Life-Threatening Allergic Reaction to Clozapine

GABRIELA STOPPE, PETER MÜLLER, THOMAS FUCHS and ECKART RÜTHER

Clozapine, an 'atypical' antipsychotic drug, rarely induces allergic complications, which usually present as cutaneous reactions. We report the case of a 69-year-old woman, suffering from chronic schizophrenia, who developed an allergic asthmatic reaction following clozapine therapy. Intensive-care treatment was necessary. The reaction could be repeated by further exposure to the drug. Skin tests for hypersensitivity were negative.

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Clozapine, a so-called 'atypical' antipsychotic drug, has been reported to produce no extrapyramidal motor symptoms of Parkinsonism and dystonia, to involve a lower or absent risk of producing tardive dyskinesia and to cause no serum prolactin elevations in man (Lieberman *et al*, 1989; Meltzer *et al*, 1989). Multicentre double-blind clinical trials (Fischer-Cornelssen *et al*, 1976; Honigfeld *et al*, 1984; Kane *et al*, 1988) showed its antipsychotic action in comparison to standard medicaments like chlorpromazine and haloperidol. Good effects, especially in therapy-resistant psychotic patients, have been reported by different authors (Honigfeld *et al*, 1984; Povlsen *et al*, 1985; Kane *et al*, 1988). Of the known side-effects, the risk of agranulocytosis with clozapine exceeds that associated with other antipsychotic drugs (Kane *et al*, 1988). Rarely, allergic reactions similar to those produced by other antipsychotic drugs have been reported. They include cutaneous reactions with urticaria or eczematous exanthema with pruritus (Drug Monitoring Centre, Sandoz Research, Internal reports; Bürki, 1983). To our knowledge there are no cases of allergic asthmatic reactions to clozapine in the literature.

Case report

A 69-year-old woman who had suffered from chronic paranoid schizophrenia since 1964 reported to our department for the first time in 1968. In spite of chronic acoustic hallucinations and sleep disturbances she had worked in a factory for a long time, and lived independently in her own apartment. Over the years she had been treated with various antipsychotic agents (zuclopenthixol, flupenthixol, trifluoperazine, fluphenazine, and haloperidol) without a marked remission of her symptoms. Since 1985, she had developed progressive tremor with a right-sided accentuation and slight perioral dyskinesia. In 1988, the patient received clozapine (75 mg daily) for more than three weeks, but this was discontinued during after-treatment for an unknown reason. However, the patient did not remember complications during this treatment. Since chronic neuroleptic treatment was not effective and because extrapyramidal side-effects developed, she was referred to our department again. On examination she had arterial hypertension, signs of chronic bronchitis (she was a smoker), and an enlarged thyroid gland. Blood count and routine serum analysis were normal. The patient was prescribed 25 mg clozapine daily. She was also taking 150 mg theophylline, p.o. daily, which had been prescribed by her physician. The patient had received a final fluphenazine injection (50 mg), i.m. nine days before commencing clozapine. It is not known whether the patient had taken theophylline regularly before, because serum drug level was below 3 μg/l (therapeutic range 45–110 μg/l) on the day after admission.

Approximately 24 hours after the first clozapine dose for two years, the patient developed an acute dyspnoea with stridor and cyanosis and had to be intubated and treated in the intensive-care unit (ICU), where no reason for the acute deterioration could be found. Serum analysis and blood count remained unchanged. A differential blood count was not performed. The patient recovered within about one hour. She stabilised on ventilation, and 48 hours later extubation was attempted but the patient became dyspnoic, cyanotic and had respiratory stridor. Repeated ear, nose and throat examinations revealed only the usual mechanical irritation induced by the tubes. A further 48 hours later the patient could be extubated after intravenous administration of 100 mg prednisolone and 5 mg biperiden. The patient returned to the psychiatric ward, where clozapine was restarted. Six hours later she developed the same symptoms, and had to be treated in the ICU again. Because clozapine was not believed to be the cause of the asthmatic reaction, we administered clozapine again (25 mg daily) following her return from the ICU. The patient developed the same symptoms for the third time. A controlled re-exposition with 12.5 mg clozapine was performed in the ICU, and the patient developed severe asthmatic symptoms after two hours. Following this we discontinued clozapine treatment, and the patient has not shown these or similar severe symptoms again under hospital treatment or during one and a half years as an out-patient.

