A comparison of the predictive therapeutic and undesired side-effects of the NMDA receptor antagonist, memantine, in mice

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Memantine (1-amino-3,5-dimethyl-adamantane) is the only clinically used NMDA (N-methyl-D-aspartate) glutamate receptor antagonist. The present experiments were carried out to compare the dose-responses for memantine's predictive therapeutic and side-effects in a variety of tests in C57BL/6J/Han mice, and to elucidate if tolerance may develop to them. Memantine produced a dose-dependent (2.5–15 mg/kg) antidepressant-like effect in the tail-suspension test (TST); this anti-immobility effect of 15 mg/kg of memantine appeared to persist with its sub-chronic administration (3 days, twice daily). Treatment with the same doses of memantine produced no effects on locomotor activity, and sub-chronic treatment with 15 mg/kg did not affect locomotor activity. Exploratory activity was assessed in the open field. Given acutely 5 min before the test, memantine reduced rearing (1.875–30 mg/kg), ambulation (7.5 and 30 mg/kg) and grooming (30 mg/kg). These effects were more pronounced 35 min after its administration. As measured in three different tests, ataxia and stereotypy appeared only at the single dose of 30 mg/kg, 5 and 35 min after administration. In mice treated sub-chronically with 30 mg/kg, the dose of 30 mg/kg increased ambulation, and continued to decrease rearing and grooming, but no signs of ataxia and stereotypy were detected. The present data indicate that different doses of memantine are required for the purportedly therapeutic and side-effects, and that tolerance may develop to the ataxic, but not anti-immobility actions. *Behavioural Pharmacology* 16:155–161 © 2005 Lippincott Williams & Wilkins.

Behavioural Pharmacology 2005, 16:155–161

Keywords: NMDA, memantine, depression, antidepressants, ataxia, locomotor activity, mouse

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Sponsorship: This study was supported by statutory activity of IF PAN, Krakow, Poland.

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Received 12 November 2004 Accepted as revised 22 February 2005

Introduction

The rise in interest in the therapeutic effects of agents that inhibit glutamatergic neurotransmission started with the discovery of antagonists of the NMDA (N-methyl-D-aspartate) receptor (Meldrum, 1992). Preliminary data indicated that antagonists of this receptor produce a number of potential therapeutic actions, including neuroprotective, antidepressive and anti-epileptic effects, as well as effects suggesting their use in the treatment of Alzheimer's and Parkinson's diseases. NMDA receptor antagonists (NMDAR-As) also appear to inhibit various manifestations of addictive disorders, and may be used in the treatment of spasticity (reviewed by Danysz and Parsons, 1998).

However, at almost the same time, researchers realized that at least some of NMDAR-As produce a number of undesired side-effects, including locomotor stimulation, ataxia, cognitive impairment and psychotomimetic actions. In particular, the discouraging human data with compounds characterized with high affinity to the NMDA receptor complex (Leppik et al., 1988; Sveinbjornsdottir et al., 1993) suppressed the initial enthusiasm for the potential clinical use of NMDAR-As. These findings also led to research on, and the development of, other compounds that could inhibit glutamatergic neurotransmission and yet produce no, or minimal, side-effects. Among such compounds are functional antagonists of metabotropic glutamate receptors (Conn and Pin, 1997) and inhibitors of glutamate carboxypeptidase II (NAAWDase), the enzyme crucial for the synthesis of glutamate (Jackson and Slusher, 2001). Although the clinical future of these compounds is at present unknown, preliminary reports suggest that these methods of decreasing the glutamatergic tone may indeed produce fewer undesired side-effects.

