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ORIGINAL INVESTIGATION

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Double blind study of tiapride versus haloperidol and placebo in agitation and aggressiveness in elderly patients with cognitive impairment

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Abstract *Objective:* The aim of the present study was to compare the efficacy and safety of tiapride versus haloperidol and placebo in the treatment of agitation and aggressiveness in elderly patients with mild or moderate mental impairment. *Method:* This international, multicentre, randomized, double blind, three parallel groups study compared efficacy and safety of a 21-day regimen of tiapride 100–300 mg/day versus haloperidol 2–6 mg/day and placebo in 306 elderly patients with mild or moderate dementia according to DSM III R and behavioural troubles with the Multidimensional Observation Scale for the Elderly Subjects (MOSES) irritability/aggressiveness subscore ranging from 16 to 30. *Results:* The percentage of responders (defined as patients with at least a 25% MOSES irritability/aggressiveness subscore decrease between the inclusion and the end of the treatment) was significantly greater in the tiapride (63%, *P*=0.04) and haloperidol (69%, *P*=0.004) groups than in the placebo group (49%), with no significant difference between the active drugs. Similar results were observed for the mean MOSES irritability/aggressiveness subscores on D_7, D_{21} and at D_{end} which were significantly smaller in the tiapride and haloperidol groups than in the placebo group. The decrease between D_0 and D_{end} was significantly greater in the tiapride (6.57, *P*=0.009) and haloperidol groups (6.75, *P*=0.005) than in the placebo group (4.71). The global improvement CGI was significantly better in the tiapride and haloperidol groups than in the placebo group (*P*=0.03 and *P*=0.02). No significant difference was observed between the two active drugs or among the three treatment groups for the Folstein's Mini Mental Status scale (MMS) total score, and there was no notable change during treatment. The number of patients with adverse events, assessed on the Udvalg Kliniske Undersogelser scale (UKU), and the number of UKU symptoms were smaller in the tiapride group (62 patients, 61%, 212 events) than in the haloperidol group (77 patients, 76%, 305 events) and identical to that observed in the placebo group (69 patients, 67%, 234 events). Of interest, the number of patients with at least one extrapyramidal symptom was significantly lower (*P*=0.003) in the tiapride group (16 patients, 16%) than in the haloperidol group (34 patients, 34%) and similar to that of the placebo group (18 patients, 17%); the difference observed between the haloperidol and placebo groups was significant (*P*=0.008). *Conclusion:* Tiapride is not different from haloperidol in the treatment of agitation and aggressiveness in elderly patients and better tolerated, in particular with significantly fewer extrapyramidal symptoms.

Key words Agitation · Aggressiveness · Dementia · Antipsychotic · Tiapride · Elderly

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Introduction

Agitation and aggressiveness are very common symptoms in elderly and especially in demented patients. Cohen-Mansfield (1996) estimated that 70–90% of demented elderly patients in nursing home display agitation. Thus agitation and aggressiveness in elderly people are a major problem for caregivers. These symptoms are often treated either with antipsychotics or benzodiazepines, though the long term benefits of benzodiazepines are unproven (Class et al. 1997) and their adverse effects in the elderly are well known (American Psychiatric Association 1987). On the other hand, classic neuroleptics are known to induce fre-

quent neurologic events, and at high dosages, induce sedation and cognitive impairment (Potenza and McDouble 1998). No consensus currently exists with regard to the drug attitude to adopt when facing these problems.

Tiapride is a substituted benzamide derivative with dopamine antagonistic effects, specifically on D_2 and D_3 dopamine receptors. However, on a clinical point of view, tiapride may be considered as an atypical antipsychotic drug with anxiolytic properties and a lower propensity for sedation, dependence and at low dosages, parkinsonism.

