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Clinical and behavioural evaluation in long-term care patients with mild to moderate dementia under Memantine treatment

Untersuchungen von Psychopathologie und Verhalten bei Altenpflegeheimpatienten mit leichter bis mittelschwerer Demenz unter Memantine

Zusammenfassung: Die klinische Wirksamkeit und Verträglichkeit von Memantine (1-Amino-3,5-Dimethyladamantan hydrochlorid, Akatinol Memantine^{R}, CAS 41100-25-1) wurde in einer doppelblinden, placebokontrollierten Studie bei 60 in Altenpflegeheimen lebenden Patienten mit leichter bis mittelschwerer Demenz (SDAT, vaskulärer und gemischter Typ) in einem Behandlungszeitraum von vier Wochen untersucht.
Die konfirmatorische Statistik ergab für die Hauptzielkriterien sowohl auf der psychopathologischen Ebene (SCAG, Globalurteil zur Wirksamkeit) als auch auf der Verhaltensebene (NOSIE-Index, BGP Subscore «Hilfsbedürftigkeit») signifikante Unterschiede zwischen Memantine und Placebo ($p < \alpha^* = 0.0125$).
Die klinische Relevanz der statistisch signifikanten Resultate wurde über eine Therapieresponder-Analyse nach dem Konzept der zufallskritischen Bewertung intraindividueller Veränderungen überprüft.
Unter Memantinebehandlung konnten in 70% der Patienten klinisch relevante Verbesserungen übereinstimmend auf zwei unabhängigen Meßebenen (SCAG Summenscore, NOSIE-Index) gefunden werden.
Die in dieser Studie gefundene Therapieresponderrate ist deutlich höher als die in Studien mit Nootropika.

Keywords: Memantine, NMDA-antagonist, dementia study, therapy responder analysis

Summary: The clinical efficacy and tolerability of Memantine (1-amino-3,5-dimethyladamantane hydrochloride, Akatinol Memantine^{R}, CAS 41100-25-1) were investigated in 60 patients suffering from dementia of mild to moderate degree living in long-term care facilities in a randomized, double-blind, placebo-controlled study.
Memantine was given at a low initial dose of 10 mg/d on days 1 and 2, followed by 20 mg/d from day 3 to day 7 and then 30 mg/d from day 8 to the end of the treatment after 28 days.
The efficacy of Memantine was judged by means of endpoint vs. baseline differences for the total score of the Sandoz Clinical Assessment Scale Geriatric (SCAG), the dimension «Need for help/care» of the Evaluation Scale for Geriatric Patients (BGP), and the Index of the Nurses Observation Scale for Inpatient Evaluation (NOSIE), as well as directly by the physicians global impression of clinical efficacy.
The tolerability of Memantine was assessed on the basis of a global assessment and the documentation of adverse events; safety parameters were also monitored during the study. Only mild and transient side effects of Memantine were observed.
The clinical efficacy of Memantine was confirmed by the statistical significant differences between Memantine and placebo treatment ($p < \alpha^* = 0{,}0125$) on independent assessment levels, i.e. the psychopathological (SCAG, global impression of efficacy) and the behavioural level (NOSIE Index, BGP subscore «need for help/care»).
The clinical relevance of the observed drug effects is based on the improvement in daily functioning and social competence resulting in reduced need of help/care, as measured on two independent levels.
Moreover clinical relevance of the observed improvements of clinical symptoms was confirmed by a therapy responder analysis using discriminant cut-off points for intraindividual change. Under Memantine a clinically relevant intraindividual improvement in two independent assessments (SCAG total score, NOSIE Index) was observed in 70% of the patients. The high therapy responder rate measured in this study differs from those known by other studies on nootropic drugs and indicates, that the NMDA-antagonist Memantine shows different profile in symptomatic treatment of dementia.

1. Introduction

Dementing illnesses are a major contributor to disability in the elderly. Current diagnostic criteria for dementia include the presence of significant impairment in social, occupational, and everyday functional abilities (DSM-III-R, 1987). Up to now, there are unsolved problems and discrepancies between the diagnostic criteria of dementia and the criteria of evaluation of efficacy for clinical trials.

The problems of evaluation of efficacy of antidementia drugs and of the clinical relevance of the measured therapeutic effects are reflected in published guidelines or in draft guidelines (AMADUCCI et al., 1990; KANOWSKI et al., 1990; Clinical Research Working Group of the Pharmaceutical Industry on Dementia, 1990; Bundesgesundheitsamt [BGA], 1991; Food and Drug Administration [FDA], 1989; European College of Neuropsychology [ECNP], 1991).

A large number of instruments for assessing the mental state of elderly has become available. Many of the published methods focus on areas such as orientation, memory, and language and make use of mental performance tests, while only a few emphasize the importance of patients functioning in their habitual surroundings. However, assessment of functional abilities is essential to demonstrate drug-linked improvement in the patient's everyday behaviour. Therefore, the documentation of changes in behavioural functions is a further important proof for the efficacy of an antidementia drug.

