

available suggests that convulsions are the only serious complication of acute zimeldine overdosage.

[Sales of zimeldine in all countries were discontinued by Astra Pharmaceuticals in September 1983 because of the company's concern about reports of serious neurological side effects including the Guillain Barré syndrome.]

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## Anaphylactic reactions to ketoconazole

Ketoconazole is an effective and widely prescribed oral antimycotic drug. We report a hitherto undescribed side effect, severe anaphylaxis, which was observed in two patients; in one anaphylaxis was probably related to prior sensitisation to miconazole.

### Case reports

#### CASE 1

A 26 year old woman was treated in July 1982 with miconazole cream (Daktarin) for suspected mycosis of the right foot. After 10 days the site of application became red, and one day later widespread macules, papules, and vesicles appeared. She was referred to a dermatologist, who diagnosed contact dermatitis to miconazole with eczematoid reaction. An epicutaneous test of the Daktarin cream base yielded a negative result.

In May 1983 she was prescribed ketoconazole 200 mg daily for dermatomycosis of the breasts (confirmed by direct microscopy). She took the first tablet at 2015. About 45 minutes later she noticed that her hands, feet, lips, and earlobes were itching and beginning to swell. She became dizzy and collapsed several times; during these periods she was incontinent for urine.

On examination, after roughly another 15 minutes, severe angio-oedema and pronounced erythema of the face, hands, and feet were found. She was fully conscious, her blood pressure was 85/50 mm Hg, and her radial pulse was weak and accelerated. She was treated with 2 mg clemastine fumarate intravenously, and within 15 minutes angio-oedema had diminished and blood pressure risen to 100/60 mm Hg. Treatment was continued with 50 mg mebhydrolin, and the following morning all symptoms had disappeared.

Besides an oral contraceptive she had not been taking any other drugs. She had never experienced an allergic reaction before except for the reported contact dermatitis to miconazole.

#### CASE 2

A 52 year old man was prescribed ketoconazole 200 mg daily for dermatomycosis of the right foot (confirmed by direct microscopy). He took the first tablet at 1915. About half an hour later he noticed that his hands and feet had begun to swell and were itching severely. His general practitioner saw him at 2050. He was unrecognisable because of severe angio-oedema of his face, hands, and feet. He was vomiting and had pronounced dyspnoea, which resolved gradually. He was alert and had a normal radial pulse rate: blood pressure was not measured. The oedema had resolved about two

hours after treatment with prednisolone 25 mg intravenously and mebhydrolin 50 mg.

He had never experienced an allergic reaction before and had not been taking any other drugs. As far as we know he had never been treated with antimycotic drugs and did not have contact with them at his work.

### Comment

Both patients developed severe angio-oedema shortly after taking the first tablet of ketoconazole. Moreover, one patient developed frank anaphylactic shock, and the other experienced dyspnoea and vomiting.

Anaphylactic reactions to ketoconazole have not been reported before. Minor allergic reactions, such as rashes and urticaria, are reported sporadically; the incidence of rashes is about 1%.<sup>1</sup> Seven cases of possible acute allergic reaction but none of anaphylactic shock to ketoconazole have been reported to the manufacturer (Janssen, Belgium), and 120 million tablets of ketoconazole have been distributed since clinical development started.

The first case is of particular interest because the patient had previously developed an allergy to miconazole. This drug is chemically related to ketoconazole, so apparently cross sensitivity between these drugs can occur. In the second patient no cause of sensitisation was evident, but possibly he had been exposed to related drugs in the past. These cases show that anaphylactic reactions to ketoconazole occur and that cross allergy with miconazole (and perhaps with other imidazoles) may exist.