Previous published clinical studies in elderly patients with senile dementia, cerebrovascular insufficiency or recent stroke suggest that tiapride is superior to placebo, chlorpromazine, lorazepam and meprobamate in relieving senile agitation and related disorders at daily doses between 200 and 400 mg/day. Tiapride maintained or improved alertness and vigilance in comparison with chlorpromazine and lorazepam, which caused more drowsiness and decreased memory performances (Peyramond et al. 1978; Rouquet et al. 1984; Shimizu et al. 1984, 1985; Ohtomo et al. 1989; Steele et al. 1995; Patat et al. 1998; Roger et al. 1999).

The aim of the present study was to compare the efficacy and safety of tiapride versus haloperidol and placebo in the treatment of agitation and aggressiveness in elderly patients with mild or moderate mental impairment.

Materials and methods

Patients

Patients aged 55–90 years, fulfilling the DSM III R criteria (American Psychiatric Association 1987) for mild or moderate dementia and presenting behavioural troubles were included. Irritability/aggressiveness was assessed through the Multidimensional Observation Scale for Elderly Subjects (MOSES) (Helmes 1988) with a score on the subscale between 16 and 30. Patients had to be hospitalized or in a nursing home for at least 21 days. The main categories of dementia (Alzheimer's disease, vascular dementia and mixed dementia) were accepted for inclusion, under the condition that behavioural symptoms were present.

Non-inclusion criterion was at least one item rated 5 or no response for at least one item on the MOSES irritability/aggressiveness subscale. Other psychiatric disorders such as depression (assessed with the Montgomery and Asberg Depression Rating Scale) and psychosis precluded the patient's inclusion in the study, as did recent stroke and more generally any condition or treatment (i.e. antipsychotics or benzodiazepines) which could interfere with the study treatment or assessment. All psychotropics drug were excluded except benzodiazepines prescribed as hypnotics, zopiclone and zolpidem and antidepressants prescribed at low doses (less than a third of the usual dose for major depression). Such drugs could be continued during the study under the condition that doses remained unchanged for a month and during the period of the study.

Study design

This was a multicentre, international (five European countries), randomized, double blind study with three parallel groups. It was conducted in 116 European centres in France (61), The Netherlands (25), Germany (19), Latvia (10) and Portugal (1) between April 25 1995 and December 17 1996. Patients were randomly allocated to tiapride 100 mg/day (50 mg twice a day), haloperidol 2 mg/day (1 mg twice a day) or placebo.

Tiapride and haloperidol doses could be progressively increased from the sixth hour after the first drug intake to day 3 according to the patient's status and treatment acceptability. Maximum accepted dose was 300 mg/day tiapride and 6 mg/day haloperidol (6 capsules a day). From day 4 up to the end of the treatment (day 21), the recommended dose was 200 mg/day for tiapride and 4 mg/day for haloperidol.

The study was conducted in accordance with the Declaration of Helsinki amended in 1989 in Hong Kong and received the agreement of the ethics committee (Brest, France). Patients or, if not possible, medical staff and the main caregiver or family, gave their written informed consent before enrolment in the study.

Efficacy and safety assessments

Clinical efficacy was assessed using the MOSES scale rated at inclusion (day 0), on day 7 and at the end of the study (day 21) and the clinical global impression (CGI) (National Institute of Mental Health 1976) rated on each day between day 0 and day 7 and on day 21. Cognitive functions were globally assessed using the Folstein's Mini Mental Status scale (MMS) (Folstein et al. 1975) on day 0 and day 21.

Primary efficacy criterion was the number of responders defined as patients with at least a 25% MOSES irritability/aggressiveness subscore decrease between the inclusion and the end of the treatment. The rationale for the choice of this boundary has been derived from previous data and international literature.

Spontaneously reported adverse events were recorded at each visit. An adverse event form was filled in, in case of serious or unexpected event or in case of a drop-out. In addition, adverse events were assessed using the UKU Scale (Lingjaerd et al. 1987) on day 0, day 7 and day 21.

Statistical analysis

Statistical analysis was performed on intention-to-treat and per protocol basis, including all randomized patients. Treatment groups comparison was performed using ANOVA for quantitative variable and Chi-square for qualitative variables. Two-by-two comparisons were performed using contrast method. All comparisons were two-sided, with a 5% significance level. The possibility of a country effect was controlled with a two-way ANOVA.

