References

Gunning, J. F., Kristinson, A., Miller, G., and Saunders, K. (1970). *British Heart Journal*, 32, 462.
Hendrix, G. H. (1969). *Southern Medical Journal*, 62, 483.
Kahler, R. L., Burrow, G. N., and Feliq, P. (1967). *Journal of the American Medical Association*, 200, 997.
Kernohan, R. J. (1966). *Lancet*, 1, 718.
Kernohan, R. J. (1967). In *Diazepam in Anaesthesia, Report of the Proceedings of a Symposium, Royal Society of Medicine*, p. 82. Bristol, Wright.
Lebowitz, W. B. (1969). *Connecticut Medicine*, 33, 173.
Lown, B. (1967). *British Heart Journal*, 29, 469.
Lown, B., Amarsingham, R., and Neuman, J. (1962). *Journal of the American Medical Association*, 182, 548.
Muenster, J. J., Rosenberg, M. S., Carleton, R. A., and Graettinger, J. S. (1967). *Journal of the American Medical Association*, 199, 758.
Nutter, D. O., and Massumi, R. A. (1965). *New England Journal of Medicine*, 650, 273.
Somers, K., Gunstone, R. F., Patel, Ashvin K., and D'Arbela, P. G. (1971). In preparation.
Thornton, J. A., and Clarke, P. F. R. (1970). *British Medical Journal*, 2, 732.
Turkel, R. A., and Lemmert, W. A. (1969). *Southern Medical Journal*, 62, 61.
Winters, W. L., McDonough, M. T., Hafer, J., and Dietz, R. (1968). *Journal of the American Medical Association*, 204. 926.
Woodbridge, J. H. (1969). *Journal of the Mississippi State Medical Association*, 10, 542.

Baclofen in the Treatment of Spasticity*

P. HUDGSON, D. WEIGHTMAN

British Medical Journal, 1971, 4, 15–17

Summary

Baclofen† (Lioresal), a derivative of gamma-aminobutyric acid, was introduced in 1966 as a possible treatment for spasticity due to corticospinal tract lesions. Preliminary studies suggested that it may be more effective than other spasmolytic agents currently available, and a double-blind controlled trial in a group of 23 patients against placebo has shown it to be significantly more effective.

Introduction

The treatment of spasticity due to spinal cord and other neurological lesions has long been unsatisfactory. Intrathecal injections of phenol (Nathan, 1959) may produce significant improvement in some patients for several months, though the risks of increasing weakness in the lower limbs and interfering with bladder function are obvious disadvantages. Various problems attend the drug treatment of spasticity, many of the agents introduced being quite ineffective when given by mouth. Chlordiazepoxide and diazepam are probably the most helpful preparations in common use, but both are likely to make patients unacceptably drowsy when effectively reducing spasticity. These drugs probably exert their effect by acting on spinal interneurones (Cook and Nathan, 1967) but their tranquillizing effects suggest that modification of supraspinal influences may also be involved.

The basis for a more rational approach to the problem has been provided by recent studies of spinal cord pharmacology (*Lancet*, 1970). Attention has been focused on gamma-aminobutyric acid, which depresses all types of spinal neurones (Curtis and Watkins, 1965) and inhibits monosynaptic and multisynaptic reflex activity in the experimental animal. A preliminary report by Birkmayer, Danielczynk, and Weiler (1967) suggested that the gamma-aminobutyric acid derivative beta-(4-chlorophenyl)-gamma-aminobutyric acid, baclofen (Lioresal), was useful in the control of spasticity, particularly in spinal cord lesions. This was supported by the studies of Pedersen, Arlien-Søborg, Grynderup, and Henriksen (1970) and of Jones, Burke, Marosszeky, and Gillies (1970), the latter a placebo-controlled trial in six patients.

*An abbreviated version of this paper was read at an International Symposium on Current Aspects of Muscle Spasticity, Vienna, April 1971.

† Proposed approved name.

