Amantadine Reduces Mania in Borna Disease Virus-Infected Non-Psychotic Bipolar Patients

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This study investigated the clinical use and safety of amantadine in acute mania in an on-off-on design. Amantadine was augmented (200 mg/day) to pre-treatment strategies for 6 days, stopped for 6 days, and administered for another 6 days (on-off-on) in 10 manic inpatients. Manic symptoms were reduced in the first study period (on) by 45.8 % [Young Mania Rating Scale (YMRS)]. Eight patients also finished the second period (off) which was not paralleled by any further reduction of mania. The third study period (on) was finished by seven patients with a further decrease of about 61.5 %. The overall reduction from baseline after 18 days was 79.2 % in this group. Amantadine augmentation reduced severe hypomania and moderate mania in BDV-infected bipolar I or II patients and was very well tolerated, especially no psychotic symptoms were observed.

Introduction

Treatment options in bipolar manic patients have been improving during the past two decades, however, strategies targeting possible aetiopathogenetic factors are still lacking. Borna disease virus (BDV) causes behavioural disturbances in animals [6,9]. Besides BDV-specific antibodies, viral components (proteins, RNA) were detected in peripheral blood mononuclear cells (PBMC) from psychiatric patients [5], and the infectious virus could be isolated from PBMCs [4] and the brain [11]. Controversial findings [10] on the prevalence of BDV appear to result from different infection markers and detection methods [2]. Correlative evidence of the clinical diagnosis with laboratory findings for monitoring BDV infection was and still is complicated by debates on the significance of infection markers [1,3]. Doubts on the specificity of the BDV detection system recently raised by Wolff et al. [13] have been refuted by Flower and Ludwig [8]. Antiviral treatment with amantadine reduces both depression and viral activity in BDV-infected patients with bipolar disorders and recurrent depression [7]. Two recent pilot studies in manic patients furthermore provided evidence that amantadine, when augmented to pre-treatment strategies, improved manic episodes [3,12].

This present study investigated the clinical use and safety of amantadine in mania in an on-off-on design to provide information that is easier to interprete regarding the *efficacy and safety* of amantadine in a naturalistic treatment of acute mania.

*The author's opinion does not reflect the opinion of the Robert Koch Institute

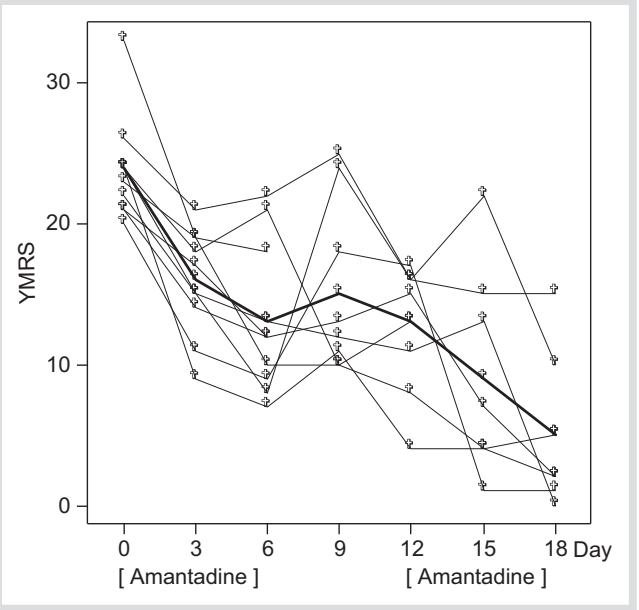

Fig. 1 The course of manic symptoms as rated on the Young Mania Rating Scale (YMRS) of the ten single patients (thin lines) and their means (thick line; day 6: n = 10, day 12: n = 8, day 18: n = 7) during the administration of amantadine in this on-off-on trial.