The number of subjects required for this study was calculated from the alternative hypothesis, which was that the proportion of responders is greater in tiapride group than in the placebo group, with a difference of 25% between tiapride and placebo (55% responders for tiapride, versus 30% for placebo). In this conditions, with α=5% and 1–β=80%, 70 patients had to be included in each group. Allowing for the non-evaluable patients (study withdrawals with no evaluation of treatment, or data missing for primary criterion), it was decided to include 100 patients in each group, with a total of 300 patients. SAS software was used for data management and data analysis.

Results

Description of patients

A total of 306 Caucasian patients were included into the study, 197 (64%) were female and 109 (36%) male patients. Their mean age was 79.6±7.6 years (55–94 years). The demographic characteristics did not significantly differ between the treatment groups. Mean ages were, re-

Table 1 Changes in MOSES irritability/aggressiveness subscores between the baseline and the end of the treatment

Mean±SD	Placebo n_1=103, n_2=101	Tiapride n_{1-2}=102	Haloperidol n_1=101, n_2=99	*P*-value
MOSES irritability/aggressiveness subscore				
Baseline	20.28±2.85	19.90±2.92	20.52±3.27	NS
D_7*	16.18±4.56	14.53±4.04	14.81±4.090.03	0.02
P vs placebo		0.007		
P vs haloperidol		0.65		
D_{21}**	15.53±5.29	13.32±4.21	13.62±4.44	0.002
P vs placebo		0.0009	0.005	
P vs haloperidol		0.64		
End point	15.53 ± 5.25	13.33±4.20	13.75±4.59	0.002
P vs placebo		0.0009	0.008	
P vs haloperidol		0.53		
D_0–D_{end}	4.71±5.01	6.57±4.60	6.75±5.46	0.007
P vs placebo		0.009	0.005	
P vs haloperidol		0.8		
Diff/D_0 (%)	23.01±24.07	32.12±21.36	31.64±25.20	

n_1: at baseline; n_2: at Dend;
**P*: *n*=95, *T*: *n*=101, *H*: *n*=96;
***P*: *n*=99, *T*: *n*=101, *H*: *n*=98;
****P*: *n*=98, *T*: *n*=101, *H*: *n*=95

Table 2 Responder patients according to MOSES irritability/aggressiveness subscale

	Placebo *n*=101	Tiapride *n*=102	Haloperidol *n*=99	*P*-value
No	52 (51%)	38 (37%)	31 (31%)	0.01
Yes	49 (49%)	64 (63%)	68 (69%)	
P vs placebo		0.04	0.004	
P vs haloperidol		0.38		

spectively, for the placebo, tiapride and haloperidol groups 78.6±7.3 years; 80.3±7.6 years; 79.9±7.9 years and sex distributions were 71 (69%) female and 32 (31%) male patients; 63 (62%) female and 39 (38%) male patients and 63 (62%) female and 38 (38%) male patients.

At baseline, the three treatment groups were comparable for the whole efficacy criteria: MOSES irritability/aggressiveness subscores (Table 1) and the four other MOSES subscores (withdrawn behaviour, self-care function, disorientation, behaviour and depressed mood), MMS total score and CGI severity of illness.

The active drug-treated patients received 175.45±44.70 mg/day of tiapride or 3.53 ± 1.05 mg/day of haloperidol, i.e. 3.51±0.89 and 3.53±1.05 capsules/day respectively. Seven tiapride-treated patients (7%) and 13 haloperidol-treated patients (13%) received the maximum dose planned in the protocol (300 mg/day and 6 mg/day, respectively). Most of the patients received the recommended dose: 68 patients (67%) in the tiapride group (200 mg/day) and 58 patients (57%) in the haloperidol group (4 mg/day).

Forty-seven patients (15%) dropped out from the study, ten in the tiapride group (adverse event five; lack of efficacy one; uncooperativeness three; recovery one), 21 in the haloperidol group (adverse event 17; lack of efficacy one; uncooperativeness two; concomitant medication one) and 16 in the placebo group (adverse event six; lack of efficacy eight; uncooperativeness two).

