TOLERANCE OF DAILY SINGLE COMPARED TO SPACE DOSE OF MERITAL

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INTRODUCTION

Merital (Nomifensine) is a tetrahydroiso quinolene which is structurally unrelated to the tricyclics or to the monoamino-oxidase inhibiters. Merital has been reported to have antidepressant properties equivalent to amitryptyline (Grof, Saxena, Daigle, and Mahutte, 1977) and imiprimine (Forrest, Hewett, and Nicholson, 1977) in the treatment of patients with depressive symptoms. Bruckner and Jansen (1977) reported that in 105 depressed patients whose mean age was 74 years, Merital produced significantly better results than placebo. It has been suggested that its mechanism of action is due to potent inhibition of dopamine reuptake at the synaptic terminals (Horn, Coyle, and Snyder, 1971).

Published reports consistently show side effects of Merital to be minimal compared to tricyclic antidepressants (Grof, Saxena, Daigle, and Mahutte, 1977; Wittenborn, 1977; Woggon and Angst, 1977). Tests of motor activity and vigilance show that patients taking Merital compared to those taking placebo perform equally well (Wittenborn, 1977). Burrows, Vohra, Dumovic, Scoggins, and Davies, 1978) found that Merital in doses of up to 200 mgs daily had no significant effect on heart rate or blood pressure. Brogden, Heel, Speight, and Avery, (1979) have given a comprehensive review of the literature of the pharmacological and therapeutic properties of Merital.

The aim of this study was to assess whether a single daily dose of Merital was as well tolerated and as effective in its antidepressant action as an equivalent amount of Merital given in spaced doses.

SUBJECTS AND METHOD

Subjects comprised 43 patients who presented to the Psychiatric Department, General Hospital, Kuala Lumpur with the prominant symptom of depression. Seven patients refused to participate in the study. Patients were allotted alternatively to two groups. Patients who were taking medication at presentation were given a pretreatment washout for one week.

Group A comprised of fourteen patients, 7 males and 7 females with a mean age of 31 (S.D. + 3.01). There were 6 Malays, 7 Chinese, 1 Indian. 6 of them were single, 7 married and 1 divorced. 10 out of the 14 subjects were from the middle income group. Patients in this group were prescribed a single daily morning dose of Merital 100 mgs for 28 days.

Fifteen patients in group B with a mean age of 37 (S.D. + 3.66) composed of 7 males and 8 females. Ethenic composition was 8 Malays, 1 Chinese and 6 Indians. As to their marital status and social class, their distribution was even with no significant difference. They were prescribed spaced doses of Merital 50 mgs in the morning and 50 mgs at midday daily for the same period as the other group. Evening doses of Merital were avoided because of its reported antisoporific properties (Hindmarch and Parrott, 1977).

Identical interviews were carried out on days 1, 7 and 28. Depression was assessed by (a) a self rating linear scale ranging from O ("not depressed at

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all") to 10 ("extremely depressed, want to die"), (b) the 21 item Hamilton Rating Scale and (c) an observer rating ranging from O ("depression absent") to 4 ("severe depression"). Since patients tend to under report side effects of medication on direct questioning and to overreport side effects when asked to respond to a check list of possible side effects, both methods were employed in this study. The check list of symptoms which aimed to assess side effects of Merital were agitation, motor unrest, tremor, motor retardation, palpitations, sleep disturbance, drowsiness, dry mouth, taste disturbance, blurred vision, excess sweating, nausea/vomiting, micturition disturbance, headache, dizziness, anorexia, weakness/lethargy, diarrhea, constipation, memory impairment and menstrual disturbance. Weight and blood pressure, both supine and sitting, were recorded on days 1, 7 and 28. Routine urinalysis and blood assays to assess liver and renal functions, serum electolytes, full blood count and erthrocyte sedimentation rate were performed a days 1 and 28.

RESULTS

Three patients in group A and four in group B failed to complete the study. Diagnoses of the remaining patients in group A, of whom five required hospitalization, were neurotic depression eight, schizo-depression three, and endogenous depression three.

Diagnoses of patients in group B, of whom three required hospitalization, were neurotic depression ten, schizo-depression one, endogenous depression three and 'mixed' depression one. Three patients in group A and four in group B were treated following a suicide attempts.

Table I

Table I gives depression scores on days 1, 7 and 28 as measured by the Hamilton Rating Scale, and observer and patient self ratings.

There was an improvement of mean depression scores on day 7 and further improvement on day 28 for patients in both groups as measured by all three depression scales.

The frequency and type of side effects reported by patients which could be attributed to Merital is given in Table II. Any symptom reported by patients for the first time following the institution of Merital was recorded as a self reported side effect. Any check list symptom to which the patient responded for the first time following the institution of Merital was recorded as a check list side effect of Merital. During the trial two patients in group A and four in group B required concurrent treatment with diazapam because of anxiety; two in group B required nitrazapam because of insomnia; three in group A and one in group B required fluaxol or phenothiazines as

Table I

Mean Depression Scores (+ S.E.)