Royal Victoria Infirmary, Newcastle upon Tyne NE1 4LP
P. HUDGSON, M.R.C.P., M.R.A.C.P., Physician in Neurology

University of Newcastle upon Tyne, Newcastle upon Tyne
D. WEIGHTMAN, Assistant in Medical Statistics

Preliminary Study

Six patients with severe spasticity in their lower limbs due to spinal cord disease (five with multiple sclerosis and one with severe residual spastic paraparesis after surgical removal of a dorsal neurofibroma) were admitted to this study. In each case baclofen was administered in a single intravenous injection of 25 mg and orally in doses of 10 mg thrice daily for 10 days. An attempt was made to monitor the effects of the intravenous injection by needle electromyography, but interpretation of the data so obtained was virtually impossible because of interference due to flexor spasms induced in the muscles sampled. However, a trend in favour of the drug was thought to be present and there was certainly an appreciable improvement in spasticity on clinical examination in each patient (Barwick and Hudgson, 1967). This was also the subjective impression of all the patients, though one (a middle-aged woman with neurofibromatosis) was unable to tolerate the oral preparation for more than two days because of nausea and vomiting (she had previously reported nausea and vertigo during the intravenous injection). Another patient had three major epileptic seizures and developed a confusional state when she was on the oral preparation. However, the situation was complicated in her case by the fact that she had moderately severe cerebral demyelination with dementia as well as spinal cord disease in addition to a fever due to urinary tract infection.

Double-blind Trial

The formal double-blind cross-over trial of baclofen was begun in mid-1968 and at the time of closing the trial 23 patients had completed it. To standardize the conditions of the trial as much as possible it was decided to limit entry to patients with lower limb spasticity due to spinal cord disease. Of the 23 patients 18 were suffering from multiple sclerosis and were in remission, but with severe residual neurological deficits; two had myelopathies associated with cervical spondylosis; one had motor neurone disease with unusually severe spasticity in his lower limbs; one was a case of familial spastic paraplegia; and one woman had a slowly progressive spastic paraparesis of uncertain nature, possibly "spinal" multiple sclerosis. Their

ages ranged from 30 to 63 years, there were 16 men and 7 women. Spasticity was arbitrarily graded from 0 (normal) to 4 according to clinical impression (Ashworth, 1964) and all the patients in the trial were either grade 3 or 4. Most of them also were troubled by aching pain in their muscles due to spasticity, frequent attacks of flexor spasms, usually most troublesome while in bed at night, and attacks of spontaneous clonus.

The patients were allocated to side A or side B of the trial according to a table of random numbers held by the chief pharmacist of the Royal Victoria Infirmary. The patients then took placebo or baclofen in doses of 10 mg thrice daily for 10 days and after a cross-over period of seven days automatically went into the opposite side of the trial. The patients were seen and examined at the beginning and end of each side of the trial, records of neurological status and blood pressure being kept, and they were always closely questioned about appetite, sudden changes in weight, and possible side effects. A full blood examination (haemoglobin, packed cell volume, white cell count, and film) was carried out on each patient before and after completion of the trial. The results of the trial were analysed by an independent statistician (D.W.) and are recorded below.

Results

The essential data showing the results in the 23 patients studied are set out in Tables I to IV. The improvement on baclofen is shown in Table I and on placebo in Table II. A within-patient comparison between mean changes in spasticity during treatment periods (Table III) shows that baclofen was significantly superior to the placebo. A comparison was made between the improvements experienced by patients while on the drug and on the placebo. On average the 23 patients improved to a greater extent while having the drug, and the mean difference of 0·9 between the two improvements is statistically significant (Table III).

The mean scores before treatment (3·74 before baclofen and 3·65 before the placebo) are not significantly different. All but four patients had returned to the first pretreatment level after the stabilizing period of one week. One starting on the placebo became worse from a score of 3 at pretreatment to 3·5 at the end of 10 days. After the rest period his pre-drug score was 4. A second patient starting on baclofen had a pretreatment score of 4 improved to a score of 1 after 10 days. After one week without treatment his pre-placebo score had worsened to 3·5, not quite reaching his first pretreatment score of 4. A third patient starting on the drug with a pretreatment score of 4 improved to a score of 1 at the end of 10 days. After a rest from treatment of one week her pre-placebo score was 3 and after 10 days on placebo had worsened to 4. These three patients preferred the drug. The fourth patient started with placebo and had a pretreatment score of 4, improving to 1 at the end of 10 days. After the rest period her pre-drug score worsened to 3·5 and this had not altered at the end of 10 days on the drug. This patient preferred the placebo.

To test whether there was a difference in response if treatment was given in the first or the second period of the trial, the improvements in the two periods were compared (see Table IV). There was no significant period effect for either drug or placebo.

