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# Evaluation of tiapride in agitated elderly outpatients: an open study

M. Tsolaki* and the Tiapride Study Group

*Aristotle University of Thessaloniki, Thessaloniki, Greece*

The aim of this study was the evaluation of the efficacy and safety of tiapride 50–100 mg administered 3 times a day to elderly patients with aggressive behavior. Data from 425 questionnaires concerning aggressive behavior in Greek elderly patients were evaluated before and after treatment. The Brief Agitation Rating Scale (BARS), which has 10 items, was used to evaluate the effectiveness of tiapride. To test the overall effectiveness of the drug during the trial, the statistical method of repeated measures ANOVA was applied to the total score and the very small $F$-value ($p < 0.0005$) led us to accept the hypothesis that tiapride significantly improves the condition of elderly patients with aggressive behavior. Only 6.2% of patients developed an adverse event during the trial. With 95% probability one may state that the probability of an adverse event occurring during the administration of tiapride is between 5% and 7.4%. We conclude that tiapride, apart from being very efficient in ameliorating aggressive behavior in elderly patients, is also very safe to administer. Copyright © 2001 John Wiley & Sons, Ltd.

KEY WORDS — agitation; tiapride; elderly

## INTRODUCTION

It is well known that agitation is perhaps the most significant problem among psychological and behavioral symptoms for the elderly, as well as their families and their caregivers, affecting the quality of their lives, their likelihood of entering a nursing care facility, and their interpersonal relationships. It is common and is often related to dementia, and is probably the foremost patient management problem in nursing homes, resulting in the use of various medication schedules, use of restraints and high staff to resident ratios.

The measurement of psychological and behavioral symptoms among the elderly has evolved in recent years from clinical ratings to more quantifiable methods of measurement. Some instruments have been constructed for the assessment of such patients, such as BEHAVE-AD (Reisberg *et al*., 1987), the Neuropsychiatric Inventory (NPI) (Cummings *et al*., 1994) and the Behavior Rating Scale in Dementia (BRSD) (Tariot *et al*., 1995). One measure of agitation that has been studied in some detail is the Cohen-Mansfield Agitation Inventory (CMAI) (Cohen-Mansfield *et al*., 1989). The Brief Agitation Rating Scale (BARS) is derived from the CMAI and is a brief and effective mechanism for assessing the presence and severity of physically aggressive, physically non-aggressive and verbally agitated behaviors in elderly nursing home residents (Finkel *et al*., 1993).

Antipsychotic medication has been shown to effectively manage psychotic and some behavioral disturbances in elderly patients. However, the use of typical neuroleptics is often complicated by extrapyramidal symptoms, sedation and cardiovascular side effects (Borson *et al*., 1997).

Tiapride is a benzamide derivative with selective dopamine $D_2$ receptor antagonist properties that appears to have preferential affinity for extrastriatal dopamine receptors (Steele *et al*., 1993). Results from clinical studies indicate that the clinical efficacy of tiapride in the treatment of agitation, aggressiveness, anxiety and sleep disorders in the elderly appears is

*Correspondence to: Magda Tsolaki, MD, Associate Professor of Neurology, Visiting Professor of Cognitive Psychology and Neurolingustics, Aristotle University of Thessaloniki, Despere 3, Thessaloniki, 54621, Greece. Tel: 00 30 31 234239, 00 30 31 283973, 00 30 31 350332. Fax: 283973.

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superior to that of placebo (Ohtomo *et al*., 1989), chlorpromazine (Shimizu *et al*., 1985), lorazepam (Rouquet and Bezaury, 1984) and meprobamate (Peyramond, 1978), and that tiapride causes less memory impairment than lorazepam (Roger *et al*., 1998). Tiapride also exerts a beneficial effect on vigilance and alertness in elderly patients and causes less sedation than chlorpromazine. It is well tolerated at the dosages recommended for elderly patients (Micheli *et al*., 1989).

