Annals of General Psychiatry

Poster presentation

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Zotepine loading in acute and severely manic patients: a pilot study

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from International Society on Brain and Behaviour: 2nd International Congress on Brain and Behaviour
Thessaloniki, Greece. 17–20 November 2005

Published: 28 February 2006

Annals of General Psychiatry 2006, **5**(Suppl 1):S173 doi:10.1186/1744-859X-5-S1-S173

Background

In clinical practice patients with severe mania (agitation, insomnia and aggressive behaviour) usually receive effective, but mostly not well tolerated typical antipsychotics. The aim of the study was to test the first generation atypical antipsychotic zotepine regarding its antimanic efficacy, tolerability and to find an adequate dosage for a loading strategy. Zotepine belongs to the group of dibenzothiepines with a tricyclic structure. It exercises a marked blocking action on the D1 and D2 receptors (on D1 receptors more marked than the classical antipsychotics) as well as on 5-HT1 and even more 5-HT2 receptors.

Materials and methods

Twelve patients (5 female, 7 male) with a severe manic episode were recruited from the Departments of Psychiatry of the Universities of Munich and Berlin. Inclusion criteria were an acute manic episode or a schizomanic episode as defined by the DSM-IV, age between 18–65, and written informed consent.

Patients were investigated by a thorough medical examination including ECG and blood tests. The following psychiatric ratings were done at baseline, day 1, day 2, day 4, day 7, day 14 and day 21: Young-Mania Rating Scale (YMRS), Hamilton Depression Rating Scale (Ham-D-17 items), and Clinical Global Impression Bipolar Version Scale (CGI-BP). Also, spontaneously expressed or observed side effects were recorded. Furthermore, changes in weight were measured at baseline and at endpoint.

All patients were loaded on day 1 with zotepine monotherapy in a median dosage of 245 ± 68.5 mg (range: 200–400 mg). During the study the dosage of zotepine was adjusted depending on the psychopathology and side effect profile of each patient ranging from 150 mg up to 600 mg daily. Additionally, oxazepam was allowed as rescue medication in a daily dosage up to 40 mg

Results

Twelve patients gave written informed consent and were included in this trial. Two male patients dropped after two days due to incompliance and due to side effects, respectively. All analyses were based on ten patients receiving zotepine for at least two days.

Nine of the ten patients fulfilled the response criterion (50% reduction in the YMRS) after two weeks. Response was observed within four days in four patients, in one patient after 7 days and in four patients after 14 days. The median YMRS declined from baseline to day 14 from 44.1 ± 7.00 (range: 36–58) to 17.6 ± 8.0 (range: 5–31). Interestingly, the median HAMD also decreased from 4.9 ± 6.1 (range: 0–18) to 2.7 ± 4.2 (range: 0–13) which suggests a non-depressiogenic profile of zotepine. The CGI-BP confirmed the clinical improvement of the patients with a change of the median baseline of 5.9 (range: 5–7) to 4.0 ± 0.9 (range: 2–5) after two weeks.

Spontaneously reported and elicited side effects were resolved either without treatment or by dosage reduction. However, one patient dropped due to side effects. After receiving 400 mg of zotepine the patient was very sedated, dysarthric and developed an increased heart rate (up to 150/min) and blood pressure (up to 150/95) the following day. The patient also withdrew his informed consent and was consecutively excluded from the study.

Four patients developed extrapyramidal motoric side effects, such as tremor (n = 2), rigidity (n = 2), akinesia (n = 1), akathisia (n = 1) and oral dyskinesia (n = 1).

One patient showed a transient increase in liver enzymes and in the EEG a general slowing of background activity and an increase in paroxysmal theta or delta activity without development of epileptiform discharges. One patient reported headache, one on nausea. Other reported side effects were: headache (n = 1), nausea (n = 1), constipation (n = 2), increased eye secretion (n = 1), accommodation disturbances (n = 3), polyuria (n = 1), dry mouth (n = 1), edema (n = 1), miction disturbances (n = 1), photosensibility (n = 2), reduced libido (n = 1) and tachycardia (n = 1). None of these side effects led to discontinuation.

Discussion

This open pilot study suggests that zotepine in a median daily dosage of 250 mg/d is an effective medication with a rapid onset in severely manic patients. In general, patients tolerated the drug reasonably well, but dose dependent extrapyramidal side effects, an increase of weight and autonomic side effects occurred in some patients. This is the first study with zotepine monotherapy in manic patients, but controlled studies are warranted to prove the efficacy of zotepine in manic patients.

References

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