Side Effects.—Two patients were withdrawn from this trial, one because of undue somnolence during the first half (when he was on placebo) and the other during the second half (when he was on baclofen). No patients reported anorexia or sudden change in weight, their blood pressures remained stable throughout, and full blood counts done before and after completion of the trial were all normal. Of the 23 patients who completed the trial nine complained of side effects—six while on the drug and three while on placebo (see Table V). The commonest complaint was of mild nausea, and one patient reported vertigo for one to two hours after taking the tablets, but it is noteworthy that side effects were experienced only during the first half of the trial in eight out of the nine cases. The possible significance of this phenomenon and that of patients developing side effects on placebo is discussed below.

Patients' Impressions.—Thirteen of the 23 patients felt better while having baclofen, but in three their improved mobility was associated with increased weakness. Five patients felt better while having the placebo and in one the improvement was accompanied by increased weakness. Five patients said they felt no difference between the periods of treatment. This result is not statistically significant though it can be stated with 95% confidence that 47% to 90% of patients with a preference will prefer the drug to the placebo.

TABLE I—*Improvement on Baclofen*

No. of patients	23
Mean spasticity score: Before baclofen	3·74
Mean spasticity score: After baclofen	2·30
Mean improvement	1·44
Standard error of mean improvement (within patients)	0·230
	P <0·001

The mean improvement of 1·44 in patients while taking the drug is highly significant.

TABLE II—*Improvement on Placebo*

No. of patients	23
Mean spasticity score: Before placebo	3·65
Mean spasticity score: After placebo	3·11
Mean improvement	0·54
Standard error of mean improvement (within patients)	0·231
	P <0·05

The mean improvement of 0·54 in patients while on the placebo is statistically significant at the 5% level.

TABLE III—*Comparison between Mean Changes in Spasticity*

No. of patients	23
Mean improvement on Baclofen	1·44
Mean improvement on Placebo	0·54
Mean difference	0·90
Standard error of difference (within patients)	0·426
	P < 0·05 significant

TABLE IV—*Comparison of Improvements during the Two Periods*

	Baclofen		Placebo	
	First Period	Second Period	First Period	Second Period
No. of patients	10	13	13	10
Mean improvement	1·45	1·42	0·60	0·50
Difference between means	0·03		0·10	
Standard error of difference	0·499		0·483	
	P >0·9 not significant		P >0·8 not significant	

TABLE V—*Side Effects Experienced by Patients during Trial*

Side Effects	No. of Patients on	
	Baclofen	Placebo
Nausea	3	1
Transient vertigo	1	
Blurring of vision		1
Upper respiratory tract infection		1
Supraorbital pain	1	
Sleepiness	1	
	6	3

Discussion

This trial has clearly shown that baclofen is an effective spasmolytic drug and that it was significantly more effective than a placebo as judged by the reduction in mean spasticity scores. Probably it would have been shown to be even more effective but for the high placebo response in some cases. This effect exerted an undue influence on the course of the trial for the following reasons: (1) because of the comparatively short treatment period (this was chosen because baclofen acts within

24 hours); (2) because of the extreme suggestibility of patients with chronic disability due to neurological disease, especially multiple sclerosis; and (3) because many of the participants had previously co-operated in trials of various treatments for multiple sclerosis conducted in this department in the past.

These patients were familiar with the double-blind technique and were predictably anxious about taking new drugs. This was highlighted by the fact that of the nine patients complaining of side effects eight experienced them during the first half of the trial. None the less the 23 patients on average improved to a greater extent on baclofen than on the placebo and the difference between the improvements was significant at the 5% level. This taken in conjunction with the absence of serious side effects, particularly intolerable somnolence, justifies extended studies of baclofen, perhaps including controlled trials against spasmolytic drugs currently in use.

Supplies of baclofen were made available by Ciba Laboratories, Horsham, Sussex. We wish to acknowledge with gratitude the ready co-operation of Dr. M. K. Flood, of Ciba Laboratories, at all times during the course of the trial. We also wish to thank Professor J. N. Walton, Dr. D. A. Shaw, and Dr. J. B. Foster, who referred some of the patients taking part. Secretarial facilities in the department of neurology, Royal Victoria Infirmary, were financed by the Multiple Sclerosis Society of Great Britain and Northern Ireland to whom we also wish to express our thanks.

ADDENDUM.—One of us (P.H.) has now treated seven patients with severe spastic paraparesis with baclofen for periods up to six months. In each case there has been a satisfactory reduction in spasticity without untoward side effects, though one man had to stop taking the drug because of an associated increase in leg weakness.

