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Differential Dosing of Trazodone in Elderly Depressed Patients: A Study to Investigate Optimal Dosing

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We investigated the comparative efficacy and tolerance of two initial starting doses of trazodone in 20 elderly inpatients suffering from depressive illness. The first 2-week phase was double-blind. Patients received either 25 mg trazodone tds or 50 mg tds. After this time the study was open, the dose of trazodone being titrated from the initial starting dose to maximise efficacy and tolerance. Patients received study medication for a total of 6 weeks.

Assessments for efficacy included the Hamilton Depression rating scale, Zung anxiety scale, visual analogue scales for depression, euphoria and tension, and global assesments of severity and improvement of condition. Tolerance was assessed by means of a checklist of symptoms and adverse effects. Assessments were performed at base line and at weekly or bi-weekly intervals thereafter.

A total of 18 patients were included in the analysis. The Zung and visual analogue scales indicated significant superiority for the high-dose group at Week 2. The Hamilton ratings indicated significant superiority for the high-dose group at Week 6 with a strong trend in favour of the high dose group at Week 2. Measures of severity of illness and improvement indicated more rapid improvement over time in the high-dose group. The treatment was generally well tolerated and at no time did adverse events outweigh therapeutic benefit. The incidence of headache and nausea was more frequent in the high-dose group in the first 2 weeks.

The group of elderly patients studied benefited from trazodone therapy initiated at a higher therapeutic dose. This dose (150 mg total daily) was well tolerated and proved effective over the course of 6 weeks' treatment.

Introduction

Trazodone (Molipaxin – Roussel Laboratories Limited) is a novel triazolo-pyridone antidepressant (Brogden *et al* 1981) with no anticholinergic activity (Hyslop & Taylor 1980), and low levels of cardiotoxicity (Gommoll & Byrne 1979, Van de Merwe *et al* 1984) and side effects at therapeutic doses (Gerson & Newton 1980, 1980a). These properties make trazodone an attractive choice for the treatment of depressive illness in elderly patients who often cannot tolerate tricyclic antidepressants (Gerner *et al* 1980). In this age group, usage of tricyclics is often contraindicated because of possible interaction with

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concomitant medication or exacerbation of associated illness such as glaucoma.

Because of the susceptibility of the elderly to the adverse events of antidepressant therapy, initial dosages of these drugs tend to be low. Dosage is then gradually increased to therapeutic levels over the next few weeks (Josephs 1983). The rationale for this approach with trazodone appears to be largely based on extrapolation from data on younger patients and on experiences with other antidepressants. This study was designed to investigate this rationale by the evaluation of two oral starting dosage regimens of trazodone. We also sought to determine the optimal oral maintenance dose in terms of efficacy and tolerance.

Materials and Methods

Study Design

The study was carried out in two phases. The first involved double-blind, random allocation of 20 elderly in-patients to one of two oral dosage regimens of trazodone for two weeks, so that 10 patients were entered into each group. The second phase immediately followed the first and involved open titration of dosage from the initial level to obtain the optimal dosage in terms of efficacy and tolerance. The open phase continued for four weeks. Patients thus received treatment for six weeks.

Suitable patients were given a 3-day placebo 'run-in', after which they were assessed for entry into the study. Patients received either 25 mg trazodone tds (low-dose group) or 50 mg trazodone tds (high-dose group) in a randomised double-blind manner. Drugs were taken after meals. The dosage allocated to each patient remained unchanged for two weeks unless significant unwanted drug-related events occurred. In this case, the code could be broken for that patient and the dosage reduced by 25 mg daily. In the second, 'open' phase of the trial, the dosage could be altered on a bi-weekly basis in 25 mg intervals to its optimal level according to clinical judgement. If the total dose was not divisible by three, the higher proportion of the dosage was given at night.

After the initial two-week, double-blind phase, patients were assessed to determine if significant clinical improvement had occurred. The code was then broken. Where clinical improvement was inadequate the dosage of drug was increased by 25 mg added to the evening dose. The bi-weekly assessments were repeated until the optimal dosage level was obtained for each patient.

Inclusion/Exclusion Criteria

Patients suitable for entry into the study were 60 years of age or older and of either sex. They were in good physical condition and were suffering from a depressive disorder severe enough to warrant treatment with an antidepressant agent. In addition, patients scored 20 or more points on the Hamilton Depression Rating Scale after the 3-day placebo 'run-in' period. Patients were excluded from the trial according to the following criteria: serious personality inadequacies, severe senile dementia according to the Criton Royal Scale, known alcoholics or drug addicts, mental deficiency. Patients were also excluded if they suffered from recent or current, significant physical illness, if they had taken psychotropic drugs during the three months prior to study entry, or if they were unable or unwilling to give informed consent to the study.