Efficacy

The percentage of responders according to MOSES irritability/aggressiveness subscale was significantly greater in both active treatment groups (haloperidol 63%, tiapride 69%) than in the placebo group (49%) ($P_{\text{tiapride vs placebo}}$=0.04, $P_{\text{haloperidol vs placebo}}$=0.004). No significant difference was observed between the tiapride and haloperidol groups (Table 2). Four patients (two placebo- and two haloperidol-treated patients) could not be assessed for response. If the rule of maximum bias was applied, i.e. placebo-treated patients with missing data were considered as responders and haloperidol-treated patients with missing data considered as non-responders, the results were similar and the comparison between tiapride and placebo was close to statistical significancy (P_{global}=0.03, $P_{\text{tiapride vs placebo}}$=0.06, $P_{\text{haloperidol vs placebo}}$=0.01).

Inter-group statistically significant difference was also observed for the mean irritability/aggressiveness subscore on D_7, D_{21} and at D_{end}. The mean subscore was significantly reduced in the tiapride and haloperidol groups when compared to placebo group. Comparable result was observed for the mean subscore decrease between D_0 and D_{end} (*P*=0.007). The mean decrease was significantly greater in the tiapride (*P*=0.0009) and haloperidol groups (*P*=0.005) than in the placebo group. No significant difference was observed between the two active treatment groups (Table 1).

Table 3 Global improvement at D_{end}

	Placebo *n*=103	Tiapride *n*=102	Haloperidol *n*=101	*P*-value
Very improved	14 (14%)	24 (24%)	31 (31%)	0.03
Much improved	35 (34%)	38 (37%)	28 (28%)	NS
Minimally improved	22 (21%)	19 (19%)	21 (21%)	NS
No change	22 (21%)	12 (12%)	12 (12%)	NS
Minimally worse	4 (4%)	8 (8%)	5 (5%)	NS
Much worse	4 (4%)	1 (1%)	4 (4%)	NS
Very much worse	2 (2%)	–	–	NS

Table 4 Patients with at least one UKU adverse event and description of UKU adverse events

	Placebo	Tiapride	Haloperidol
Count of UKU symptoms	234 (100.0%)	212 (100.0%)	305 (100.0%)
Population treated	103 (100%)	102 (100%)	101 (100%)
At least one UKU symptom	69 (67%)	62 (60.8%)	77 (76.2%)
P vs placebo		0.35	0.14
P vs haloperidol		0.02	
At least one extrapyramidal symptom[a]	18 (17.5%)	16 (15.7%)	34 (33.7%)
P vs placebo		0.73	0.008
P vs haloperidol		0.003	
At least one endocrine symptom[b]	8 (7.8%)	10 (9.8%)	6 (5.9%)
P vs placebo		0.61	0.61
P vs haloperidol		0.31	
Psychic events	140 (59.8%)	121 (57.1%)	147 (48.2%)
Impaired concentration	19 (8.1%)	18 (8.5%)	21 (6.9%)
Asthenia	14 (6%)	19 (9%)	26 (8.5%)
Sleepiness	19 (8.1%)	24 (11.3%)	30 (9.8%)
Amnesia	25 (0.7%)	21 (9.9%)	27 (8.9%)
Nervousness	19 (8.1%)	10 (4.7%)	10 (3.3%)
Somnolence	8 (3.4%)	8 (3.8%)	9 (3%)
Sleep decreased	10 (4.3%)	5 (2.4%)	5 (1.6%)
Indifference	10 (4.3%)	5 (2.4%)	8 (2.6%)
Neurologic events	26 (11.1%)	19 (9 %)	67 (22%)
Dystonia	2 (0.9%)	4 (1.9%)	13 (4.3%)
Muscle rigidity	5 (2.1%)	3 (1.4%)	20 (6.6%)
Hypokinesia	4 (1.7%)	5 (2.4%)	14 (4.6%)
Autonomic events	41 (17.5%)	41 (19.3%)	60 (19.7%)
Other events[c]	27 (11.5%)	31 (14.6%)	31 (10.2%)

