Eur Arch Psychiatry Clin Neurosci (1996) 246:79–82

ORIGINAL PAPER

Jürgen Staedt · Gabriela Stoppe · Göran Hajak
Eckart Rüther

Rebound insomnia after abrupt clozapine withdrawal

Received: 18 July 1995 / Accepted: 6 November 1995

Abstract Rebound insomnia has been reported upon discontinuation of benzodiazepines. We describe the first case of a sleep polygraphically documented rebound insomnia with an unusual somatic fatigue syndrome after long-term use of clozapine in a 30-year-old schizophrenic male. The withdrawal symptoms occurred the first day after drug discontinuation and could be stopped by readministering clozapine. In our opinion, the sudden occurrence of the withdrawal symptoms cannot be explained by a dopaminergic hypersensitivity *or a cholinergic rebound,* but indicates an involvement of GABAergic and perhaps antiglutamatergic properties of clozapine.

Key words Rebound insomnia · Withdrawal symptoms · Clozapine

Introduction

The dibenzodiazepine derivative clozapine, an atypical neuroleptic with good antipsychotic properties and minimal extrapyramidal side effects (overview: Klimke and Klieser 1995), is restricted in Europe due to the risk of agranulocytosis (Anderman and Griffith 1977; Krupp and Barnes 1992; Lieberman and Alvir 1992) to acute and chronic forms of schizophrenia. In addition to allergic reactions to clozapine, severe withdrawal syndromes (supersensitivity psychosis or rebound psychosis) have been described after abrupt discontinuation of long-term treatment with clozapine in several studies (Dickson et al. 1994; Ekblom et al. 1984; Eklund 1987; Parsa et al. 1993; Perenyi et al. 1986; Simpson et al. 1978; Zapletalek et al. 1980). For the first time we describe the results of a sleep polygraphically documented rebound insomnia after abrupt withdrawal of clozapine.

Jürgen Staedt (✉) · Gabriela Stoppe · Göran Hajak
Eckart Rüther
Department of Psychiatry, Georg August University,
D-37075 Göttingen, Germany

Case report

A 30-year-old male patient suffers from schizophrenia according to the DSM-III-R critera and was treated with clozapine since his first hospitalization 2 years ago in our outpatient clinic. At his initial admission the patient exhibited auditory and olfactory hallucinations and persecutory delusions. His affect was blunted, his attention was poor, and he was ambivalent to pharmacological treatment approaches. First, he was treated with benperidol. This therapy was successful within 2 weeks, but the patient developed severe parkinsonian symptoms. Therefore, benperidol was replaced by clozapine (250 mg/day). Then, 144 days after hospitalization, the patient was discharged.

During the following 2 years the patient remained fully remitted and because of excessive sedation the clozapine dosage was reduced step by step to 75 mg/night (serum level 55 µg/l). Then, the medication was abruptly withdrawn for 1 week because of a suspected thrombopenia, which could not be confirmed later (computer error). During this week the patient complained within 24 h of severe insomnia, restlessness, and had every day several periods of chills and chattering of the teeth without having a fever. No changes in the mental status occurred during that time. At the end of the week clozapine treatment was reinitiated at 75 mg/night and the withdrawal symptoms disappeared within 24 h. In order to prove the reported rebound insomnia, we conducted a sleep polygraphic controlled clozapine withdrawal 3 months later (informed consent was obtained from the patient).

All-night polysomnographic recordings (PSG) including EMG of anterior tibialis muscles were performed for two consecutive nights, the first night with clozapine, and the second night without clozapine. The PSG recording and staging was done according to the standard criteria (Rechtschaffen and Kales 1968). The PSG recordings of the baseline night with 75 mg clozapine (serum level 55 µg/l) showed some difficulties in initiating sleep (sleep latency 104 min), but the sleep period was compact with