The purpose of this Greek open national study was to evaluate the efficacy and safety of tiapride in agitated elderly.

## MATERIALS AND METHODS

### *Study design*

The purpose of this study was the evaluation of the efficacy and safety of tiapride 50–100 mg administered 3 times a day to elderly patients with aggressive behavior. Data from questionnaires concerning aggressive behavior in 425 Greek elderly patients in various Greek cities were entered into the database; 22 of these patients did not meet the inclusion criteria and were therefore dropped from the study. The data analysis was implemented in three stages: coding and database design, data entry and statistical analysis.

For the description of the population on Day 0 frequency tables were used for the quantitative variables and descriptive statistics (means, standard deviations, and minima, maxima and quartiles) for the qualitative variables. The Brief Agitation Rating Scale which was used as the main evaluation criterion consists of 10 items that refer to different types of aggressive behavior and their occurrence is scaled from 1 (never) to 7 (several times an hour). For the purpose of evaluating the overall effectiveness of tiapride, the total score of the 10 items of the BARS was computed for each subject per patient's visit to the hospital (Day 0, Day 2, Day 7 and Day 14).

Tiapride effectiveness was tested using descriptive statistics along with statistical tests. For the purpose of evaluating the effectiveness of tiapride between visits, repeated measures ANOVA and paired-sample *T*-test procedures were applied to the total BARS scores. The only criterion for the evaluation of the safety of tiapride was the number of patients developing an adverse event during the trial. The number of adverse events was computed according to a Council for International Organization of Medical Sciences (CIOMS) report form. That is, if an occurrence of an adverse event was regarded as reliable, the adverse event was entered into the CIOMS report form. With 95% probability we may state that the probability of an adverse event occurring during the administration of tiapride is between 5% and 7.4%. These numbers were computed according to the CIOMS form, i.e. if an adverse event was reported on the CIOMS form on Day 2, Day 7 or Day 14, then this adverse event was used in the calculations. In order to test safety, 95% confidence intervals were computed for both the percentage of adverse events during the trial and adverse events that led to dropout. All statistical procedures were applied using the statistical software SPSS 8.0 for Windows.

### *Description of the sample and the trial process*

The sample consisted of 425 Greek patients with aggressive behavior, 22 of whom did not meet the criteria for inclusion and were therefore dropped from the study. Of the remaining 403 patients, 42% were females and 58% were males. The mean age of these patients was 73.6 years. The number and percentage of these patients having diseases associated with aggressive behaviour and the type, number and percentage of associated diseases on Day 0 are given in Tables 1 and 2.

The number and percentage of patients that received treatment for aggressive behavior and the types of treatment are given in Tables 3 and 4.

Table 1. No. of patients ($N = 403$) with associated diseases

| | | No. | % | % valid |
|---|---|---|---|---|
| Validated | No | 78 | 19.4 | 20.1 |
| | Yes | 311 | 77.2 | 79.9 |
| | Total | 389 | 96.5 | 100.0 |
| Missing | | 14 | 3.5 | |

Table 2. Types of associated diseases at Day 0

| | No. | % |
|---|---|---|
| Nervous | 230 | 50.9 |
| Cardiovascular | 118 | 26.1 |
| Metabolic | 53 | 11.7 |
| Other | 51 | 11.3 |
| Total | 452 | 100.0 |

Table 3. Treatment for aggressive behavior

| | | No. | % | % valid |
|---|---|---|---|---|
| Validated | No | 216 | 53.6 | 59.7 |
| | Yes | 146 | 36.2 | 40.3 |
| | Total | 362 | 89.8 | 100.0 |
| Missing | | 41 | 10.2 | |

Table 4. Patients with other diseases and treatment for aggressive behavior at Day 0

| | No. | % |
|---|---|---|
| Cardiovascular | 1 | 0.7 |
| Neurological | 144 | 98.6 |
| Other | 1 | 0.7 |
| Total | 146 | 100.0 |

