Bovine gangliosides and acute motor polyneuropathy

Albert Figueras, Francisco J Morales-Olivas, Dolors Capellà, Vicente Palop, Joan-Ramon Laporte

Unitat de Farmacologia Clínica, Institut Català de Farmacologia, Universitat Autònoma de Barcelona, CSU Vall d'Hebron, Barcelona, Spain
Albert Figueras, *assistant professor*
Dolors Capellà, *associate professor*
Joan-Ramon Laporte, *professor of clinical pharmacology*

Departament de Farmacologia, Facultat de Medicina, Universitat de València, València
Francisco J Morales-Olivas, *associate professor*

Centre de Farmacovigilància de la Comunitat Valenciana, València
Vicente Palop, *drug surveillance officer*

Correspondence to:
Professor J R Laporte, Servei de Farmacologia Clínica, CSU Vall d'Hebron, Universitat Autònoma de Barcelona, 08035 Barcelona, Spain.

BMJ 1992;**305**:1330-1

Gangliosides—glycosphingolipids in mammalian cells—have a role in promoting nerve repair by increasing collateral sprouting.[1] Trials of exogenous gangliosides as adjuvant treatment for various neuropathies, however, either have had gross methodological deficiencies or have shown lack of clinical improvement.[2] In 1989 Cronassial, a ganglioside prepared from bovine brain, was withdrawn in Germany after reports of Guillain-Barré syndrome and amyotrophic lateral sclerosis in patients given it.[3,4]

The Spanish national drug surveillance system receives reports from physicians and hospital pharmacists, covers three quarters of the general population, and has over 18 000 reports in its database. We review the 17 cases of Guillain-Barré syndrome and other acute motor polyneuropathy associated with use of gangliosides reported up to 29 February 1992.

Present series and results

All 17 patients (10 women) had received fixed dose bovine gangliosides containing GM_1 (17-25%), GD_{1a} (36-46%), GD_{1b} (12-18%), and GT_{1b} (14-22%) (Nevrotal). Three had died (table). The 17 cases had been reported to six different regional centres, and in all the diagnosis had been confirmed by a neurologist. Fifteen patients had started Nevrotal within four weeks before the diagnosis. In the other two the date was unknown, though it preceded the acute motor polyneuropathy.

In eight patients the clinical indication for gangliosides either was not related to any prodrome of Guillain-Barré syndrome or acute motor polyneuropathy or had been present for too long to be interpreted as a prodrome. These cases are listed as "probable" in the table. One patient had a cold and two patients an episode of diarrhoea in the month before diagnosis. Electromyography reports were available in all eight cases. In the remaining nine cases we could not exclude the indication for using gangliosides as a prodrome. We refer to these cases as "possible."

In 14 cases the indications for using gangliosides were not among those approved in Spain (that is, diabetic and post-traumatic neuropathies). Nine patients had taken other drugs with Nevrotal (analgesic/anti-inflammatory drugs, antihypertensive agents, vitamins). Overall, 13 patients were partially or completely recovered from the complication within three months. Of the others, three died and one was continuing with gangliosides.

Albuminocytological dissociation in cerebrospinal fluid was present in seven patients. Serological tests and cerebrospinal fluid cultures for common infective agents in Guillain-Barré syndrome (*Brucella*, *Campylobacter*, *Mycoplasma*, herpes simplex virus, hepatitis B virus) gave negative results in all nine cases for which this information was available. Lyme disease may cause similar neuropathies.[5] Antibodies to *Borrelia* were sought unsuccessfully in three patients.

Comment

Assessing a causal relation between exposure to bovine gangliosides and acute motor polyneuropathy is problematical. Firstly, the symptoms of these conditions are heterogeneous and the time courses unknown. Hence it may be difficult to establish whether the drug was administered before the onset of neurological disturbances or if it was prescribed to treat early symptoms. Secondly, antecedent infections by various agents are reportedly associated with Guillain-Barré syndrome. However, the agents which might be involved and how infection triggers the disease are unknown. We know even less about the aetiology of acute motor polyneuropathy. It is difficult to support the lack of a causal relation in some cases solely on the basis of an antecedent of the common cold, flu, or diarrhoea several days before the onset of symptoms.