Other investigations revealed coronary heart disease with slight ventricular extrasystoles, a large arteriosclerotic aneurysm of the abdominal aorta and a diffuse suprasternal struma with peripheral euthyreosis in the patient. A skin test performed two months later to prove an allergic reaction was negative.

Discussion

Clozapine is an 'atypical' antipsychotic agent, which should probably be reserved for individuals who are suffering from severe psychotic symptoms that are unrelieved by their medications, or those with severe extrapyramidal symptoms or tardive dyskinesia, if it can be done safely with necessary laboratory controls especially in the first 18 weeks of treatment (Kane *et al*, 1988; Marder & Van Putten, 1988). Some authors even recommend it as a therapeutic agent for tardive dyskinesia (Simpson, 1978; Grohmann *et al*, 1980; Lieberman *et al*, 1989). Recent studies (Meltzer, 1989) regard the longer-term effects of clozapine as promising, and suggest that a clozapine trial should last at least three months, and preferably much longer, before a patient should be considered a non-responder.

Our patient suffered from chronic psychosis for 26 years. Treatments with zuclopenthixol, flupenthixol, trifluoperazine, fluphenazine, and haloperidol afforded no remission of her symptoms, so she had been regarded as therapy-resistant. For this reason, and because she progressively developed tardive dyskinesia, clozapine was tried, starting with a dose of 25 mg daily and then, once only, 12.5 mg. The patient had been treated with this medicament for a short time two years previously without complications. Repeatedly, within hours of the administration, she developed acute stridor and cyanosis requiring intubation and treatment on the ICU. Even 48 hours after the administration of clozapine the state of the patient worsened shortly after extubation. Because no other reason for this hypersensitivity reaction could be found and because symptoms were reproduced after further exposure to the drug but disappeared on withdrawal, it was thought that clozapine was responsible.

There was no doubt that our patient had some other diseases besides her mental disorder. We could confirm the diagnosis of arterial hypertension, an aneurysm of the abdominal aorta, a struma with slight impression of the larynx and a slight gastritis. But none of these diseases can account for a severe asthmatic reaction in this woman. The chronic bronchitis, however, which had been treated with theophylline by her family doctor, may have been a predisposing factor, but it had not led to severe asthmatic reaction with cyanosis and the need for intubation before. One may argue that chronic obstructive bronchitis, coronary heart disease and arterial hypertension may be complicated by known side-effects of clozapine, especially hypersalivation/hypersecretion, orthostatic hypotension and tachycardia. But our patient did not show remarkable reductions of blood pressure or increasing bronchial secretion or hypersalivation during those asthmatic reactions.

Tachycardia could be explained by clozapine as well as by dyspnoic situation. Clinical signs of myocardial infarction were absent.

Besides a (compared to 'typical' neuroleptics) weak binding to D_1 and D_2 dopamine receptors, clozapine blocks S_2 serotonergic, alpha$_1$ adrenergic, muscarinic, and H_1 histamine receptors. Blockade of H_1 receptors is comparable to the mode of action of classical antihistamines. They antagonise bronchial constriction as well as arteriolar constriction. Blockade of alpha$_1$ adrenergic receptors on the smooth vascular muscles leads to vasodilation (epinephrine conversion). Thus both effects can explain a decrease of blood pressure but no increase of bronchial obstruction. However, the reaction could be a delayed hypersensitivity or pseudoallergic reaction to the drug. The skin test could have ascertained the clinical impression. Its negativity is not counter-evidence.