Table 5. Medications terminated at Day 0

| | No. | % |
|---|---|---|
| Anti-hypertensive | 2 | 2.1 |
| Cardiovascular | 2 | 2.1 |
| Neurological | 91 | 93.8 |
| Other | 2 | 2.1 |
| Total | 97 | 100.0 |

Table 6. Medications continued

| | No. | % |
|---|---|---|
| Anti-hypertensive | 41 | 11.8 |
| Cardiovascular | 106 | 30.5 |
| Neurological | 92 | 26.4 |
| Other | 109 | 31.3 |
| Total | 348 | 100.0 |

The type, number and the percentages of medications terminated at Day 0 and medications continued are presented in Tables 5 and 6.

## RESULTS

### *Efficacy evaluation*

The BARS was the only evaluation criterion. The scale consisted of 10 items that refer to different expressions of aggressive behavior and were scaled from 1 (never) to 7 (several times an hour). In order to summarize the effectiveness of tiapride for each item, the mean and the standard deviation of each BARS item was computed for each visit (Day 0, Day 2, Day 7 and Day 14) (Table 7).

For the purpose of evaluating the overall effectiveness of tiapride, the total score of the 10 items of the BARS was computed for each person per visit. The means of these total scores are presented in Table 8.

Considering that a decrease in the total BARS score indicates improvement in the patient's condition and that the scores decrease in severity over the course of the study, the table indicate the strong overall efficacy of tiapride.

Table 7. The efficacy of tiapride on each item of the Brief Rating Scale

| | Hitting | | Grabbing | | Pushing | | Wandering | |
|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| Day 0 | 2.29 | 2.04 | 2.46 | 2.13 | 2.90 | 2.35 | 4.51 | 2.44 |
| Day 2 | 2.12 | 1.83 | 2.29 | 2.00 | 2.67 | 2.17 | 4.04 | 2.24 |
| Day 7 | 1.77 | 1.37 | 1.86 | 1.46 | 2.12 | 1.58 | 3.13 | 1.87 |
| Day 14 | 1.51 | 1.07 | 1.57 | 1.13 | 1.67 | 1.16 | 2.46 | 1.72 |

| | Does | | Rest lessness | | Screaming | | Repetition | |
|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| Day 0 | 2.61 | 2.41 | 6.21 | 1.24 | 2.22 | 2.11 | 3.71 | 2.48 |
| Day 2 | 2.20 | 1.99 | 5.27 | 1.59 | 2.00 | 1.82 | 3.12 | 2.13 |
| Day 7 | 1.88 | 1.59 | 3.93 | 1.68 | 1.67 | 1.38 | 2.43 | 1.71 |
| Day 14 | 1.67 | 1.39 | 3.05 | 1.72 | 1.47 | 1.11 | 2.04 | 1.49 |

| | Makes | | ???? | |
|---|---|---|---|---|
| | Mean | SD | Mean | SD |
| Day 0 | 2.09 | 1.96 | 4.80 | 2.28 |
| Day 2 | 1.96 | 1.74 | 4.12 | 2.15 |
| Day 7 | 1.71 | 1.44 | 3.26 | 1.89 |
| Day 14 | 1.46 | 1.08 | 2.52 | 1.73 |

Table 8. Means and SDs of the total scores of the Brief Agitation Rating Scale for each visit

| | Mean | SD |
|---|---|---|
| Day 0 | 33.79 | 8.61 |
| Day 2 | 29.75 | 8.93 |
| Day 7 | 23.74 | 8.77 |
| Day 14 | 19.41 | 8.45 |

Table 9. The percentage of improvement at each visit

| Improvement | Day 2 | | Day 7 | | Day 14 | |
|---|---|---|---|---|---|---|
| in score (%) | No. | % | No. | % | No. | % |
| $<0$ | 20 | 5.1 | 13 | 3.4 | 10 | 2.7 |
| 0 | 114 | 29.2 | 19 | 5.0 | 6 | 1.6 |
| 0–25 | 210 | 53.7 | 124 | 32.9 | 62 | 16.7 |
| 25–50 | 31 | 7.9 | 165 | 43.8 | 136 | 36.7 |
| $>50$ | 16 | 4.1 | 56 | 14.9 | 157 | 42.3 |

For the purpose of evaluating the improvement in the total scores of the BARS, for each patient the percentage of improvement was computed for each visit according to the formula (Total score Day 0 − Total score Day k ($k=2,7,14$))*100/Total score Day 0 (Table 9).

