Journal of Neurology, Neurosurgery, and Psychiatry 1985;**48**:65–69

Guillain-Barré syndrome following zimeldine treatment

JAN FAGIUS,* PER OLOF OSTERMAN,* ÅKE SIDÉN,† BENGT-ERIK WIHOLM‡

From the Departments of Neurology, University Hospital, Uppsala and Huddinge Hospital, Huddinge† and the Department of Drugs, National Board of Health and Welfare, Uppsala,‡ Sweden.*

SUMMARY Thirteen cases of the Guillain-Barré syndrome are reviewed, all occurring with a similar relationship to recent commencement of treatment with the antidepressive drug zimeldine. The risk of developing Guillain-Barré syndrome was increased about 25-fold among patients receiving zimeldine, as compared with the natural incidence of the disorder. The cases described provide strong evidence that Guillain-Barré syndrome may occur as a specific, probably immunologically mediated, complication of drug therapy.

It is well known that polyneuropathy may evolve as an adverse effect of certain drugs.[1 2] As a rule, symptoms and signs of peripheral nerve dysfunction are insidious and there is usually some correlation between the cumulative dose of the drug and the degree of polyneuropathy. One exception is polyneuropathy following gold therapy, which may present subacutely, similar to the Guillain-Barré syndrome.[3]

In March 1982 a new antidepressive drug, zimeldine, was introduced in Sweden. This drug differs chemically from other antidepressants (fig) and has the unique pharmacological property of selectively blocking the reuptake of serotonin in the neurons.[4] Clinically the major advantages seemed to be a reduction of anticholinergic and cardiovascular side effects, compared with other antidepressive agents, and zimeldine was also less toxic when taken in an overdose.[4] However, suspected hypersensitivity reactions resembling acute attacks of influenza had been reported to occur during the clinical trials.

Within 1½ years after the introduction of the drug the Swedish Adverse Drug Reactions Advisory Committee of the National Board of Health and Welfare received 13 reports on cases of Guillain-Barré syndrome, occurring with fairly similar relationships to the commencement of zimeldine treatment. These events prompted the manufacturer to withdraw the drug from the market, but since the reactions are of some importance for the comprehension of the aetiology of Guillain-Barré syndrome, these cases are briefly reported here.

Address for reprint requests: Jan Fagius, MD, Department of Neurology, University Hospital, S-751 85 Uppsala, Sweden.

Received 21 March 1984 and in revised form 22 June 1984.
Accepted 25 June 1984

Material and methods

In Sweden, a system whereby physicians spontaneously notify the above committee of any suspected adverse drug reactions has been in existence since 1965. All reports are evaluated with regard to causality, first by a medical officer at the Department of Drugs of the National Board of Health and Welfare and then by the full committee. Experts are consulted for advice in complicated cases. Thus, the patients reported here were examined and treated at different Swedish hospitals and the diagnostic procedures were not uniform. Complete patient records were evaluated independently by three consultant neurologists, three of the authors (JF, POO, ÅS). The present report only includes patients whose records contain enough information to make the diagnosis of a subacutely developing generalised affection of the peripheral nervous system certain or highly probable.

Information on total sales of drugs is stored in the Swedish Drug Information System. The sale can be expressed in monetary terms or as the number of packs, tablets or so called Defined Daily Doses (DDD) sold. The latter is an estimated average daily dose.[5] These data, together with prescription

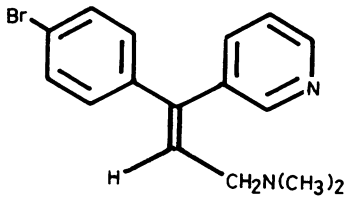

Fig *Zimeldine: (Z)-4-Bromo-NN-dimethyl-γ-(3-pyridyl) cinnamylamine dihydrochloride monohydrate.*

data from a random prescription sample, are published yearly by the National Corporation of Swedish Pharmacies.[6] Thus, data on the total sales and on the prescribed average daily dose in relation to age and sex are available for zimeldine.