While the clinicians await inhibitors of glutamatergic neurotransmission that are effective and free of side-effects, it is worth noting that the NMDAR-A, memantine (Axura™, Ebixa™, Namenda™) has been used clinically in Europe for more than 20 years, as Akatinol. Memantine has recently been registered in the EU and USA for the treatment of Alzheimer's disease. This uncompetitive NMDAR-A, with fast binding kinetics and relatively moderate (~1 μmol/l) affinity (for an extensive
review see Parsons et al., 1999), was synthesized as an agent to lower elevated blood sugar levels (Gerzon et al., 1963), although it appeared to be devoid of such activity. At present, the pharmacological profile of memantine is well known. It produces neuroprotective, antidepressant-like and antiparkinsonian effects in animals, and inhibits various manifestations of drug dependence, seizures/epilepsy and chronic pain (Parsons et al., 1999).

In the present study we compared the doses of memantine necessary to produce predictive therapeutic and unwanted side-effects in mice, in the same laboratory settings. We investigated the potential antidepressant-like effect using the tail-suspension test (Steru et al., 1985), accompanied by investigation of possible locomotor stimulatory actions that could account for the decrease of immobility. Although the antidepressant-like effects of memantine have been reported in rats (Moryl et al., 1993), to our knowledge such activities have not been investigated in mice. Second, we investigated the dose- and time-related effects of memantine on open-field behavior (exploratory activity, including ambulations, rearing and grooming) as well as on ataxia and stereotypy.

At present it is unknown whether NMDAR-A subtypes such as memantine will be used for the treatment of depression and/or other chronic diseases beyond Alzheimer’s; however, treatment of such disorders would require prolonged drug administration. Therefore, we investigated whether some of the predictive therapeutic and unwanted side-effects of memantine would tolerate with time.

Methods

All experiments were carried out according to the National Institutes of Health Guide for Care and Use of Laboratory Animals (revised 1996) and were approved by the Institute of Pharmacology, Polish Academy of Sciences in Kraków Animal Care and Use Bioethics Commission.

Subjects

The study was carried out on male C57BL/6J/Han mice (M. Staniszewska breeding facility, Ilkowice, Poland) weighing ~22 g at the start of the experiment. Mice were housed in standard laboratory cages (40 x 25 x 15 cm (l x w x h)) in groups of 10 per cage, under standard colony conditions: room temperature 21 ± 2°C, 12-hour light/dark cycle (light on: 07.00 hours) with free access to commercial food and tap water. Unless indicated otherwise, 10 mice were used for each dose treatment. In the experiment employing acute treatment with memantine, mice that were used for the tail suspension test (TST) were used 1 week later in the locomotor activity study. Otherwise, all subjects were used once.

Procedures

Tail suspension test

Mice were transferred from the housing room to the testing area in their home cages and allowed to adapt to the new environment for at least 1 h before drug treatment. Vehicle or memantine were administered 40 min before the test. In the case of sub-chronic treatment, vehicle or memantine (15 mg/kg) were administered twice a day for 3 days, with the last dose given on the fourth (test) day. Immobility was induced by tail suspension according to the procedure of Steru et al. (1985). Mice were attached individually on a paper adhesive tape, 65 cm above the table top. The tape was placed approximately 1 cm from the tip of the tail. Animals were suspended for 6 min and the duration of immobility was recorded using the ‘Porsolt’ data collection program (Infallible Software, California, USA). Mice were considered immobile only when they were completely motionless.

Locomotor activity

At least 1 h before the start of the experiment, mice were transferred to the experimental room for acclimation. The spontaneous locomotor activity was measured in custom-made circular aluminum actometers (30 cm diameter, 10 cm height, with two light sources and two photoresistors, arranged so the beams crossed at the center). The construction of the apparatus allowed collection of only the gross movement data. Subjects were injected 40 min before the test and placed individually in an actometer for 6 min of measurement. This way, mice were not adapted to the apparatus, to mimic the conditions of the TST (see above).

Phencyclidine-like side-effects battery test

Drugs were administered 5 min before the beginning of test battery. After the tests, mice were returned to their home cages and assessed in the test battery for the second time, 35 min after drug administration. In the case of sub-chronic treatment, vehicle or memantine (30 mg/kg) were administered twice a day for 3 days, with the last dose provided on the fourth (test) day.