Table 10. Patients experiencing adverse events ($N = 403$)

| | | No. | % | % valid |
|---|---|---|---|---|
| Validated adverse event | Fatigue | 4 | 1.0 | 16.0 |
| | Hypertension | 1 | 0.2 | 4.0 |
| | Extrapyramidal symptoms | 8 | 2.0 | 32.0 |
| | Sleepiness | 6 | 1.5 | 24.0 |
| | Death | 1 | 0.2 | 4.0 |
| | Fatigue, dizziness | 1 | 0.2 | 4.0 |
| | Mild tremor | 2 | 0.5 | 8.0 |
| | Diarrhea | 1 | 0.2 | 4.0 |
| | Acute cerebral stroke | 1 | 0.2 | 4.0 |
| | Total | 25 | 6.2 | 100.0 |
| No adverse events | | 378 | 93.8 | |

To test the overall effectiveness of tiapride during the trial, the statistical method of repeated measures ANOVA was applied to the total score. The very small *F*-significance ($p < 0.0005$) led us to accept the hypothesis that tiapride significantly improves the aggressive behavior of elderly patients. In order to test the effectiveness tiapride between visits, the paired sample *T*-test procedure was applied to the total BARS scores for consecutive visits.

According to the mean scores we accept the hypothesis (with the probability of reaching the wrong conclusion ($\alpha$ or type I error) less than 0.0005%) that tiapride improves the overall condition of elderly patients with aggressive behavior after the first 2 days of administration, at one week of administration and even more at two weeks of administration.

### *Safety*

The only criterion for the safety evaluation of tiapride was the number of patients developing an adverse event during the trial. The number of adverse events was computed according to the CIOMS report form. That is, if the report of an adverse event was regarded as reliable, the adverse event was entered into the CIOMS report form.

Only 6.2% of patients developed an adverse event during the trial. With 95% probability we may state that the probability of developing an adverse event during the administration of tiapride was between 5% and 7.4%. Table 10 shows the types of adverse event occurring during the treatment.

## DISCUSSION

This study indicates that tiapride is an effective and safe drug for treating agitation in elderly outpatients. As is well known, most studies which examine the efficacy and safety of different drugs for agitation or other behavioural problems are of nursing home patients. It is also imperative to identify effective and well-tolerated treatment strategies to reduce the morbidity of this distressing and burdensome symptom in elderly outpatients.

Also well known is that neuroleptic agents have been used for the management of both psychotic and non-psychotic disruptive behavior in elderly patients for more than 40 years (Borson, 1997). The first placebo-controlled trials of chlorpromazine and haloperidol demonstrated improvement in overactivity, hostility, aggression, irritability and excitability. Excessive sedation, worsening cognitive function extrapyramidal signs, tardive dyskinesia and gait impairment militated against the usefulness of these drugs. All these side effects suggest that the use of these drugs should be selective and generally reserved for patients with persistent psychosis and associated disruptive or dangerous behavior, as well as for some with severe behavioral dyscontrol without psychosis. All experts agree that treatment must be actively monitored to determine its effectiveness and required duration.