A historical cohort study aimed at determining the

Clinical features of 17 cases of acute motor polyneuropathy associated with exposure to gangliosides reported to Spanish drug surveillance system

Case No	Sex	Age (years)	Indication for gangliosides	Time from start of treatment to clinical diagnosis (weeks)	Clinical diagnosis recorded on yellow card	Findings on electromyography	Recovery period (weeks)
				"Probable" cases			
1	M	68	Carpal tunnel syndrome	1	Polyradiculoneuritis	Acute polyradiculoneuritis	>12
2	F	50	Lumbago for one year	2	Guillain-Barré syndrome	Compatible with Guillain-Barré syndrome	>24
3	F	59	Chronic bone pain	<4	Strength loss, atypical Guillain-Barré syndrome	Axonal polyradiculoneuritis without demyelination	12
4	F	68	Ankle pain for seven months	Unknown	Guillain-Barré syndrome	Acute polyradiculoneuritis	Died
5	F	60	Osteoarthritis	<1	Severe—tetraparesis, respiratory failure	Compatible with Guillain-Barré syndrome	Died
6	M	70	Osteoarthritis in knee	2	Guillain-Barré syndrome	Demyelinating polyradiculoneuritis	5
7	F	44	Self limiting pain in spine and legs	3	Guillain-Barré syndrome	Demyelinating polyradiculoneuritis	>20
8	F	41	Arm pain for two months	2	Polyradiculoneuritis	Demyelinating motor polyneuropathy	<8
				"Possible" cases			
9	M	38	Pain in right thigh	<4	Toxic polyradiculoneuritis	Acute polyradiculoneuritis	>24
10	M	35	Neuralgia, rhinitis, vertigo	2	Guillain-Barré syndrome	Compatible with Guillain-Barré syndrome	3
11	F	64	Left sciatic pain	<2	Flaccid—tetraparesis, areflexia, dyspnoea	Diffuse polyneuropathy	Died
12	F	19	Post-traumatic strength loss in legs	4	Guillain-Barré syndrome	No data	Still receiving gangliosides; acute motor polyneuropathy persisting
13	M	61	Strength loss	Unknown	Guillain-Barré syndrome, limb weakness increased	No data	?
14	M	47	Pain in ankle and proximal limb, paraesthesia, strength loss	2-3	Guillain-Barré syndrome	Motor polyradiculoneuritis	>16
15	M	60	Arm pain probably related to post-traumatic neuritis	3	Mixed polyneuropathy	Demyelinating sensory motor polyneuropathy	?
16	F	63	Right intercostal neuralgia	<4	Guillain-Barré syndrome	Slow conduction, amplitude reduction	>12
17	F	44	Hand pain	1	Polyradiculoneuritis	Demyelinating polyneuropathy	>4

safety of bovine gangliosides was carried out in Ferrara, Italy. No case of Guillain-Barré syndrome was found, but the sample was small (18 945 person years) given the incidence of the syndrome (0·6 to 1·9/100 000 population yearly).[5]

Studying the aetiology of conditions whose pathophysiology and clinical course are poorly understood may be difficult and controversial. Formal epidemiological studies in this setting, however, can be justified only if the efficacy of the suspected causal drug is clearly delineated. This is not the case with gangliosides, and hence the Spanish National Commission of Pharmacovigilance has proposed their withdrawal.

We thank Drs A Arias and M M Laínez (Granada); Drs J R Castillo and J Torelló (Sevilla); Drs J M Rodríguez-Sasiain and I Ayani (Bilbao); Dr E J Sanz (Sta Cruz de Tenerife); and Drs F Tato and M Martí (Santiago de Compostela) from the regional centres of Andalucía, Euskadi, Canarias, and Galicia.

1 The regenerative nervous system. *Lancet* 1985;i:1137-8.
2 Bradley WG. Critical review of gangliosides and thyrotropin-releasing hormone in peripheral neuromuscular diseases. *Muscle Nerve* 1990;**13**:833-42.
3 Schönhöfer PS. Guillain-Barré syndrome and parenteral gangliosides. *Lancet* 1991;**338**:757.
4 Latov N, Koski C, Walicke P. Guillain-Barré syndrome and parenteral gangliosides. *Lancet* 1991;**338**:757.
5 Ropper AH. The Guillain-Barré syndrome. *N Engl J Med* 1992;**326**:1130-6.

(Accepted 1 September 1992)

The incidences of lung cancer and breast cancer in women in Glasgow

Charles R Gillis, David J Hole, Douglas W Lamont, Ann C Graham, Stella Ramage

West of Scotland Cancer Surveillance Unit, Ruchill Hospital, Glasgow G20 9NB
Charles R Gillis, *consultant epidemiologist*
David J Hole, *principal epidemiologist*
Douglas W Lamont, *senior statistician*
Ann C Graham, *cancer records officer*
Stella Ramage, *programmer*

Correspondence to: Dr Gillis.