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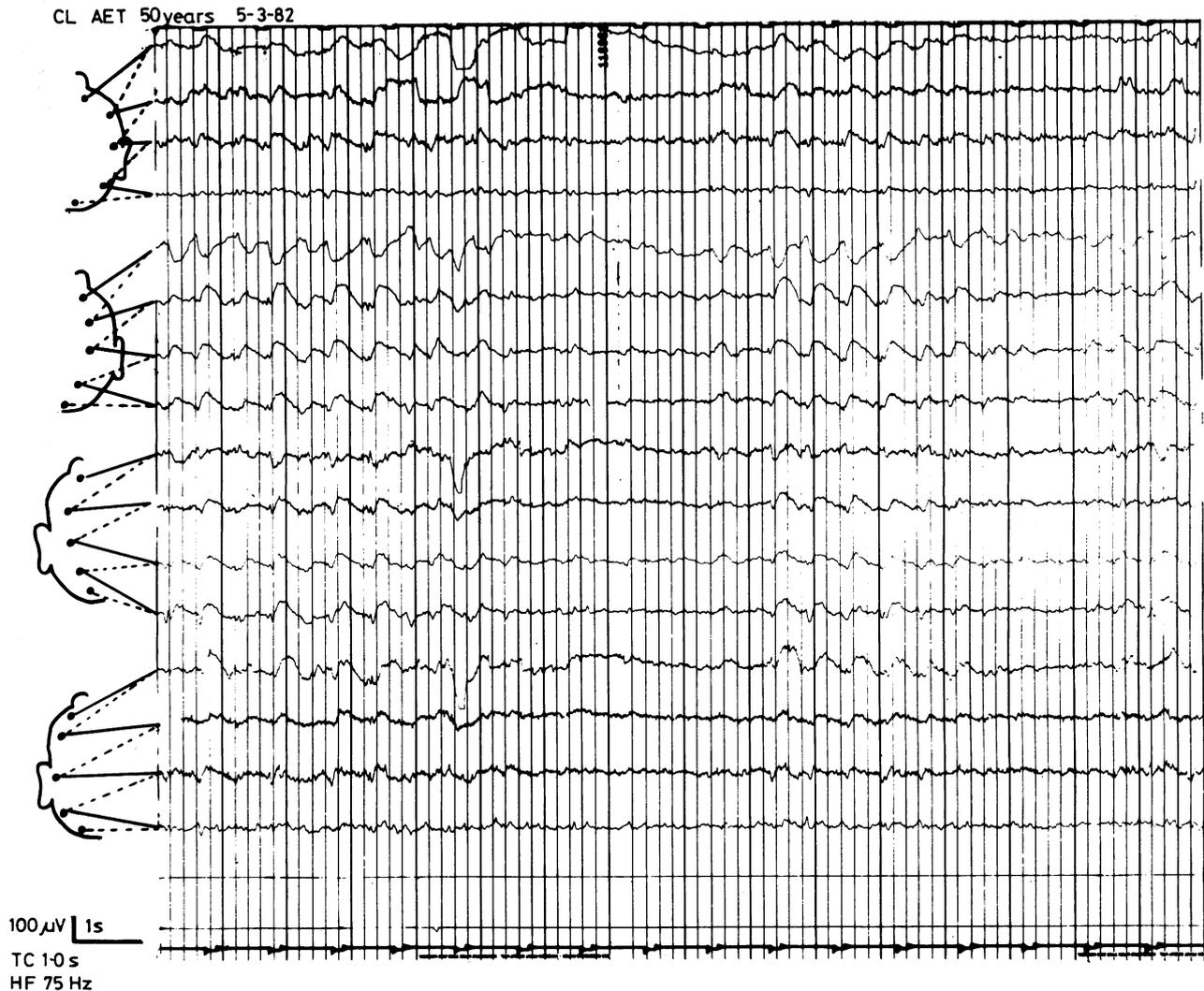
## De novo minor status epilepticus of late onset presenting as stupor

Minor status epilepticus<sup>1</sup> occurring in patients with established epilepsy is well recognised, presenting as a confusional state without psychiatric symptoms.<sup>2</sup> It has also been described occurring de novo in middle age.<sup>3</sup> The clinical picture in these cases is variable: some patients show typical features of minor status epilepticus, and others present with a confusional state with psychotic symptoms but without stupor.<sup>4,5</sup> Diagnosis of de novo status epilepticus of late onset may be delayed and initial treatment inappropriate because of this variability in presentation. We report a case of de novo minor status epilepticus of late onset presenting with stupor and subsequent psychotic features, which was followed by a postictal organic brain reaction.

### Case report

A 50 year old widow had become increasingly withdrawn, depressed, and confused over the 10 days before admission to hospital. She was admitted after being found mute by a friend. She had no history of epilepsy. Eighteen months previously she had developed an acute paranoid psychosis with auditory hallucinations and paranoid delusions after her husband's death. Electroencephalography was not performed on that occasion, and her psychosis had resolved over a week without specific treatment. Four months before admission she had been confused for three days but had recovered without medical attention.

On admission she was stuporous, did not respond to commands, and made no spontaneous movements. Her face was expressionless, and she showed waxy flexibility. Results of general and neurological examination were otherwise normal. Over the next few days she occasionally responded



Electroencephalogram performed three days after admission to hospital.

to commands and experienced complex visual hallucinations, saying that blood was pouring out of her body and collecting in bags around the bed and that the doctor was being sprayed with blood. She thought that her two sons had had their limbs amputated and exhibited many delusional ideas of reference.

Full haematological and biochemical investigations, including measurement of urea, electrolyte, calcium, and glucose concentrations and free thyroxine index and liver function tests gave normal results. Cerebrospinal fluid was normal apart from a protein concentration of 1.24 g/l. A computed tomogram of the brain showed no abnormality. Three days after admission electroencephalography was performed, which showed generalised atypical spike and slow wave discharges occurring in prolonged runs with brief periods of generalised slow between the episodes (figure).

She was treated with intravenous diazepam. Her mental state immediately improved and the electroencephalogram returned to normal. She remained, however, disorientated and inattentive and experienced auditory hallucinations and delusional ideas of reference over the next three weeks before making a full recovery.

#### Comment

The patient's clinical state of stupor with paranoid delusions and complex visual hallucinations was due to minor status epilepticus without a history of major epilepsy. This presentation is dramatically different from the recognised picture of late onset minor status epilepticus<sup>3</sup> but shows some similarity to the cases reported by Ellis and Lee.<sup>4</sup> None of their patients, however, was stuporous, and most had a predisposing metabolic abnormality or systemic illness, which was not a feature of this case.

The patient's minor status epilepticus may possibly have been recurrent, the first episode occurring after her husband's death and the second later. The continuing acute organic brain reaction was most probably postictal as repeated electroencephalograms were

normal and a three hour period of continuous electroencephalographic monitoring failed to show any abnormality.

Depressive or catatonic stupor was initially diagnosed because of lack of familiarity with the presentation of de novo status epilepticus with stupor and psychiatric features. Possibly, some similar cases are not recognised, and this report emphasises the usefulness of electroencephalography in differentiating functional and organic psychoses, so facilitating earlier diagnosis and allowing appropriate treatment to be started.

We thank Dr E A Spriggs for his permission to report this case.

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- <sup>4</sup> Ellis JM, Lee SI. Acute prolonged confusion in later life as an ictal state. *Epilepsia* 1978;19:119-28.
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