Patients and Methods

The study was approved by the local ethics committee, and the ten manic inpatients who were included in this trial gave written informed consent. All fulfilled DSM-IV criteria of bipolar I (n = 7) or II (n = 3) disorder – one patient with rapid cycling – recently manic (5 men and 5 women; mean age: 56.6 ± 8.9 years; educational years: 14.0 ± 4.2 years; mean duration of disease: 24.7 ± 10.3 years; mean duration of the current episode: 27.2 ± 14.6 days; mean frequency of episodes: 2.5/year) with a score on the Young Mania Rating Scale (YMRS) of at least 20 (mean 23.7 ± 3.7). Their ability to give informed consent was confirmed by another psychiatrist not participating in the study. Other DSM-IV disorders and suicidality were defined as exclusion criteria. Blood samples were taken to exclude other major diseases and to investigate the BDV-infection during this trial. Nine of 10 patients were BDV-infected. BDV-specific CICs were detected as described by Bode [2]. Baseline medication with mood-stabilizers (e.g., lithium, carbamazepine, valproate) was not changed during the study period. A co-medication with oxazepam (10 mg/d) or diazepam (5–10 mg/d) was used in 3 patients.

Amantadine was augmented (200 mg/day, given not later than 2:00 pm) to pre-treatment strategies for 6 days, stopped for the following 6 days, and administered for another 6 days (on-off-on). Mania-related symptoms and unwanted effects as well as BDV activity were documented with regard to amantadine treatment.

Results

All 10 patients finished the first study period (on). The manic symptoms (YMRS) were reduced by 45.8 % ($p < 0.001$). Eight patients also finished the second period (off) which was not paralleled by any further reduction of mania. The third study period

(on) was finished by seven patients with a further decrease of about 61.5% in these six days ($p=0.018$). The overall reduction from baseline after 18 days was 79.2% ($p<0.001$) in this group (**Fig. 1**). The clinical improvement was not paralleled by a reduction of BDV parameters during this rather short treatment period. Regarding side effects, one patient reported temporary dryness of the mouth and another patient itching of the scalp. The drop-out of the three patients was not related to severe side effects.

Discussion

Amantadine augmentation reduced hypomania and moderate mania in BDV-infected bipolar I or II patients and was very well tolerated, especially no psychotic symptoms were observed. Furthermore, patients even felt better during the amantadine treatment periods compared to the non-treatment periods. The latter may explain the low drop-out rate of only 3 patients by the end of this trial. As amantadine could be expected to even increase manic symptoms due to its versatile pharmacological properties, the antimanic effects observed in our patients remarkably contrasted this view. No reduction of BDV parameters at the blood level could be determined due to the short period of 18 days. However, peripheral blood levels do not necessarily reflect the brain levels which may not only be different between brain and periphery, but also between brain areas. Prospective, double-blind and placebo-controlled studies seem reasonable.

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Choreatic Symptoms During and After Treatment with Paliperidone and Escitalopram

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Paliperidone, the first orally applicable atypical neuroleptic marketed as an extended-release preparation, is generally well tolerated [1,5]. Over the last weeks, we have observed several young patients with schizophrenia, who showed significant akathisia during paliperidone treatment. Here we report the case of a depressed and psychotic patient who developed a dramatic choreatic syndrome during treatment with escitalopram and paliperidone.

Case Report

A 62-year-old patient had been admitted with major depression and psychotic features (ICD 10 F33.3). Earlier treatment with valproate and quetiapine had no lasting beneficial effect, and she was therefore started on escitalopram 10 mg/day and paliperidone 6 mg/day. During that treatment she showed remarkable fluctuations of affective and psychotic symptoms from day to day. After 25 days she developed a moderate rigidity of both arms and severe hypomimia, together with distressing motor restlessness (akathisia, fidgeting movements). The patient appeared agitated and "nervous" without being overconcerned. Paliperidone was discontinued. Three days after the discontinuation of paliperidone, she suffered from incapacitating and nearly constant choreo-athetotic movements of her extremities and tongue, interrupted by frequent myoclonic jerks. These symptoms could not be suppressed deliberately, but subsided promptly after the administration of lorazepam, 2 mg. Benzodi-