[a] Includes tremor, muscle rigidity, hyperkinesia, hypokinesia, akathisia, dystonia, saliva increased, ataxia
[b] Includes amenorrhoea, libido increased or decreased, impotence, ejaculation failure, anorgasmia, vaginal discomfort
[c] Includes accommodation disturbance, vomiting, diarrhoea, constipation, polyuria, micturition disorder, palpitation, sweating increased, tachypnoea, urinary incontinence, hypertension, hypotension

The four other MOSES subscores (withdrawn behaviour, self-care function, disorientation behaviour, depressed mood) decreased between the baseline and the end of the treatment in the three groups without significant difference. Regarding the MOSES withdrawn behaviour scale, (D_0–D_{end}), a statistical trend was observed in favour of tiapride compared to placebo. CGI (global improvement) was significantly different between the three treatment groups at the end of the treatment (*P*=0.03). The global improvement was significantly better in the tiapride and haloperidol groups than in the placebo group (*P*=0.03 and *P*=0.02). No significant difference was observed between the two active drugs (Table 3). No statistical significant difference was observed among the three treatment groups for the other two CGI items (severity of illness and therapeutic index) and the MMS total score.

Safety

The number of drop-outs was smaller in the tiapride group (*n*=5) than in the haloperidol group (*n*=17). The number of patients with UKU adverse events was significantly smaller (*P*=0.02) in the tiapride group (62 patients, 61%) than in the haloperidol group (77 patients, 76%) and identical to that observed in the placebo group (69 patients, 67%) (Table 4). The number of patients with at least one extrapyramidal symptom was significantly smaller (*P*=0.003) in the tiapride (16 patients, 16%) than in the haloperidol group (34 patients, 34%) and identical to that observed in the placebo group (18 patients, 17%); the difference observed between the haloperidol and placebo groups was also statistically significant (*P*=0.008). No significant difference was observed among the three treatment groups

for the number of patients presenting endocrinological side-effects.

The number of UKU symptoms was smaller in the tiapride group (212 events) than in the haloperidol group (305 events) as well as in the placebo group (234 events). Neurological events were 3.5 times less frequent in the tiapride group (19 events) than in the haloperidol group (67 events) and 1.4 times less frequent than in the placebo group (26 events) (Table 4).

Autonomic events were 1.5 times less frequent in the tiapride group (39 events) than in the haloperidol group (56 events) and as frequent as in the placebo group. Accommodation disturbances and urinary disorders were more frequent in the haloperidol group (seven and five, respectively) than in the tiapride group (three and none, respectively).

Four deaths were reported: one in the placebo group (stroke), one in the tiapride group (pneumonia) and two in the haloperidol group (stroke and heart failure) which were considered by the investigators as unrelated to the treatment. Twenty-eight adverse events led to study treatment discontinuation: six in the placebo group, five in the tiapride group and 17 in the haloperidol group. No clinically significant abnormalities in vital signs or laboratory data were observed throughout the study.

Discussion

This international, multicentre study was conducted in 306 patients recruited by 116 investigators in Europe. This was a randomized, double-blind study with three parallel groups of patients treated for 3 weeks: 102 patients received 100–300 mg/day tiapride, 101 patients received 2–6 mg/day haloperidol and 103 received placebo. It is important to point out that a 2–6 mg/day dose of haloperidol has been recommended for the treatment of agitation and aggressiveness in people with dementia (Sultzer et al. 1997). The patients were 79.6 (±7.6) years old on average and 64% were female. The mean MOSES irritability/aggressiveness subscore was comparable in the three treatment groups at inclusion and ranged from 19.90±2.92 in the tiapride group to 20.52±3.27 in the haloperidol group.