References

Ashworth, B. (1964). *Practitioner*, **192**, 541.
Barwick, D. D., and Hudgson, P. (1967). Unpublished observations.
Birkmayer, W., Danielczynk, W., and Weiler, G. (1967). *Wiener medizinische Wochenschrift*, **117**, 7.
Cook, J. B., and Nathan, P. W. (1967). *Journal of the Neurological Sciences*, **5**, 33.
Curtis, D. R., and Watkins, J. C. (1965). *Pharmacological Reviews*, **17**, 347.
Jones, R. F., Burke, D., Marosszeky, J. E., and Gillies, J. D. (1970). *Journal of Neurology, Neurosurgery and Psychiatry*, **33**, 464.
Lancet, 1970, **2**, 918.
Nathan, P. W. (1959). *Lancet*, **2**, 1099.
Pedersen, E., Arlien-Søborg, P., Grynderup, V., and Henriksen, O. (1970). *Acta Neurologica Scandinavica*, **46**, 257.

Prenatal Diagnosis of Tay-Sachs Genotypes

RUTH NAVON, BARUCH PADEH

British Medical Journal, 1971, **4**, 17–20

Summary

Hexosaminidase activity was determined in cultured and uncultured amniotic fluid cells taken from seven pregnant women who had previously given birth to infants with Tay-Sachs disease. Complete deficiency of hexosaminidase A was found in one case, indicating a Tay-Sachs fetus. The diagnosis was confirmed on examination of various tissues after therapeutic abortion. Of the other six cases three were considered heterozygous and three homozygous normal. These diagnoses were confirmed postnatally on examination of cord blood leucocytes, peripheral leucocytes, and urine. The activity of hexosaminidase A is appreciably decreased in dead cells and hence in uncultured amniotic fluid cells. Hence reliable identification in utero of the three genotypes may be achieved only by examining the cultured living amniotic cells.

Introduction

Tay-Sachs disease is a lipid-storage disease inherited as an autosomal recessive trait and is invariably fatal. The ganglioside GM_2 accumulates in the central nervous system and to a lesser extent in other tissues, including cultured skin fibroblasts. A complete absence of β-D-*N*-acetylhexos-aminidase A in tissues of Tay-Sachs patients was found by Okada and O'Brien (1969), whereas both forms A and B of the enzyme are found in normal individuals (Robinson and Stirling, 1969). Obligatory heterozygotes showed intermediate levels of hexosaminidase A, between those of patients with Tay-Sachs disease and normal controls (Friedland *et al.*, 1970; O'Brien *et al.*, 1970; Padeh and Navon, 1971; Navon and Padeh, 1971).

Hexosaminidase A and B have been found also in amniotic fluid cells of normal individuals (Okada and O'Brien, 1969; Rattazzi and Davidson, 1970; Schneck *et al.*, 1970; Padeh and Navon, 1971). This enables one to make a prenatal diagnosis of the disorder since an affected fetus will probably have a deficiency of hexosaminidase A in the amniotic cells originating from its skin.

Schneck *et al.* (1970) reported one case of Tay-Sachs disease diagnozed during the second trimester of pregnancy (18 weeks). They showed in this case an absence of hexosaminidase A activity in cultured and uncultured amniotic fluid cells by acryamide-gel electrophoresis. The diagnosis was confirmed by showing a deficiency of form A of *N*-acetylhexosaminidase in the liver and brain of the abortus.

A false-positive diagnosis was reported by Rattazzi and Davidson (1970). Using an electrophoretic method of assaying hexosaminidase from an extract of uncultured amniotic cells, they showed the absence of hexosaminidase band A, whereas the aborted fetus and subsequently the cultured amniotic cells had a normal ratio of hexosaminidase A and B.

The purposes of this paper are to report and to discuss our experience in identification of the various genotypic possibilities with regard to Tay-Sachs disease by assaying the activity of hexosaminidase A after heat inactivation.

Patients and Methods

Amniotic fluid was obtained by transabdominal puncture from seven pregnant women who had previously given birth to Tay-Sachs disease offspring and from 10 other pregnant women who served as controls. Amniocentesis was performed

Department of Human Genetics, Tel-Aviv University Medical School and Tel-Hashomer Hospital, Israel
RUTH NAVON, M.SC., Research Biochemist
BARUCH PADEH, M.D., Associate Professor of Medicine