Newer drugs such as olanzapine, which has an affinity for a variety of receptor types, including dopamine ($D_{1-4}$) receptors and serotonin ($5\,HT_{2A/2C}$) receptors, have also been established as effective atypical antipsychotic agents for the treatment of Behavioral and Psychological Symptoms of Dementia (BPSD). The main adverse events for olanzapine are sleepiness ($P < 0.001$) for the dose of 15 mg and abnormal gait ($P < 0.01$) for the dose of 5 mg. Given the in vitro affinity for cholinergic receptors shown by olanzapine, this drug might be expected to be associated with anticholinergic adverse events, including cognitive decline, which can be problematic for elderly patients. However, no such effects were recorded in one study with Mini Mental State Examination (MMSE) before and after the trial (Street *et al*., 2000). Adverse events increased by 17% with the dose of 15 mg, compared with 4.3% with placebo, and only 66% of patients treated with the dose of 15 mg and 80% with the dose of 5 mg completed the trial.

To date, two large multicenter trials of risperidone in BPSD have been conducted. Risperidone is a selective monoaminergic antagonist with high affinity for serotoninergic $5\,HT_2$ and dopaminergic receptors. It binds also to $\alpha_1$-adrenergic receptors and, with lower affinity, to $H_1$-histaminergic and $\alpha_2$-adrenergic receptors. Risperidone at a dose of 1 mg/day has been found to be superior to placebo in the treatment of

 

BPSD, particularly for aggressive behavior in demented patients, but also for psychotic symptoms in the elderly. Risperidone at this dose is well tolerated and has an extrapyramidal signs profile that is similar to placebo (M Brecher, 1997, personal communication) and significantly lower than that of the haloperidol group (De Deyn *et al*., 1999). These studies were completed by 70% of patients and the adverse events were more than 10%.

Our data suggest that tiapride has fewer side effects (only 6.2% of patients), and all patients completed the study. Nobody presented with tardive dyskinesia, while risperidone was associated with a low incidence of tardive dyskinesia (5%) and haloperidol with the high incidence of 30% (Jeste *et al*., 1999). We should mention, however, that the duration of our study was only 14 days, while the duration of the study of risperidone was 12 weeks.

Two early clinical drug discontinuation trials have shown that long-term antipsychotic therapy may not be necessary in all patients who previously benefited from it. In one study, after a 6-week period with placebo only one of the eight patients was slightly more agitated, two were unchanged and five were less agitated after antipsychotics were discontinued (Risse *et al*., 1987). In the other study of 47 very old (mean age approximately 85), mainly female demented nursing home patients (mean MMSE score $< 10$), including 30 with Alzheimer's disease, 50% required reinstitution of antipsychotic medication, most within 6 weeks of withdrawal (Horwitz *et al*., 1995). This is the reason why this study was terminated after 2 weeks even though more than 40% of patients had an improvement in the BARS score of $>50\%$, while other recent large studies with risperidone or olanzapine were not terminated until after 12 weeks.

In the present study most of the patients continued their medication for other diseases (Table 6). No problems with interactions with other drugs or other forms of interaction were noticed.

After our experience with tiapride, we suggest that future trials with elderly patients with BPSD and on medication should have the following characteristics. Firstly, a suitable instrument should be used to track and measure cognitive and functional changes. MMSE was used in the risperidone trials, and this did not change. But MMSE is a short cognitive scale and small changes in cognition are not detected. We would suggest ADAS-COG (Mohs and Cohen, 1988) or CAMCOG (Roth *et al*., 1988) for cognition and DAD (Gelinas *et al*., 1999) or FUCAS (F Kounti, 2000, personal communication) for activities of daily living. Secondly, two weeks should be enough for some patients to control BPSD, and then a step by step discontinuation of treatment in these patients could reveal the percentage of patients who would need antipsychotic treatment for more time. Thirdly, comparative studies of the newer antipsychotic drugs (tiapride, risperidone, olanzapine) are needed. Studies comparing the new and old drugs have already been done and have shown that the new neuroleptics are better as far as the side effects are concerned.

Inconclusion, tiapride is a good medication for management of agitation and has a low percentage of side effects, so it can be used safely as a drug of first choice for at least 14 days, and then one may add another new neuroleptic drug.

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