The elevated platform test (Evoniuk et al., 1991) consisted of placing individual mice on a glass Petri dish (15 cm diameter, 0.5 cm deep), mounted on the top of a rigid (60 cm height) platform. Normal mice stay on the elevated Petri dish; mice displaying a ‘phencyclidine-like syndrome’ walk out of it (Evoniuk et al., 1991). The latency to fall from the platform was measured for up to 4 min. Falling mice were gently caught by the experimenter.

Immediately after the elevated platform test, mice were placed in the open-field arena, where exploratory activity was assessed. Subjects were placed at the center of the
black-painted plywood rectangular arena \([60 \times 60 \times 20 \text{ cm}} \)] \((l \times w \times h)\) divided into a uniform grid \((20 \times 20 \text{ cm})\) by horizontal and vertical lines. The test lasted for 4 min and the horizontal activity (ambulation) was recorded by counting the number of lines crossed by the mouse. Vertical activity was measured by counting the number of rearings performed by the mouse. The number of grooming bouts was also scored. The test arena was uniformly lit \((150 \text{ Lux})\) and was cleaned after each mouse.

During the open-field test, mice were also inspected for ataxia and stereotypy. Ataxia intensity was measured according to Danysz et al. (1994) as: no ataxia = 0, 'duck' walking = 1 and strong 'duck' walking = 2 points, respectively. Stereotypies recorded were: sniffing, circling, penile licking and head waving. The global stereotypy score was the sum of these behaviors.

**Drugs**

Memantine HCl and ketamine HCl [10% aqueous solution \((115.34 \text{ mg/ml})\)] were purchased from Tocris, Ellisville, USA and Biowet, Pulawy, Poland, respectively. All drugs were dissolved in sterile \(0.9\% \text{ NaCl}\) solution (physiological saline), used as the vehicle. All injections were given in a volume of \(10 \text{ ml/kg}\).

**Statistics**

Data were analyzed statistically using Statistica 5.0 for Windows. To assess effects of acute treatments on TST and locomotor activity, one-way ANOVAs followed by Duncan's test were used. For the assessment of effects of sub-chronic treatment, Student's \(t\)-test was used. The effects of both acute and sub-chronic treatments on the phencyclidine-like side-effects test battery were assessed with two-way repeated-measures ANOVAs followed by Duncan's test.

**Results**

**Effects of memantine on the TST and locomotor activity**

Given 40 min before the test, memantine produced a dose-dependent reduction of immobility in the TST \([F(6.63) = 21.10, P < 0.001]\) (Fig. 1). Only one dose \((1.875 \text{ mg/kg})\) did not significantly decrease immobility time. In a separate group of mice, a significant reduction of immobility produced by \(5 \text{ mg/kg}\) of memantine was detected as long as 240 min after administration: the immobility times in vehicle- and memantine-treated mice were 171.7 ± 15.9 and 109.4 ± 11.6 s, respectively \([t(18) = 3.16, P < 0.001]\). In contrast, none of the investigated doses of memantine affected locomotor activity \([F(5,54) = 1.86, NS]\) (Fig. 2).

Sub-chronic treatment with \(15 \text{ mg/kg}\) of memantine did not affect the ability of the same dose to decrease immobility time \((t = 5.06, P < 0.001)\) (Fig. 3). The same drug treatment regimen did not appear to affect locomotor activity significantly \((t = 0.93, NS)\) (Fig. 4).

**Effects of memantine in phencyclidine-like side-effects battery test**

Preliminary experiments with ketamine demonstrated that administration of this compound 5 min before the test produced falling from the elevated platform with a minimum effective dose (MED) of \(25 \text{ mg/kg}\) (data not shown, manuscript in preparation). In contrast, neither acute, nor sub-chronic administration of memantine resulted in falling from the elevated platform (Table 1). Ataxic ('duck' walking and strong 'duck' walking) effects
Effects of sub-chronic treatment with 15 mg/kg of memantine on the immobility time in the tail suspension test (TST) in C57BL/6J/Han mice. Memantine (15 mg/kg) was given twice a day for 3 days and 40 min before the test on day 4. The animals were observed for 6 min. The results are presented as mean ± SEM; n = 10 per dose. ***P < 0.001 versus vehicle.