Results

The typical course of events is illustrated by the following case history.

A 65-year-old man, a teetotaller, had suffered from psoriasis for many years, but had otherwise been healthy. He developed depressive symptoms and zimeldine, 200 mg/day, was prescribed on 18 April, 1983. On 5 May he developed fever and had pronounced muscle pains in the back and legs and a sore throat. The following day he complained of leg numbness, which deteriorated over the next few days, and weakness of the legs supervened. Neurological examination on 10 May revealed reduced sensation in all four limbs and marked weakness of the legs. The tendon reflexes in the legs were sluggish and bladder paresis was discovered, with a residual urine volume of 1000 ml. Zimeldine treatment was discontinued on 10 May. On 11 May the patient's legs were almost paralytic and no tendon reflexes could be elicited in the legs. Two days later he had regained slight ability for extension and flexion of the knees, but areflexia and inability to void persisted. Slow but steady improvement followed, and on 8 June, when he was admitted to a rehabilitation clinic, he was able to walk with the support of an accompanying person; at that time he was again able to perceive bladder distension.

The protein concentrations in the CSF were 1·40, 1·82 and 1·64 g/l on 10 May, 18 May and 2 June, respectively (normal upper limit 0·5 g/l). The highest CSF cell count was 6 polymorphonuclear and 2 mononuclear cells (10 May).

At electromyography on 24 May, signs of peripheral denervation were observed in muscles of both legs. The conduction velocities of the peroneal, posterior tibial and sural nerves were normal on 11 May, but some of these nerves showed moderately slowed conduction on 24 May. (Case 5; cf Tables 1–4.)

Summarised clinical data. Details of the 13 reported patients are presented in tables 1, 2 and 3, including information concerning zimeldine treatment, symptoms, signs and clinical course, and results of cerebrospinal fluid (CSF) analysis and nerve conduction velocity measurements.

Within 6–17 days (mean 12·4 days) after the start of zimeldine treatment, all patients developed an acute adverse reaction to the drug, with influenza-like symptoms, mainly fever and myalgia (two patients had no myalgia). The cumulative doses of zimeldine at this time were 900–3,400 mg (mean 1,800 mg)—the recommended daily dose was 100 or 200 mg. Within a further 1–20 days (11–30 days after commencement of zimeldine treatment), all patients developed widespread, symmetrical dysfunction of peripheral nerves with subacute onset. The cumulative doses of zimeldine were then 1,200–4,400 mg (mean 2,500 mg).

Table 1 *Age and sex of the patients, drug dose and course until occurrence of neurological symptoms*

Patient	*Sex*	*Age yr*	*Zimeldine treatment Duration Dose*	*Time of initial symptoms Cumulative dose*	*Initial symptoms*	*Time of first neurological symptoms Cumulative dose*
1	F	47	14 days 200 mg/d	Day 11 2,200 mg	Fever, myalgia, photophobia	Day 14 2,800 mg
2	M	61	15 days 200 mg/d	Day 6 1,200 mg	Fever, myalgia, headache, nausea	Day 11 2,200 mg
3	F	81	23 days 100 mg/d	Day 15 1,500 mg	Fever, myalgia	Day 23 2,300 mg
4	M	49	22 days 100 mg/d	Day 14 2,800 mg	Fever, myalgia	Day 26 4,400 mg (withdrawn)
5	M	65	23 days 200 mg/d	Day 17 3,400 mg	Fever, sore throat, myalgia	Day 18 3,600 mg
6	F	63	12 days 100 mg/d	Day 9 900 mg	Fever, myalgia, headache	Day 22 1,200 mg (withdrawn)
7	M	72	15 days 200 mg/d	Day 14 2,800 mg	Fever, myalgia, nausea	Day 20 3,000 mg (withdrawn)
8	F	70	25 days 100–200 mg/d	Day 14 2,000 mg	Fever, sore throat, myalgia	Day 18 2,800 mg
9	M	52	14 days 100 mg/d	Day 14 1,400 mg	Fever, nausea	Day 27 1,400 mg (withdrawn)
10	M	68	14 days 100 mg/d	Day 9 900 mg	Fever, myalgia	Day 16 1,400 mg (withdrawn)
11	F	52	35 days 100 mg/d	Day 14 1,400 mg	Fever, myalgia, exanthema, headache, nausea, conjunctivitis	Day 24 2,400 mg
12	M	72	10 days 200 mg/d	Day 8 1,600 mg	Fever	Day 17 2,000 mg (withdrawn)
13	M	68	30 days 100 mg/d	Day 16 1,600 mg	Myalgia, fever	Day 30 3,000 mg