Assessements

On entry to the study, demographic data, history of illness and informed consent were recorded. Patients underwent a physical examination, ECG and standard laboratory screening to exclude any physical abnormality. Efficacy of treatment was measured by the following methods on entry and at weekly or bi-weekly intervals thereafter:

- Hamilton Depression Rating Scale (weekly), Items 19 and 21 relating to paranoid symptoms and obsessional symptoms were not recorded, hence a 19-item scale was used.
- Zung self-assessed anxiety rating scale (weekly).
- 10 cm visual analogue scales (weekly) for euphoria, depression and tension.
- Severity of illness (bi-weekly) – a 7-point scale ranging from 1 = normal to 7 = severely ill.
- Global improvement with respect to baseline (bi-weekly, follow-up only), a 7-point scale of 1 = very much improved to 7 = very much worse.
- Efficacy rating (bi-weekly, follow-up only)

– a grid system which combines therapeutic effect (marked, moderate, minimal or unchanged/worse) with occurrence of side-effects (none, not significantly interfering with patient functioning, significantly interfering with patient functioning or outweighing therapeutic effect).

– Adverse symptoms – (recorded at baseline and weekly) checklist for commonly occurring adverse events to psychotropic drugs. Symptoms were recorded as absent, mild, moderate or severe.

Statistical Analysis

Patient characteristics recorded on entry were tabulated to assess treatment group comparability. For the Hamilton scale, Zung anxiety scale, and visual analogue scales for euphoria, depression and tension, analysis of covariance (checking for parallelism) with a factor of treatment and the result at Week 0 as the covariate, was used to test for differences between the two groups at Week 2 and at Week 6. Any non-significant covariate was removed from the model.

Results

Twenty patients entered the study. Of these, two were ineligible on the basis of the Hamilton depression rating scores. The remaining 18 patients had a median age of 68 yrs (range 60–78 years). Of these 18, four were male. In general, the two treatment groups were comparable at entry.

Three patients withdrew from the study, two in the low-dose group, one due to lack of response and one due to development of a chest infection. In the high-dose group one patient withdrew due to development of a medical complication (a hypoglycaemic episode in a diabetic patient). All data on patient withdrawals were included in the analysis up to the point of withdrawal.

During the initial 2-week, double-blind phase all patients except one in the low-dose group (whose dosage was increased because of inefficacy at week 1.5), remained on the initial allocated dosage level of trazodone. By week 2.5 only one patient in the low-dose group remained at 25 mg tds; all other patients were receiving 50 mg tds. Dosage in one patient was then increased to 75 mg tds by week 4.5 prior to withdrawal. By week 5.5 all remaining patients in the low-dose group were receiving 50 mg tds.

In the high-dose group, all but three patients remained on 50 mg tds for the six weeks of the study. The maximum dosage reached by the remaining three patients was 225 mg (two patients) and 250 mg (one patient) total daily dose.

Efficacy

The mean Hamilton scores for each treatment group are summarised in Figure 1. The mean scores decrease over time, the mean for the high-dose group being consistently lower than that for the low-dose group. Although the difference was not statistically significant at Week 2 ($p = 0.06$) the least squares mean for the high-dose group is 13.50 and for the low dose group 20.25. This mean difference of −6.75 (95% confidence interval −13.8, 0.3) indicates a strong trend in favour of the high-dose group. The difference was more marked at Week 6 ($p = 0.03$) with the least squares mean for the high-dose group of 3.1 and for the low-dose group of 6.4; mean difference of −3.3 (95% confidence interval of −6.2, −0.5).

Analysis of the Zung and the visual analogue scales for euphoria, depression and tension also indicate superiority of the high-dose group at Week 2 ($p = 0.007$, 0.02, 0.004, 0.005, respectively). These differences were not evident by Week 6. Results are summarised in Table 1.

Measures of severity of illness indicate improvement over time in both groups; By Week 3, five patients in the high-dose group were considered to be only 'border-line ill', while six in the low-dose group were still moderately ill. By Week 6 the majority of patients in the high-dose group were classed as normal or 'border-line', with one patient in the low-dose group being mildly ill. Global improvement results indicate a more rapid improvement in the high-dose group, with the majority very much improved by Week 4 and in the low-dose group by Week 5.5.

Efficacy rating indicates that no patient experienced any adverse events which outweighed clinical response. In the low-dose group, four had a marked therapeutic response at Week 5, and all except one at Week 6. In the high-dose group, four patients had a