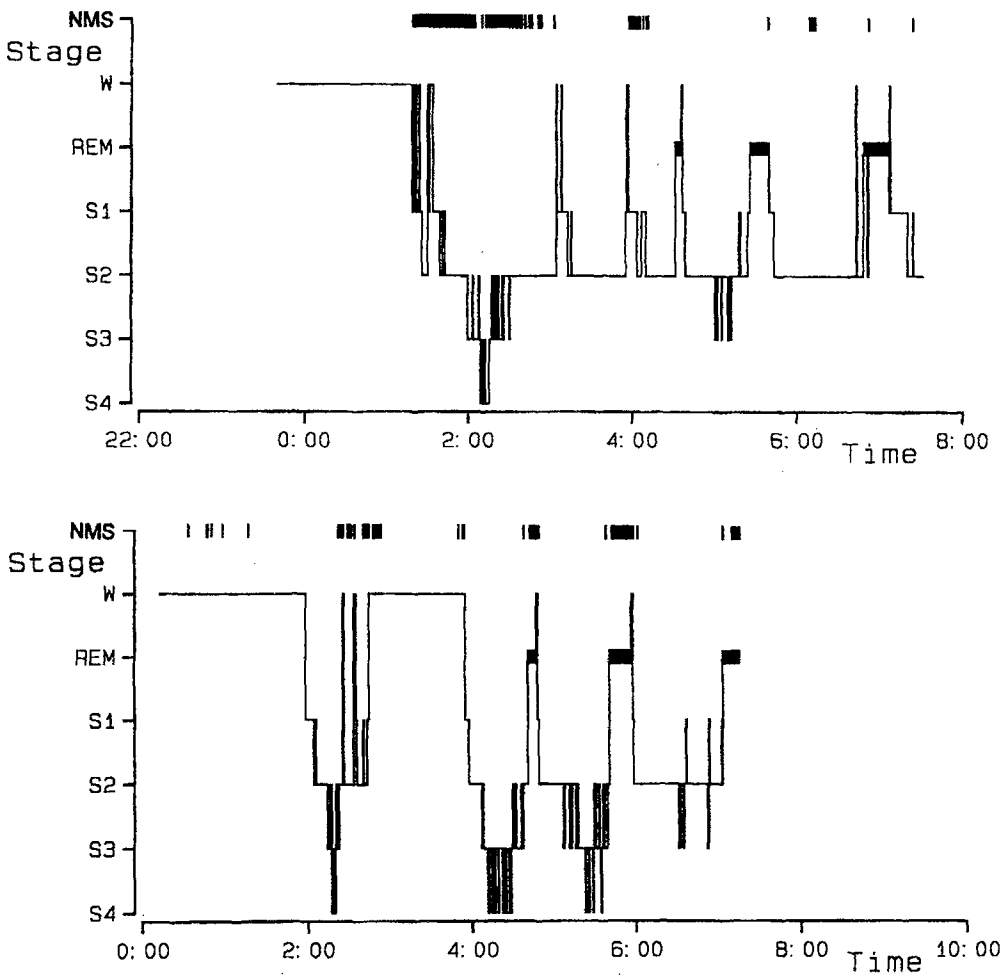

Fig. 1 Polysomnograms of a schizophrenic patient (sleep stages 1–4) *Top:* Somnogram of the first night on regular medication of 75 mg clozapine/night. *Bottom:* Somnogram of the second night without clozapine. NMS nocturnal myoclonus syndrome (see Staedt et al. 1995); REM rapid-eye-movement sleep; W wake (From Rechtschaffen and Kales 1968)

some slow-wave sleep (25 min; Fig. 1, top). In the first part of the night, the sleep quality was reduced by the appearence of a nocturnal myoclonus syndrome (NMS; see Staedt et al. 1995). The patient himself rated this night as representative. The second night without clozapine (serum level at 9:30 p.m.:46 µg/l; next day, serum level at 7:30 a.m.:44 µg/l) showed a fragmented sleep with a long period of wakefulness (Fig. 1, bottom). In comparison with the clozapine night, the patient had an increased wakefulness after sleep onset of 69 min compared with 2 min during the clozapine night.

Sleep efficiency was 56% compared with 78% during the clozapine night. After the withdrawal night, the patient was restless again and had a period of chills and chattering of the teeth, without having a fever. A relapse did not occur and the rebound insomnia disappeared after clozapine treatment was reinitiated at 75 mg/night.

Discussion

This case study is in accordance with previous results published by Zapletalek et al. 1980. They reported that an interruption of clozapine treatment can cause withdrawal symptoms including insomnia. In these cases therapy approaches with typical neuroleptics were unsuccessful and the withdrawal symptoms disappeared after clozapine reinitiation. In other patients different authors found an exacerbation of psychosis (Alphs and Lee 1991; Dickson et al. 1994; Ekblom et al. 1984; Eklund 1987; Parsa et al. 1993; Perenyi et al. 1986; Simpson et al. 1978).