Up to now, these criteria are not fullfilled in most studies with nootropic drugs (see WEYER, 1992). For the NMDA (N-methyl-D-aspartate) antagonist Memantine however it was demonstrated in previous clinical studies that the drug not only improves vigilance (KUGLER, 1975; SCHULZ et al., 1992) and cognitive disturbances (DITZLER, 1991), but also drive, motivation, emotional conditions, motor functions in activities of daily living, and social behaviour (DITZLER, 1991; PARSONS & PANTEV, 1991; GÖRTELMEYER & ERBLER, 1992).

The aim of the present study was to test the clinical efficacy and the tolerability of Memantine at doses of 20–30 mg/day in patients with mild to moderate dementia, living in long-term care facilities. Evaluation of drug effects was made on two independent assessment levels, the psychopathological and the behavioural level. On the behavioural assessment level the target efficacy criterion was focussed on the functional status as an decisive aspect in patients' care.

Emphasis was put on the clinical relevance of changes by using a therapy responder analysis.

2. Methods

2.1. Study Design, Sample and Procedure

The study was designed as a prospective, randomized, placebo-controlled double-blind study with independent parallel groups of 30 patients each.

The study was performed under guidance of Dr. Ritter, Freiburg/Brsg.

All patients were investigated by the abovementioned physician who was in charge of the long-term care facilities.

The functional abilities and the behaviour in everyday life were rated by trained nurses.

The study was supervised, conductet and monitored by the Clinical Research Dept. of Merz + Co., Frankfurt/Main.

The blinding of the drugs was performed in the Dept. of Pharmaceutical Technology of the manufacturing company.

2.1.1. Inclusion Criteria

Male and female patients living in long-term care facilities, aged between 50 and 80 years suffering from primary degenerative and vascular dementia of mild to moderate degree were included.

The diagnosis of dementia was established on clinical assessment according to the DSM-III-R criteria.

The degree of dementia was assessed using the Lausanne scheme (LAUTER, 1973) and the Sandoz Clinical Assessment Geriatric Scale (SCAG) (SHADER et al., 1974), cut-off: total score of at least 80 points and more.

CT-scan and laboratory assessments were used to exclude secondary dementias. Since Memantine as a NMDA-antagonist is supposed to be efficacious in all types of dementia of prima-

ry cerebral origin, no differentiation of subgroups was performed in the present study.

2.1.2. *Exclusion Criteria*

Patients were excluded from the study by the following criterial:

- participation in a study within the preceding four weeks
- drug and/or alcohol abuse/dependence
- known intolerance to the test product
- severe chronic or terminal diseases
- decompensated hypertension, haemodynamically relevant heart diseases, myocardial or cerebral infarction within the previous three months
- impairment of liver function (elevation transaminases to more than the twice of normal level)
- impairment of kidney function (serum creatinine level above 1.8 mg/dl)
- secondary dementia
- psychiatric disorders
- Parkinson's disease
- Seizure disorders

Concomitant Medication

- Patients receiving concomitant psychotropic medication (tranquilizers, antidepressants, daytime sedatives, vasodilatators, or central nervous stimulants) were excluded from the study with the following exceptions:
  Occasional night sedation with chloral hydrate and in exceptional cases (chronic users) a benzodiazepine with a short half-life.
- Antihypertensive medications having psychotropic effects such as reserpine or propranolol were not allowed during the study.
- Anti-parkinson or anticonvulsant drugs were not permitted.
- Other necessary medication (basic therapy of multimorbid patients) was permitted during the course of the study only with stable and constant doses.

At each visit of the patient, the identity, dosage and frequency of administration of all concomitant medications were recorded.

The following wash-out periods were advised before the patients were randomized to treatment:

- Tricyclic antidepressants: one week, with the exception of fluoxetine requiring four weeks
- Benzodiazepines: two weeks (with the exception of an occasional bedtime hypnotic)
- Antipsychotics: two weeks

2.1.3. *Medication*

The treatment phase lasted four weeks including a run-in period of ascending doses of seven days and was preceded by the wash-out phase depending on premedication, see 2.1.2.

The test drugs were Memantine as tablets of 10 mg Akatinol Memantine^{R} (Batch No. 90101); manufacturer: Merz + Co., Frankfurt/Main, and placebo tablets of identical appearance. The tablets were to be taken at mealtimes (no special dietetic restrictions), the last tablet not later than 4.00 pm to avoid sleep disturbances.

The dose regimen was: one tablet of Memantine/day on days 1 and 2, two tablets/day from day 3 to day 7, and three tablets/day through days 8–28. The dose was allowed to be reduced to two tablets per day in case of intolerance of 30 mg/d.

2.1.4. *Study Schedule*

The clinical and behavioural baseline examination was carried out after the initial wash-out period. Three subsequent examinations followed in intervals of one and two weeks. All four examinations of each patient were carried out by the same physician and the same nurse staff.

The schedule of the entire study is shown in Table 1.

2.1.5. *Efficacy Assessment*

As main target criteria for efficacy the following assessment scales were used:

- Global assessment of clinical efficacy (4 point scale) by the physician,
- the Sandoz Clinical Assessment Geriatric Scale SCAG (total score) (VENN, 1983; CIPS, 1986), rated by the physician,

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