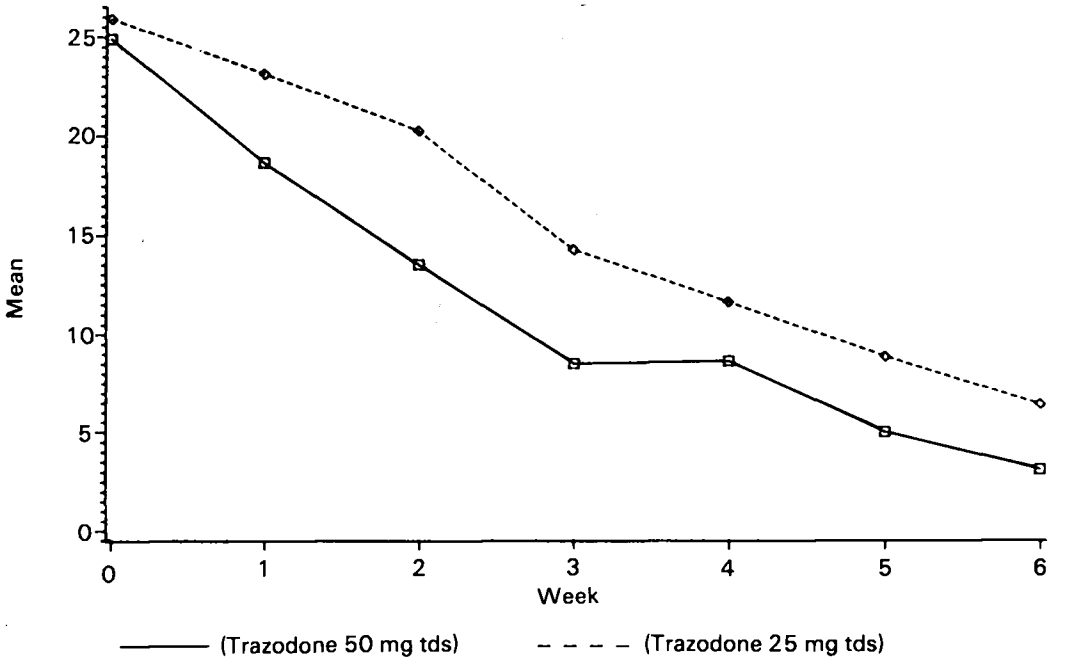

Fig 1 *Hamilton Depression Rating Scale measured weekly (mean values only).*

Table 1

Summary of Self-Rating Scales at Weeks 2 & 6

Week		*Zung*		*Visual Analogue: Depression*		*Visual Analogue: Euphoria*		*Visual Analogue: Tension*	
		Low Dose	*High Dose*	*Low Dose*	*High Dose*	*Low Dose*	*High Dose*	*Low Dose*	*High Dose*
2	Mean	59·4	46·1	80·6	41·3	15·8	46·1	68·8	34·3
	Standard deviation	6·3	10·1	10·7	29·4	15·3	30·1	20·0	19·7
		p=0·007		p=0·004		p=0·02		p=0·005	
6	Mean	30·2	29·6	13·0	8·4	83·0	86·9	14·2	8·4
	Standard deviation	2·9	4·1	9·5	3·5	10·4	5·6	10·7	5·9
		NS		NS		NS		NS	

Note: NS = not significant

marked response at Week 4, and all had a marked response at Week 6.

Tolerance

In general, the treatment was well-tolerated. The number of adverse events by groups is shown in Table 2. The major difference between the two groups lies in the higher incidence of headache and nausea in the high-dose group. Headache was a problem in four patients in the high-dose group at Week 2 (two mild, one moderate and one severe). However, this problem was not as marked after Week 2.

Discussion

Many clinicians, psychiatrists and general practitioners alike, often initiate anti-depressant therapy at low dosage, because they fear side-effects which may make the treatment unacceptable to the patient. This tendency is perhaps even more prevalent in elderly populations (Pitt 1985, Jacoby 1981) where recommended dosages are already lower than in younger age groups, and the margin between effective and ineffective dosing is narrower.

It is nevertheless important when treating depressive illness with drugs to minimise the time before obtaining a notable clinical response. Antidepressant drugs often appear slow to take effect. This discourages the patient, who may stop therapy (Johnson 1981). A balance must therefore be struck between using a maximal dosage to achieve a good clinical effect and risking the emergence of discouraging side-effects by too high a dose.

This study has investigated one anti-depressant, trazodone, in an attempt to determine the effects of initiating treatment at two dosage levels – 25 mg tds, a conservative low starting dose, and 50 mg tds, a higher therapeutic dose. The results indicate that, in general, antidepressant therapy should be initiated at a reasonable therapeutic dose. If this is not possible, an initial low dose should be increased as quickly as possible to maximise response.

More specifically, the study demonstrates that trazodone at the more rapidly effective dosage of 50 mg tds is well-tolerated in an elderly population. The therapeutic benefit of the higher dose was not outweighed by adverse events. This initial 50 mg tds dosage also appears to be optimal in terms of efficacy and tolerance as maintenance therapy.

Table 2

Summary of Side-Effect Symptom Check List

Number of patients reporting side-effect while on study medication (ie excluding Week 0)

Side Effect	*Treatment Group*	
	25 mg tds trazodone	*50 mg tds trazodone*
Drowsiness	3	3
Insomnia	7	6
Restlessness	7	5
Apprehension	2	1
Headache	2	6
Fainting	2	1
Dizziness	2	2
Dry Mouth	5	3
Palpitations	2	2
Constipation	0	1
Blurred Vision	1	0
Sweating	5	0
Flushing	0	0
Rash	0	0
Nausea	2	4
Indigestion	1	2
Weakness	2	0
Tremor	0	0

Conclusion

In an elderly population, an initial starting dose of trazodone (Molipaxin) 50 mg tds proved more rapidly effective in the treatment of depressive symptoms than 25 mg tds. Both treatments were generally well-tolerated; at no time did adverse events outweigh therapeutic response. The optimal therapeutic dose for the majority of patients in the study was 150 mg total daily, in divided doses. If lower doses are given as initial therapy, the dose should be rapidly increased to maximise response and to minimise time before this reponse is seen.

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