One explanation for the rapid deterioration after clozapine withdrawal could be a clozapine-induced supersensitivity of central dopamine (DA) receptors. Based on behavioral studies in rats, Ungerstedt and Ljungberg (1977) first presented this hypothesis. Later, Chouinard and Jones (1980) emphasized that an essential feature for the supersensitivity psychosis is "positive" schizophrenic symptoms. But this concept is not consistent with the following observations:

1. Compared with typical neuroleptics, Alphs and Lee (1991) and Borison et al. (1988) observed a marked deterioration especially after clozapine withdrawal.
2. We observed the occurrence of rebound insomnia 28 h after clozapine withdrawal, despite only a slight reduction in the clozapine serum level from 55 µg/l to 46 µg/l (13.5 h withdrawal), and to 44 µg/l (35.5 h withdrawal).
3. In vivo positron emission tomography (PET) investigations (Baron et al. 1989; Cambon et al. 1987) following withdrawal fo oral neuroleptics found a return to normal

striatal dopamine receptor availability not before 3–15 days.

These findings suggest that the marked withdrawal syndrome after clozapine discontinuation is due to specific clozapine side effects, but not to a clozapine-induced dopamine supersensitivity because most of the DA receptors are still blocked and will return to a normal availability 72 h after withdrawal at the earliest.

The increased basal DA release after clozapine withdrawal (demonstrated by Meltzer et al. 1989 in animal experiments) has to compete with clozapine for the already-clozapine-occupied dopamine receptors and is not likely to cause a dopamine-supersensitivity syndrome.

Another explanation for the withdrawal syndrome after sudden clozapine discontinuation could be explained by a cholinergic rebound, because it is known that there is a greater frequency of withdrawal symptoms in patients receiving neuroleptics with potent anticholinergic effects (for a review see Luchins et al. 1980). Following this point of view, we would have expected a pronounced rapid-eye-movement sleep (REM) rebound after discontinuing the highly anticholinergic clozapine, due to an increased cholinergic activity. However, that was not the case compared with the clozapine night. The time spent in REM even decreased during the withdrawal night (35.5–33.5 min). This should exclude the possibility of a cholinergic rebound phenomenon. The abrupt occurring of the withdrawal syndrome with reduced total sleep time, reduced sleep efficiency, increased sleep latency, and increased total wake time resembles what can be observed after discontinuation of short half-life benzodiazepines (Gillin et al. 1989), and therefore could be mediated by GABAergic qualities of clozapine. Using in vivo animal experiments, Drew et al. (1990) found that the acute administration of clozapine increases cerebral GABA release. Graham and Kokkinidis (1993) reported that clozapine, in contrast to haloperidol, produced a kindling inhibition which was dependent on daily clozapine administration. Clozapine and its active metabolites have along half-life (16–24 h), and according to their observations, changes in the steady state of clozapine serum level could promote kindling by the inhibition of GABA release. By the same mechanism the abrupt withdrawal of clozapine could mediate the acute sleep disturbances.

Based on these considerations, daily-dose-dependent influences of clozapine on the GABAergic system may play a role in its withdrawal side effects. In addition, clozapine is more effective than haloperidol in displacing [H3]MK-801 (noncompetitive NMDA antagonist) binding to glutamate receptors (Lidsky et al. 1991). Thus, antiglutamatergic mechanisms could also be involved in clozapine withdrawal effects.

Taking these considerations into account, the occurrence of a so-called rebound psychosis after clozapine withdrawal could be promoted by sleep disturbances, because it is known that the withdrawal of antipsychotic drugs is often associated with insomnia (Luchins et al. 1980). Individuals with sleep disturbance experience more psychological distress, which may increase the vulnerability for a relapse. Clinicians should be careful in cases of abrupt clozapine withdrawal. Further efforts to elucidate the GABAergic properties are necessary.