Effects of sub-chronic treatment with 15 mg/kg of memantine on locomotor activity in C57BL/6J/Han mice. Memantine (15 mg/kg) was given twice a day for 3 days and 40 min before the test on day 4. The time of observation was 6 min. The results are presented as mean ± SEM; n = 10 per dose.

Similarly, stereotypies (sniffing, circling, penile licking and head waving) were present only at the highest dose investigated (30 mg/kg) and disappeared after sub-chronic administration.

Given acutely, memantine produced different effects on exploratory activity in the open-field test. The number of lines crossed (horizontal activity) was decreased by administration of memantine at the doses of 7.5 and 30 mg/kg, 5 min after administration, as well as at 30 mg/kg, 35 min after administration. Control, vehicle-treated mice demonstrated a diminution of horizontal activity in the second test. A similar diminution of horizontal activity was observed in mice treated with 1.8, 15 and 30 mg/kg of memantine, 35 min after its administration. Treatment with memantine reduced also rearing and grooming in the open field; the decrease of grooming was more apparent on the second measurement carried out 35 min after drug administration.

Administration of memantine, at 30 mg/kg, to mice treated sub-chronically with the same dose, resulted in an increase of horizontal activity, an effect opposite to the acute action of the same dose of memantine. However, in sub-chronically treated mice, memantine continued to decrease rearings and groomings.

**Discussion**

Experience with clinical use of memantine suggests that, if properly dosed (with an increasing dose titration regimen over 2–4 weeks, 5–30 mg), it produces minimal or no side-effects; however, the large (≥5 mg) doses taken acutely may result in drowsiness, dizziness or fainting (Bisaga and Evans, 2004). The fact that memantine is well tolerated in humans is most likely due to its moderate affinity (~1 μmol/l) at NMDA receptors, fast binding kinetics and strong voltage dependency; this relationship was proposed more than 10 years ago (Parsons et al., 1993; Rogawski, 1993).

At doses of 2.5–15 mg/kg, memantine produced a dose-dependent antidepressant-like effect in the TST; this anti-immobility effect of memantine (15 mg/kg) appeared not to tolerate with its sub-chronic (3 days, twice daily) administration. Similar antidepressant-like effects of memantine have been described in the forced swim (Porsolt's) test in rats for doses of 5–20 mg/kg (Moryl et al., 1993), and agree well with similar actions of other NMDAR-As, including MK-801, ACPC and AP-7 (Trullas and Skolnick, 1990; Maj et al., 1992). Moreover, this antidepressant-like effect of memantine is not surprising in light of the involvement of NMDA receptors in the neurochemical effects of antidepressants (Paul et al., 1994; Skolnick et al., 1996). Recent data demonstrate similar behavioral antidepressant-like effects of other inhibitors of glutamatergic neurotransmission, including...
The reduction of exploratory activity in the open field by antidepressant-like effects (ONeil and Moore, 2003). A field test (Moryl et al., 2003) at doses 5–20 mg/kg did not affect ambulation in an open-field test. Similar results were reported for rats, in that memantine treatment with memantine at 15 mg/kg to mice treated sub-chronically with the same dose still produced an antidepressant-like action and still did not affect locomotor activity. These findings may suggest that prolonged treatment with memantine would not result in the development of tolerance to its potentially therapeutic effect. It is known that the therapeutic effects of memantine (as used in the treatment of Alzheimer’s disease) do not tolerate with time (Parsons et al., 1999).

<table>
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<tr>
<th>Memantine</th>
<th>Treatment (mg/kg)</th>
<th>% drug falling</th>
<th>Ataxia intensity ± SEM</th>
<th>Global stereotypy score ± SEM</th>
<th>Open field (episodes/4 min) ± SEM</th>
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Statistics

- *P =< 0.05 versus vehicle
- *P < 0.05 versus corresponding dose at time 5 min
- Duncan’s test.