In a study on 959 patients treated with clozapine (Grohmann *et al*, 1989) the authors found severe and potentially life-threatening adverse drug reactions in 3.7%. Toxic delirium, grand mal seizures, leucopenia and hypotension were reported (Gärtner *et al*, 1989; Grohmann *et al*, 1989). Collapse with respiratory depression was reported in four patients receiving a combination of clozapine and benzodiazepines (Grohmann *et al*, 1989). Only one fatal adverse drug reaction was reported, the aetiology of which remained unclear.

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*Gabriela Stoppe, MD; Peter Müller, MD, *Professor*; Eckart Rüther, MD, *Professor, Head of Department, University of Goettingen, Department of Psychiatry, Von-Siebold-Str. 5, 3400 Goettingen, Germany*; Thomas Fuchs, MD, *University of Goettingen, Department of Dermatology, Von-Siebold-Str. 3, 3400 Goettingen, Germany*

*Correspondence

Successful Treatment of Episodic Dyscontrol with Carbamazepine

JONA LEWIN and DAVID SUMNERS

Following a road-traffic accident, an 18-year-old man developed episodic dyscontrol which brought him into conflict with the law. Two years after the accident, treatment with carbamazepine was initiated and further aggressive outbursts subsided. The efficacy and mode of action of carbamazepine is discussed and the literature reviewed.
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Bach-Y-Rita *et al* (1971) studied 130 patients with episodic dyscontrol (ED), and found that a large proportion of these patients had histories of birth injury, mental retardation, coma-inducing illness, head injury, episodes of unconsciousness, and seizure-like episodes. Investigations revealed a high incidence of abnormality on electroencephalography (EEG) and psychometric testing. Most patients with ED may not be diagnosed as having intermittent explosive disorder according to DSM–III–R as they do not meet the third criterion: absence of generalised impulsiveness or aggression between episodes.

The relationship between aggressive behaviour and neurological illness is controversial (Shaffer *et al*, 1980; Stevens & Herman, 1981). Elliott (1982) investigated 286 patients with episodic dyscontrol and found that 94% had evidence of brain dysfunction: primarily minimal brain dysfunction, complex partial seizures, or a history of significant brain trauma. Mark & Ervin (1970) summarised several studies which showed high but variable rates of electroencephalographic abnormalities in people prone to violence.

We report a young man who suffered a brain injury in a road-traffic accident at the age of 18. Following the head trauma he appeared to undergo a personality change, developing irritability and violent outbursts which brought him into conflict, for the first time, with the law.

Case report

The patient was run over by a car while riding a motorcycle at the age of 18. In the casualty department he complained of diplopia, altered smell and taste sensations, and back pain. Examination showed left facial weakness, left-sided deafness and a watery discharge from the left ear. His level of consciousness was reduced. A subsequent computerised tomography (CT) scan revealed generalised brain oedema, blood in the ventricular system and some intracranial air. The patient was discharged after several weeks of observation.

He was seen by a neurologist six months later who noted that his mood fluctuated. Four months later, the same neurologist noted irritability and violent outbursts which were not within the patient's control.

Fourteen months after the incident, the patient was assessed by a neuropsychologist who noted marked cognitive deficits and a tendency to perserverate. The patient had difficulty in abstract reasoning and there was impairment of verbal and visual memory. The neuropsychologist concluded that there was evidence of bilateral frontal and temporal lobe lesions.

At this time the patient came into conflict with the law, and was charged with actual and grievous bodily harm. He was subsequently assessed by a psychiatrist who noted that the patient had violent outbursts which he could not control. In addition, there were signs of depression: tearfulness, anxiety, poor self-image, and suicidal ideation.

Two years after the accident the patient was assessed at the North West Thames Regional Health Authority Brain Injury Rehabilitation Unit (BIRU). On examination he was