The primary efficacy criterion was the number of responders judged on the MOSES irritability/aggressiveness subscale (at least a 25% decrease in MOSES irritability/aggressiveness subscore at the end of the treatment with respect to the baseline). The percentage of responders was significantly greater in the tiapride (P=0.04) and haloperidol (P=0.004) groups than in the placebo group. Applying the principles of maximum bias for missing data in the placebo and haloperidol groups led to similar results (addition of two responders in the placebo group led to a difference close to statistical significance (P=0.06) between the tiapride and placebo groups). In both analyses, there was no significant difference between the two active drugs.

The statistical significant superiority of tiapride and haloperidol over placebo and the equivalence of both active drugs observed in the primary efficacy criterion was confirmed by the MOSES irritability/aggressiveness subscore after 7 treatment days (tiapride versus placebo: P=0.007; haloperidol versus placebo: P=0.03) and 21 treatment days (tiapride versus placebo: P<0.001; haloperidol versus placebo: P=0.005) treatment days and at the end of the treatment (tiapride versus placebo: P<0.001; haloperidol versus placebo: P=0.008). In the same way, the MOSES subscore decrease between the baseline and the end of the treatment was significantly greater in the tiapride (P=0.009) and haloperidol (P=0.005) groups than in the placebo group.

These results were consistent with those observed in two previous studies which showed that 400 mg/day IM tiapride administered for 3 days in 20- to 92-year-old patients and 150 mg/day tiapride orally administered for 7 days in elderly patients was effective on agitation and aggressiveness (Peyramond et al. 1978; Rouquet et al. 1984). In addition, in those studies, tiapride was more effective than comparative drugs, meprobamate 800 mg/day IM and oral lorazepam 3 mg/day.

In the present study, the global improvement was significantly better in the tiapride and haloperidol groups than in the placebo group (P=0.03). This result confirmed the results of one previous study conducted in 324 elderly patients with recent stroke (Ohtomo et al. 1989). In this study, patients treated with oral tiapride at a dose ranging from 75 mg/day to 150 mg/day for 4 weeks had a significant better global improvement than patients treated with oral chlorpromazine 19–75 mg/day or placebo. Furthermore, a recent study (Gutzmann et al. 1997) conducted in elderly patients with psychomotor agitation and light or moderate intellectual deterioration, demonstrated that tiapride administrated orally at a 400 mg/day for 4 weeks was as effective as melperone 100 mg/day.

Tiapride as haloperidol did not differ from placebo when considering withdrawn behaviour, self care function, disorientation behaviour and depressed mood measured using MOSES subscale. The four MOSES subscores decreased between baseline and the end of the treatment in the two active treatment groups without significant difference, as had been previously shown by Leger et al. (1997) for tiapride 300 mg/day and pipamperone 60 mg/day administered for 4 weeks.

Cognitive functions, globally assessed by the Folstein Mini Mental Status (orientation, learning, memory, vigilance, calculation and language), were not modified by any of the two active treatments indicating that tiapride at 100–300 mg/day as haloperidol at 2–6 mg/day did not impair cognitive functions after this 4-week treatment period.

The numbers of patients with UKU adverse events and number of UKU symptoms were smaller in the tiapride group (62 patients, 61%, 212 events) than in the haloperidol group (77 patients, 76%, 305 events) and identical to those observed in the placebo group (69 patients, 67%, 234 events).

Of interest, the number of patients with at least one extrapyramidal symptom was significantly smaller

(P=0.003) in the tiapride group (16 patients, 16%) than in the haloperidol group (34 patients, 34%) and identical to that observed in the placebo group (18 patients, 17%).

In conclusion, oral tiapride at 100–300 mg/day was not different from haloperidol at 2–6 mg/day in the treatment of agitation and aggressiveness of elderly patients with mild or moderate mental impairment. The hypothesis of a lack of statistical power to detect a difference in efficacy between tiapride and haloperidol should be raised. Neither treatment impaired, or improved, cognitive functions. The tiapride safety profile was better than that of haloperidol for clinical acceptability, particularly when considering extrapyramidal symptoms significantly more frequent with haloperidol.

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