Table 1: Effects of acute and sub-chronic (3 days, twice daily, 30 mg/kg) administration of memantine on ‘phencyclidine-like side-effect’ battery tests in C57BL/6J/Han mice

Two-way repeated-measure ANOVA symbols: *P < 0.05 versus vehicle, *P < 0.05 versus corresponding dose at time 5 min. Duncan’s test.

an antagonist of mGlu 5 receptors, MPEP (Tatarczynska et al., 2001). While the clinical usefulness of NMDAR-As, including memantine, in the treatment of depressive disorder remains to be critically elucidated, Berman et al. (2000) demonstrated that ketamine decreased the symptoms of depression in patients and that these effects substantially outlasted ketamine-induced psychotomimetic actions.

Treatment with doses of memantine that effectively shortened immobility (2.5–15 mg/kg) did not affect locomotor activity in actometers, and exploratory activity in the open-field test was even reduced. These data indicate that the anti-immobility effects of memantine in the TST were not due to a general increase of activity. Similar results were reported for rats, in that memantine at doses 5–20 mg/kg did not affect ambulation in an open-field test (Moryl et al., 1993). This is important information because drugs that increase locomotor activity (such as amphetamine) are known to be ‘false-positives’ in the screening tests that predict potential antidepressant-like effects (ONeil and Moore, 2003). The reduction of exploratory activity in the open field by memantine given acutely suggests its sedative effects, agreeing with similar observations in humans (Bisaga and Evans, 2004).

Administration of memantine at 15 mg/kg to mice treated sub-chronically with the same dose still produced an antidepressant-like action and still did not affect locomotor activity. These findings may suggest that prolonged treatment with memantine would not result in the development of tolerance to its potentially therapeutic effect. It is known that the therapeutic effects of memantine (as used in the treatment of Alzheimer’s disease) do not tolerate with time (Parsons et al., 1999).

Treatment with memantine did not produce falling from the elevated platform, but did produce ataxia and stereotypy, though only at the single dose of 30 mg/kg, 5 and 35 min after administration. The ataxic effects of memantine (20 mg/kg) have been described in the rat (Hesselink et al., 1999) and mouse (ED_{50} ~ 24 mg/kg) (Geterdouglas and Witkin, 1999). Doses producing ataxia agree with observations of Neznanova et al.
(2000) and our data (30 mg/kg), despite the use of different tests. Ataxic effects were also reported by some patients treated acutely with relatively high doses of memantine (Bisaga and Evans, 2004). As in the former (Neznanova et al., 2000) and the present study with mice, the ataxic effects of memantine in rats appeared to tolerate with repeated administration (see Hesselink et al., 1999, and references therein, regarding similar phenomena with other NMDAR-As). Moreover, Hesselink et al. (1999) also reported that the amnesic effects of a high dose of memantine tolerated with repeated administration.

Stereotypies (head waving, etc.) are typically attributed to NMDA receptor blockade with a strong dopaminergic component of action. The data of Danysh et al. (1994) showed that memantine produces such effects at extremely high doses (≥ 60 mg/kg). Stereotypies observed in the current study also occurred at the high dose studied (30 mg/kg) and tolerated with repeated administration.

Exploratory activity, assessed in the open field, was differently affected by acute and sub-chronic treatment with memantine. Acutely, as measured 5 min after administration, memantine reduced rearing, ambulation and grooming, and these effects were more pronounced 35 min after memantine administration. The inhibition of grooming by memantine may reflect a behavioral disturbance, but relatively intense grooming observed in control mice might instead be due to displacement behavior, a manifestation of anxiety in a novel or stressful environment (Kalin, 1989). Its inhibition might thus reflect the anxiolytic action produced by memantine. The memantine-induced decrease of ambulation and rearing could be due to several factors, including numerous methodological issues. Moryl et al. (1993) reported that doses of 3–20 mg/kg did not affect ambulation, peeping + rearing behavior and walking time in Wistar rats. Others reported an increase of locomotor activity in the holeboard apparatus (Ljungberg, 1986); however, this was investigated in well-habituated animals and for a longer duration of testing. The decrease in rearing (i.e. vertical activity) might be due to myorelaxation, but other explanations cannot be ruled out. For instance, the relatively high intensity of rearing in control mice might be due to the fear of searching for predators, and its diminution could reflect an anxiolytic action (Adamec et al., 1999).