References

Alphs LD, Lee HS (1991) Comparison of withdrawal of typical and atypical antipsychotic drugs: a case study. J Clin Psychiatry 52:346

American Psychiatric Association (1987) Diagnostic and statistical manual of mental disorders (DSM-III-R), 3rd edn, revised. American Psychiatric Press; Washington, DC

Anderman B, Griffith RW (1977) Clozapine-induced agranulocytosis: a situation report up to 1976. Eur J clin Pharmacol 11: 199–201

Baron JC, Martinot JL, Cambon H, Boulenger JP, Poirier MF, Caillard V, Blin J, Huret JD, Loc'h C, Maziere B (1989) Striatal dopamine receptor occupancy during and following withdrawal from neuroleptic treatment: correlative evaluation by positron emission tomography and plasma prolactin levels. Psychopharmacology 99:463–472

Borison RL, Diamond BI, Sinha D, Gupta RP, Ajiboye PA (1988) Clozapine withdrawal rebound psychosis. Psychopharmacol Bull 24:260–263

Cambon H, Baron JC, Boulenger JP, Loc'h C, Zarifian E, Maziere B (1987) In vivo assay for neuroleptic receptor binding in the striatum: positron emission tomography in humans. Br J Psychiatry 151:824–830

Chouinard G, Jones BD (1980) Neuroleptic-induced supersensitivity psychosis: clinical and pharmacologic characteristics. Am J Psychiatry 137:16–21

Dickson R, Williams R, Dalby JT (1994) Dystonic reaction and relapse with clozapine discontinuation and risperidone initiaton. Can J Psychiatry 39(3):184

Drew KL, O'Connor WT, Kehr J, Ungerstedt U (1990) Regional specificity of clozapine and haloperidol on GABA and dopamine release in rat basal ganglia. Eur J Pharmacol 187:385–397

Ekblom B, Eriksson K, Lindstrom LH (1984) Supersensitivity psychosis in schizophrenic patients after sudden clozapine withdrawal. Psychopharmacology 83:293–294

Eklund K (1987) Supersensitivity and clozapine withdrawal. Psychopharmacology 90:135

Gillin JC, Spinweber CL, Johnson LC (1989) Rebound insomnia: a critical review. J Clin Psychopharmacol 9(3):161–172

Graham SR, Kokkinidis L (1993) Clozapine inhibits limbic system kindling: implications for antipsychotic action. Brain Res Bull 30:597–605

Klimke A, Klieser E (1995) The atypical neuroleptic clozapine (Leponex): state of the art and recent clinical aspects. Fortschr Neurol Psychiatrie 63:173–193

Krupp P, Barnes P (1992) Clozapine-associated agranulocytosis: risk and aetiology. Br J Psychiatry 160 (Suppl 17):38–40

Lidsky TI, Alter E, Banerjee SP (1991) Effects of clozapine on glutamatergic transmission. Soc Neurosci 17:686

Lieberman JA, Alvir JM (1992) A report of clozapine-induced agranulocytosis in the United States. Drug Safety 7 (Suppl 1): 1–2

Luchins DJ, Freed WJ, Wyatt RJ (1980) The role of cholinergic supersensitivity in the medical symptoms associated with withdrawal of antipsychotic drugs. Am J Psychiatry 137(11): 1395–1398

Meltzer HY, Bastani B, Ramirez LF, Matsubara S (1989) Clozapine: new research on efficacy and mechanism of action. Eur Arch Psychiatry Clin Neurosci 238:332–339

Parsa MA, al-Lahham YH, Ramirez LF, Meltzer HY (1993) Prolonged psychotic relapse after abrupt clozapine withdrawal. J Clin Psychopharmacol 13(2):154–155

Perenyi A, Kuncz E, Bagdy G (1986) Early relapse after sudden withdrawal or dose reduction of clozapine. Psychopharmacology 86:244

Rechtschaffen A, Kales A (1968) A manual of standarized terminology, techniques and scoring system for sleep stages of human subjects. Public Health Service, Washington DC, NIH, Pub No 204, US Government Printing Office

Simpson GM, Lee JH, Shrivastava RK (1978) Clozapine in tardive dyskinesia. Psychopharmacology 56:75–80

Staedt J, Stoppe G, Kögler A, Riemann H, Hajak G, Munz DL, Emrich D, Rüther E (1995) Nocturnal myoclonus syndrome (periodic movements in sleep) related to central dopamine D2 receptor alteration. Eur Arch Psychiatry Clin Neurosci 245: 8–10

Ungerstedt R, Ljungberg T (1977) Behavioral patterns related to dopamine neurotransmission: effects of acute and chronic antipsychotic drugs. In: Costa E, Gessa GL (eds) Advances in biochemical psychopharmacology, vol 16. Raven Press, New York, pp 193–199

Zapletalek M, Preiningerova O, Hanus H (1980) Does clozapine cause dependence? Agressologie 21(A):19–22