BMJ 1992;305:1331

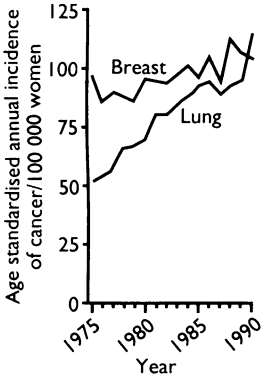
Death rates from lung cancer have been increasing steadily in women since the 1950s.[1] We report changes since 1975 in the incidence of breast and lung cancer in women in Glasgow, an area where the incidence of lung cancer is particularly high.[2]

Methods and results

We studied all incident cases of lung cancer (ICD (ninth revision) code 162) and breast cancer (ICD (ninth revision) code 174) that occurred during 1975-90 in women resident in the City of Glasgow local government district (population in 1990, 689 000). Incidence rates were standardised for age against the population for 1981. Population data were obtained from the annual reports of the registrar general for Scotland.

The age standardised incidence of lung cancer increased from 52/100 000 in 1975 to 115/100 000 in 1990. That of breast cancer increased slightly from 97/100 000 in 1975 to 105/100 000 in 1990 (figure). Women aged 55-64 were the youngest group in whom the incidence of lung cancer increased. The steepest increase occurred in women aged 65-74: in these women the rate for 1990 was 3·6 times that for 1975 ($p < 0.001$). Women born during 1915-29 experienced the highest rates of lung cancer. The incidence for a given age progressively decreased for women born after 1930. The median age at diagnosis of lung cancer was 62 for women born during 1915-29.

Ratios of mortality to incidence for breast and lung cancer in Glasgow changed little between 1975 and 1990. Registrations based solely on death certification data showed a similar pattern for both sites over the period.



Incidence of breast and lung cancer in women in the City of Glasgow, 1975-90

Comment

The increase in the incidence of lung cancer is unlikely to be due to bias in the registration of cancer in Glasgow. It is also unlikely to be an artefact of lung cancers being registered without histological verification. A case-control study carried out in western Scotland during 1976-81 compared exposure to cigarette smoke for patients with lung cancer with and without histological verification and showed no difference in the relative risk.[2]

Our results are consistent with the considerable time lag between exposure to risk and onset of lung cancer. Smoking became common among men before the first world war and among women some 40 years later.[1] The first effects of this on rates of lung cancer were observed in men from the late 1940s onwards,[1] consistent with a latent period for lung cancer related to smoking of roughly 40 years.[3] Comparable mortality from lung cancer in women was seen from 1980 onwards.[2] The highest age specific rates of lung cancer in Glasgow were found in women born during 1915-29. On average, these women started smoking at the age of 20 and developed lung cancer at 62. A case-control study of smoking and lung cancer in Glasgow and western Scotland[2] and a study of a cohort of the general population of Renfrew and Paisley[4] suggest that these women were more likely to have taken up cigarette smoking, were less likely to have given up, smoked more per day, and started smoking earlier than women born before 1915. Women born after 1930 had similar smoking habits to those born in 1915-29 except that a higher proportion smoked lower tar cigarettes.

The risk of lung cancer is now set for many women. Only a reduction in cigarette smoking will prevent young women experiencing the premature morbidity of their elders, but they are unlikely to achieve this without help. More effective methods of preventing and stopping smoking are required. Forty years after Doll and Hill's seminal paper linking lung cancer to cigarette smoking[5] this cancer, for which prospects for long term prevention are good, has paradoxically become more common than breast cancer, whose causes are less well understood and for which prospects for primary prevention seem limited.

We thank Tracy Marr, Eileen Dott, Ena Macpherson, Patricia Williams, Rena Mauchin, and Ann Clark for their clerical, technical, and secretarial help.

1 Royal College of Physicians of London. *Smoking and health now.* London: Pitman, 1971.
2 Gillis CR, Hole DJ, Boyle P. Cigarette smoking and male lung cancer in an area of very high incidence. I. Report of a case-control study in the west of Scotland. *J Epidemiol Community Health* 1988;**42**:38-43.
3 Schottenfeld D, Fraumeni JF. *Cancer epidemiology and prevention.* Philadelphia: W B Saunders, 1982.
4 Gillis CR, Hole DJ, Hawthorne VM. Cigarette smoking and male lung cancer in an area of very high incidence. II. Report of a general population cohort study in the west of Scotland. *J Epidemiol Community Health* 1988;**42**:44-8.
5 Doll R, Hill AB. A study of the aetiology of carcinoma of the lung. *BMJ* 1952;ii:1271-86.

(Accepted 30 September 1992)