Table 2 *Symptoms and clinical course of the neurological illness*

Patient No.	*Neurological symptoms*	*Duration of progression*	*First sign of recovery after onset of neurological symptoms*	*Follow-up*
1	Limb weakness and paraesthesiae. Cranial nerve palsies. Areflexia in arms and legs. Respiratory paralysis.	2 d	Day 5	Recovered 8 wk
2	Severe limb weakness. Mild sensory loss. Cranial nerve palsies. Postural hypotension. Areflexia in arms and legs.	1 w	Day 14	Recovered 5 wk
3	Severe leg weakness. Sensory loss in arms and legs. Areflexia in the legs. Plantar response extensor?	< 2 w	Day 15	Recovered 7 wk
4	Severe distal limb weakness, inability to walk unaided. Sensory loss in arms and legs. Facial nerve palsy. Areflexia in the legs.	8 w	Day 60	Moderately improved 22 wk
5	Severe leg weakness. Sensory loss in arms and legs. Bladder paresis. Areflexia in the legs.	1 w	Day 7	Improved 4 wk
6	Severe limb weakness. Sensory loss in arms and legs. Ataxia. Areflexia in arms and legs.	1 w	Day 14	Improved 12 wk
7	Slight leg weakness. Paraesthesiae in arms and legs. Leg ataxia. Areflexia in the legs.	3 d	Day 4	Markedly improved 8 wk
8	Severe leg weakness, slight arm weakness. Limb paraesthesiae. Leg ataxia. Areflexia in the legs.	1 w	Day 30	Moderately improved 10 wk
9	Slight foot weakness. Numbness and paraesthesiae in the feet. Facial nerve palsies. Areflexia in the legs.	1 w	Day 15	Markedly improved 23 wk
10	Moderate leg weakness, with inability to walk unaided. Mild sensory loss. Leg ataxia. Facial nerve palsies. Areflexia in the legs.	11 d	Day 22	Recovered 6 wk
11	Sensory loss in trunk, face and tongue. Facial nerve palsies. No areflexia.	1 w	Day 11	Recovered 7 wk
12	Severe limb weakness with muscle wasting. Sensory loss in arms and legs. Areflexia in arms and legs.	15 w	Day 130	Moderately improved 31 wk
13	Severe limb weakness with muscle wasting. Sensory loss in legs. Painful paraesthesiae in legs and hands. Areflexia in arms and legs.	16 w	Day 130	Markedly improved 28 wk

In six patients the medication had already been withdrawn at this time. Ten patients (Nos 1–10 in the tables) displayed clinical symptoms and a clinical course typical of acute Guillain-Barré syndrome, as seen in Table 2. One patient (No 11) had no limb weakness or areflexia, but had bilateral facial weakness and symmetrical widespread sensory loss, with good recovery. The recovery was good in most patients, although two patients (Nos 12 and 13) ran a subacutely progressive course with the first sign of recovery after about 18 weeks of observation. All patients exhibited CSF features consistent with Guillain-Barré syndrome, and the nerve conduction velocities were reduced in all six patients in whom these measurements were performed (Table 3). No other possible causes of the polyneuropathy were