	GROUP A (N=14)			Group B (N=15)		
	Day 1	Day 7	Day 28	Day 1	Day 7	Day 28
Self Rating Scale 0 -- 10	3.5(+0.61)	2.9(+0.53)	2.1(+0.43)	5.0(+0.45)	4.5(+0.57)	3.8(+0.60)
Observer Rating Scale 0 – 4	2.4(+0.17)	1.3(+0.13)	1.1(+0.20)	2.5(+0.17)	2.1(+0.23)	1.5(+0.26)
Hamilton Rating Scale 0 – 21	13.9(+1.20)	8.4(+1.18)	4.4(+0.61)	17.7(+1.56)	9.7(+1.79)	8.0(+2.33)

* P / < 0.05 (t test, two-tailed)

maintenance prophylaxis against psychotic symptoms and one in group B required septrin for an intercurrent urinary tract infection. In these twelve patients, any side effect which was reported for the first time after day 1 was attributed to Merital.

With regard to diastolic or systolic blood pressure, it was found that when changing from the supine to sitting position, in group A blood pressure fell by at least ten mm. Hg. in one patient on day 7 and in four on day 28 and in group B in two patients on day 7 ad in two on day 28. A similar fall in blood pressure was recorded in three patients on day 1, prior to the introduction of Merital. With regard to weight, three patients in group A and four in group B gained between one and two kilograms. A total of three patients lost a similar amount of weight.

Table II

Frequency and type of side effects attributed to Merital

		Group A (N=14)*		Group B (N=15)*	
		Day 7	Day 28	Day 7	Day 28
SELF REPORTED					
Present :	Dizziness	2	0	0	0
	Dry mouth	0	0	0	0
	Nocturnal Sweating	0	0	1	0
	Weakness	0	1	0	0
	Headache	0	1	0	0
Absent :		12	13	14	13
IN RESPONSE TO CHECK LIST:					
Definite or Probable :	Dizziness	1	2	1	1
	Dry mouth	3	0	3	4
	Sweating	0	0	1	0
	Drowsiness	1	0	0	0
Possible	Dry mouth	1	5	1	1
	Dizziness	3	1	1	2
	Weakness	1	2	0	2
	Drowsiness	1	1	0	0
	Headache	0	1	0	2
	Blurred vision	1	0	1	0
	Sweating	0	1	0	0
	Taste	0	2	0	0
Absent :		6	8	9	8

* some patients complained of more than one symptom.

Routine urinanalysis was within normal limits for all but one patient who developed a urinary tract infection during the trial. Three patients on day 1 and a further 11 on day 28 refused to allow venipuncture. For the remaining 15 patients, routine haemotological and biochemical assays were within normal limits.

DISCUSSION

The results of this study indicate that ingestion of a daily single dose of Merital compared to a spaced dose schedule does not appreciably increase the frequency of side effects. A similar number of patients taking the daily single dose compared to those taking the split dose schedule complained of side effects which could be attributed to Merital. In none of the patients were side effects severe enough to warrant withdrawal of medication.

Table III shows that when patients were asked to volunteer side effects which could be attributed to Merital, at least 86% reported no side effects. However, when they were asked to respond to a check list of possible side effects, approximately half the patients complained of side effects. Difficulty in assessing side effects due to Merital are compounded by the fact that during the trial five patients in group A and eight in group B required medication other than Merital. The 13 patients taking concurrent medication complained of more side effects than the 16 who were taking Merital only. It is therefore likely that at least some side effects attributed to Merital were in fact produced by concurrent medication. An additional problem is that patients with a depressive mood frequently have numerous somatic complaints (Mayer-Gross, Slater, and Roth, 1970, pp. 79) and these may incorrectly be attributed to the side effects of Merital. On the other hand patient frequently take less medication than prescribed (Wilcox, Gillan, and Hare, 1965) so that the side effects of Merital would tend to be underreported. Since it was not possible to assay serum Merital levels, (and anyway nearly half the patients refused to allow venipuncture on day 28) the number of patients to whom this applied is not known.

During the drug trial there was an improvement in mood in all patients on day 7 and further improvement on day 28 as measured by the three depression rating scales. The methodology utilized for this study does not allow the conclusion that Merital is an effective antidepressant agent since no allowance has been made for a placebo effect (Lasagna, Mostellar, Felsinger, 1954) or for spontaneous improvement unrelated to medication. However previous studies by Bruckner and Jansen (1977) and by Kroger (1977) have shown the antidepressant efficacy of Merital over placebo.

Serious side effects of the traditional tricyclic antidepressant medication such as urinary retention, postural hypotension and cardiac arrythmias may prevent the physician from prescribing the full desired does of medication. These side effects do not appear to be a problem with Merital. If overseas reports concerning the antidepressant efficiacy of Merital are confirmed, then Merital may well become the treatment of choice in many patients with depressive illness especially in those for whom tricyclic medication is contraindicated such as elderly males with enlarged prostate, in patients with cardiac ischaemia, and in those who have suffered a recent cardiac infarct.

SUMMARY

Merital is a recently introduced antidepressant agent which is structurally unrelated to the traditional antidepressant agents and which is reported to have minimal side effects. This study aimed to establish the tolerance of a single compared to a spaced dose schedule of Merital. It was found that a single morning dose of Merital 100 mgs compared to a similar dose of the drug given in two divided doses did not appreciably increase the frequency or severity of side effects.

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