Interestingly, in mice treated sub-chronically with 30 mg/kg of memantine (the dose that produced reliable side-effects), this dose increased ambulation, and continued to decrease rearing and grooming. An increase in ambulation after repeated treatment could be due to several factors. For instance, mice might have developed tolerance to the inhibitory effects on exploratory activity (e.g. sedation), as they did to the ataxic effects, and the stimulating effects could become unblocked/revealed. It is also possible that memantine produced a locomotor sensitization, as seen in the rat study (Hesselink et al., 1999) that revealed a similar increase of horizontal activity by a relatively high (20 mg/kg) dose administered intermittently. The persistence of memantine-induced diminution of rearing and grooming behaviors, purportedly reflecting anxiolytic actions (Kalin, 1989; Adamec et al., 1999), could be due to the fact that these effects of memantine neither tolerate nor sensitise due to the sub-chronic treatment.

In the present study we explicitly used different doses of memantine to evaluate the development of tolerance to the antidepressant-like and side-effects. The reason of such an asymmetrical design was twofold. First, the use of the dose of 15 mg/kg in the side-effects study could be viewed as inappropriate, because memantine given acutely produced ataxia and stereotypy only at 30 mg/kg. Second, the use of the dose of 30 mg/kg in the antidepressant-like effects study could also be regarded as unfortunate because the drug reduced immobility at the dose as low as 2.5 mg/kg. Another limitation of the present study lies in the fact that mice treated sub-chronically with the high dose frequently experienced ataxia and stereotypy, and thus had a chance to develop behavioral tolerance to the actions of memantine (e.g. by recruiting counteracting adaptive mechanisms; O’Brien et al., 1986). In contrast, mice treated sub-chronically with a lower dose (15 mg/kg) were tested in the TST only once, and had no chance to adapt their behavior to the effects of memantine prior to testing. Whether this discrepancy could account for the development of tolerance to the side-effects but not antidepressant-like actions could not be answered in the present experiments, which employed a simple screening test for antidepressant effects that requires only one behavioral test.

Taken together, if one would assume that ataxia and stereotypies represent the distinctively measurable undesired side-effects of NMDAR-As in rodents, our data suggest that: (1) these effects of memantine occur at much higher doses than those required for the purportedly therapeutic actions; and (2) tolerance develops to the side-effects but not antidepressant-like actions. It is also worth noting that doses reducing immobility time in the TST produce the most relevant brain concentrations, because in rats, acute i.p. administration of 5–10 mg/kg of memantine leads to plasma levels of 1.0–3.2 µmol/l, corresponding to rat brain microdialysate levels in the range of 0.3–1.0 µmol/l (Parsons et al., 1999). Since memantine displaces the binding of [3H]MK-801 in human cortex, rat cortex and the CA1 region of hippocampus, with Kᵦ of ~1 µmol/l, and antagonizes NMDA receptor-mediated inward currents with similar
potency (Parsons et al., 1999), one may conclude that administration of the doses of ~5 mg/kg would produce the pharmacodynamically most relevant effects. Indeed, this is the ED50 that antagonizes NMDA-induced convulsions in mice (Bisaga et al., 1993) and inhibits morphine withdrawal (Popik and Skolnick, 1996).

From this perspective, the present data, indicating significant separation of doses required for the predictive therapeutic and side-effects, support earlier findings demonstrating that memantine could be a well-tolerated NMDA receptor antagonist.

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