Table 3 *Results of CSF analysis and nerve conduction studies*

Patient No.	*CSF*				*Nerve conduction velocities†*
	Cells		*Total protein content g/l*	*Protein profile**	
	poly	*mono*			
1	0	1	0·73	Barrier damage	NP
2	0	1	0·8	NP	NP
3	2	8	0·6	Normal	NP
4	2	4	1·44	Barrier damage	Reduced
5	6	2	1·82	Barrier damage	Reduced
6	4	10	1·3	Barrier damage	Reduced
7	3	13	1·10	Barrier damage	Reduced
8	0	8	1·20	NP	NP
9	1	7	1·06	Barrier damage	NP
10	7	8	1·70	NP	NP
11	0	10	0·9	Barrier damage	NP
12	4	18	1·42	Barrier damage	Reduced
13	0	0	0·67	Barrier damage	Reduced

NP = Not performed
poly = polymorphonuclear leukocytes
mono = mononuclear leukocytes
*Barrier damage: CSF/serum albumin ratio above the age-related normal value
†Reduced: Motor and/or sensory nerve conduction velocities below lower normal limit as defined for the individual laboratory

Table 4 *NINCDS diagnostic criteria for Guillain-Barré syndrome applied to present cases*

Features required		*Features strongly supportive*								
A. Weakness	*B. Areflexia*	*1. Progression* *3. Mild sensory symptoms* *5. Recovery* *7. CSF features*				*2. Symmetry* *4. Cranial nerve involvement* *6. Autonomic dysfunction* *8. Nerve conduction slowing*				
Patient No.	*Required*	*Strongly supportive*								*Diagnosis*
	A	*B*	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	
1	+	+	+	+	+	+	+	−	+	NP	GBS
2	+	+	+	+	+	+	+	+	+	NP	GBS
3	+	+	+	+	+	−	+	−	−	NP	GBS
4	+	+	+	+	+	+	+	−	+	+	GBS
5	+	+	+	+	+	−	+	+	+	+	GBS
6	+	+	+	+	+	−	+	−	+	+	GBS
7	+	+	+	+	+	−	+	−	+	+	GBS
8	+	+	+	+	+	−	+	−	+	NP	GBS
9	+	+	+	+	+	+	+	−	+	NP	GBS
10	+	+	+	+	+	+	+	−	+	NP	GBS
11	(+)	−	+	+	+	+	+	−	+	NP	Atypical GBS
12	+	+	+	+	−	−	+	−	+	+	Chronic inflammatory polyradiculoneuropathy
13	+	+	+	+	+	−	+	−	+	+	Chronic inflammatory polyradiculoneuropathy

NP = not performed.
(+) indicates that weakness was only facial, not in limbs.

found in any of the patients.

In table 4 the NINCDS diagnostic criteria for Guillain-Barré syndrome[7] are applied to the clinical and laboratory findings in the patients. The diagnoses are summarised as definite Guillain-Barré syndrome in ten patients, atypical Guillain-Barré syndrome in one patient and chronic inflammatory polyradiculoneuropathy[8] in two patients.

Epidemiological data. During the first 16 months (1982 and 1983) following the introduction of zimeldine on the market, $4{\cdot}2 \times 10^6$ DDDs were sold in Sweden (DDD for zimeldine = 200 mg). The average prescribed daily dose was 170 mg, roughly corresponding to $4{\cdot}9 \times 10^6$ treatment days. This figure can be converted to 14,000 "treatment years".

Cases 2–9 (definite Guillain-Barré syndrome) and 11–13 (probable Guillain-Barré syndrome or Guillain-Barré syndrome-related disorder) occurred during this 16-month period (case 1 occurred at a clinical trial in 1979; case 10 occurred after the period mentioned).

