression, the initial level was double the normal (71 microgram). It is also evident that the suicide attempters excreted lesser quantity of melatonin than the non attempters and this was particularly observable in the night volumes. A score on suicidal ideas ranged

from 2—4 in HRSD in all cases. Following treatment, the score came to zero in all but two of the twelve cases. In both these cases, there was no attempt though they harboured suicidal ideas. While in the endogenous depression cases there was an elevation in the 24 hour melatonin excretion, in the neurotic depressive the levels fell after the treatment. It is to be commented at this point that a low level of 24 hour melatonin parallels suicide behaviour although a high level with this behaviour was noted in non endogenous type.

Insomnia : All the cases had sleeplessness at index evaluation and 8 of them (endogenous depression) had late night insomnia. The other 4 patients on the other hand (Neurotic depression) suffered early night insomnia and scored higher on anxiety on the Hamilton's scale for de-

pression. The endogenous depressives (N=8) had a low nocturnal melatonin level, besides a low 24 hour level, while the neurotic depressives (N=4) with early night insomnia had night levels that exceeded the day levels. Following the treatment the levels went up with regaining of normal sleep in six cases of endogenous depression. In two other endogenous depressives, there was a negligible fall in one and a drastic fall in the other. Among the four neurotic depressives, the levels fell in three but rose in one. The fall in the levels with clinical improvement is not explainable at present.

Pretreatment insomnia score on H RSD ranged from 3-6 in all cases. Some degree of insomnia persisted 2 weeks after treatment except in a single case in whom there was no insomnia. The scores declined considerably in all the eleven cases (score of 1 in seven; 2 in two; 3 in two). With a marked improvement in insomnia (0-1) and elevation of 24 hour and night levels was observed in 7 cases of endogenous depression while there was a fall in night level in a single case.

Diurnal variation : Pretreatment diurnal variation was present in seven of the eight endogenous depressives (morning worse, evening better) and this receded in four of them but persisted in rest of the three. Where the diurnal variation has disappeared, the 24 hour melatonin elevations were on the higher side.

Psychomotor activity : Psychomotor activity was retarded in seven of the endogenous depressives (N=8) and it improved in five and remained unchanged in two after treatment. In the non endogenous group on the other hand (N=4), two out of three who had psychomotor retardation improved after treatment. The 24 hour level of melatonin was lower than normal in those with psychomotor retardation which rose to normal following treatment and improvement of psychomotor retardation.

The mean of the total symptom rating in HRSD dropped to one third of pretreatment value in endogenous group whereas it came down to half the pretreatment value in the non endogenous group.

An important observation from this study was, though the total urinary melatonin rose in 7 cases of endogenous depression the day levels continued to exceed the night levels except in three cases. This trend is in keeping with the observation of Mendelwicz et al. (1980) who reported the reversal to a normal pattern with treatment in only three out of their four cases. The failure to rise in our cases is not explainable. This may be a prognosticator of relapse as has been shown in respect of other biological indicators. Such instances of a failure of biochemical reversal to occur in the face of a clinical remission is reported with Dexamethasone suppression test and also with levels of 5HIAA in the cerebrospinal fluid (Van Praag, 1982).

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