The annual incidence of Guillain-Barré syndrome is reported to be 1–2 per 100,000 population.[9–12] A small epidemiological investigation in the county of Uppsala in 1979–82 showed an annual incidence in adults of 2·1 per 100,000 (Osterman, PO, unpublished data). Assuming a "true" incidence in adults of 2·5 per 100,000, approximately 0·35 cases of Guillain-Barré syndrome should be expected among zimeldine-treated subjects during the time period in question. Eight cases of Guillain-Barré syndrome (patients 2–9) means a 23-fold increase in the incidence. If 11 cases are accepted (thus including patients 11–13, who had a somewhat atypical clinical course), the increase will be 31-fold.

Discussion

The present ten patients with an indisputable diagnosis of Guillain-Barré syndrome constitute a homogeneous group. They all fell ill in a similar manner, shortly after the institution of zimeldine treatment. Another three patients had similar symptoms and much in common with the first ones, but did not fulfil the diagnostic criteria[7] for Guillain-Barré syndrome to the same extent. In this context it should be remembered that the NINCDS criteria have met with criticism, on the grounds that they may lead to exclusion of atypical, though true, cases of Guillain-Barré syndrome.[13] As seen from table 2, evolution of symptoms and improvement was rapid in some patients; this observation does not necessarily indicate a real difference between the illness reported here and the course ordinarily seen in Guillain-Barré syndrome, with over 50% of cases having reached the nadir by two weeks.[14]

Any of the influenza-like symptoms preceding the neurological illness may have been caused by a coinciding viral infection, but the uniform temporal relationship between these symptoms and the commencement of zimeldine treatment makes such a coincidence unlikely as the major determinant of the events observed. The cases appeared sporadically dur-

ing the time period when zimeldine was on the market and there was no simultaneous epidemic of influenza. The accumulation of Guillain-Barré syndrome in a relatively small population treated with zimeldine and the similar clinical courses speak strongly in favour of a causal relationship between this drug and the neurological disorder.

The total dose of zimeldine was low in all patients at the time when the influenza-like reaction and the acute polyneuropathy appeared. Thus, a direct toxic effect seems unlikely. The fact that many other patients have received zimeldine for many months, with very high cumulative doses, without developing polyneuropathy, also renders a neurotoxic effect of the drug *per se* improbable. Many features point, instead, to an immunological mechanism triggered by the drug, namely the early onset, the uniform occurrence of influenza-like symptoms preceding the neurological disorder, and the course of the neurological disorder, which could not be distinguished from "ordinary" Guillain-Barré syndrome.

Guillain-Barré syndrome may occur in serum sickness,[15] and a few years ago an outbreak of Guillain-Barré syndrome followed vaccination against swine influenza in the United States.[16] Among drugs causing polyneuropathy, gold salts have been reported to give rise to a subacute variety indistinguishable from Guillain-Barré syndrome,[3 17 18] but gold polyneuropathy may also occur as chronic mixed sensorymotor polyneuropathy.[19]

From the present data it cannot be decided conclusively whether the influenza-like illness and the Guillain-Barré syndrome are both triggered primarily by zimeldine, or whether the primary drug reaction induces the immunological events which result in Guillain-Barré syndrome. Whatever the exact mechanism might be, the present cases provide strong evidence that Guillain-Barré syndrome may occur as a specific complication of drug therapy.

This work was supported by the Sätra Brunn Fund for Medical Research. The Swedish Adverse Drug Reactions Advisory Committee acknowledges the clinical observance by which the connection was first suspected and the effort made in order to investigate and report the actual cases by Drs R Andersson, Gothenburg, P-E Åbom, Borås, A-K Aminoff, Stockholm, R Matell, Stockholm, J Fornander, Växjö, K Malmgren, Gothenburg, R Wottrich, Norrköping, A Gard, Umeå, R Ekberg, Lund, R Jonsson, Örebro, H Locht, Eksjö, S Persson, Värnamo.

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