

Evaluation of baclofen (Lioresal) for spasticity in multiple sclerosis

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Summary

The effect of baclofen on spasticity and muscle spasms was assessed in thirty-five patients with multiple sclerosis. Benefit from reduction of spasticity was obtained in sixteen patients. A higher proportion of patients confined to a wheelchair was helped than ambulant patients, but overall functional improvement was limited. Twenty-one of the thirty-five patients had troublesome spasms and thirteen of them had significant relief on baclofen. Substituting identical dummy tablets confirmed that benefit was attributable to the pharmacological effects of baclofen in ten of the sixteen patients whose spasticity was reduced and in eight of the thirteen whose muscle spasms were relieved. In two of the remainder, benefit appeared to be due to placebo effect, and the others maintained their improvement after stopping the drug.

The drug had to be withdrawn in nine patients because of increased weakness and in ten other patients who had intolerable side effects. The optimum dose of baclofen tolerated ranged from 15 mg to 80 mg daily. The importance of adjusting the dose regime to the requirement of each individual and starting with small doses in multiple sclerosis is emphasized.

Introduction

The basis of spasticity is overactivity of the stretch reflexes and Burke and Ashby (1972) suggest that this is best explained by suppression of 'presynaptic' inhibitory mechanisms. Curtis and Felix (1971) postulated that γ -aminobutyric acid (GABA) is the hyperpolarizing inhibitory transmitter responsible for the prolonged postsynaptic inhibition of spinal motoneurons. However, attempts to use GABA in the treatment of spasticity were unsuccessful, and a number of derivatives were synthesized with lipophilic substituents; of these, β (4-chlorophenyl) γ -amino butyric acid, baclofen, was found to be the most active, and clinical trials of its effect on spasticity have been encouraging (Jerusalem, 1968;

Pedersen *et al.*, 1970; Hudgson and Weightman, 1971; Polacek and Schuppien, 1972). According to Faigle and Keberle (1972) baclofen was well absorbed when administered orally, reached a maximum plasma concentration in 2 hr and had a half-life of approximately 3 hr, being excreted largely unchanged in the urine. Recent studies have suggested that baclofen reduces the excitability of the monosynaptic reflex arc from dynamic spindles (McLellan, 1973) and acts by reducing gamma motor activity (Knutsson, Lindblom and Martensson, 1973). However, its exact mode and site of action are not yet certain, although it is thought to have a direct action at the spinal level since it is effective in clinically complete as well as partial spinal cord lesions (Jones *et al.*, 1970; Burke, Andrews and Knowles, 1971; Ashby and White, 1973). It is now regarded by many as the drug of choice in the treatment of spasticity due to spinal cord lesions, and is claimed to be relatively free from side effects and from impairment of voluntary muscle power. Tudor (1974) reported that patients with severe spasticity treated with baclofen in the Royal Hospital for Incurables had a decrease in spasm attacks coupled with increased mobility and ease of nursing, and she remarked that such measures as tenotomies and intrathecal phenol, once fairly frequently resorted to, were no longer required.

We have been particularly interested in the use of baclofen for the treatment of spasticity in patients with multiple sclerosis (MS). In the absence of any specific therapy for MS at the present time, symptomatic measures such as the relief of spasms and spasticity may make a vast difference to the patient's comfort and capacity to cope with the disease. Assessment of the drug in MS, however, presents special problems because spasticity may not be the only factor contributing to the disability and also because spontaneous remissions and relapses may occur during treatment. It should be emphasized that we have not been so concerned with slight changes in spasticity and associated signs, as with clear-cut functional benefits such as an increase in

daily living activities and improvement of the patient's quality of life. We also set out to ascertain the limitations of treatment in this group of patients.

Patients and methods

Thirty-six patients with MS were initially selected for this study, the diagnosis having been established as 'definite' or 'probable' according to McAlpine's criteria (McAlpine, Lumsden and Acheson, 1972), and they were attending regularly for follow-up at the neurological clinics of the Derbyshire Royal Infirmary and the Nottingham General Hospital. Thirteen were female and twenty-three male and the age range was 25-65 (mean, 47) years. The duration of the disease from first symptoms to the date of starting treatment with baclofen ranged from 2 to 25 years, and the duration of the current disability from 1 to 6 years with an average of 3 years.

Patients were considered to be suitable for treatment with baclofen if they had disability due to spasticity in the presence of reasonable voluntary muscle power or, in the more severe cases, if spasticity was causing difficulty in day-to-day care, and also if they had troublesome muscle spasms. The degree of spasticity was graded 0 (normal) to 4 (rigid) by the simple clinical criteria of Ashworth (1964) before and during treatment with baclofen and details of the disability due to spasticity and other neurological manifestations were recorded. In addition to the clinical assessment of spasticity, the patient's own impressions were noted and accounts obtained from the families, nurses and physiotherapists involved in the day-to-day care, regarding daily living activities such as dressing, feeding and washing, as well as the ease of movements and any changes in mood or sleep.

In view of the enthusiastic reports of the efficacy of baclofen and the fact that many of our patients had already been treated with other antispastic agents such as diazepam, we decided that we would not be justified in doing a formal double blind trial. Patients were started on the drug usually 5 mg t.d.s., gradually increasing either to an effective dose or to the limits of tolerance. Side effects were recorded and when severe the dose was reduced or the drug withdrawn. As Hudson and Weightman (1971) pointed out, patients with severe chronic neurological disease tend to be highly suggestible and we attempted to identify any placebo effect of the baclofen in the patients who appeared to benefit from the drug by substituting, unbeknown to them, dummy tablets equivalent in number to the optimum dose of baclofen. When reassessed after a week on dummy tablets, those who had deteriorated were restarted on their previously determined optimum dose of baclofen; those who did not deteriorate stopped treatment, were reassessed a week later and

followed up. In this way we tried to overcome one of the chief disadvantages of double blind trials, i.e. lack of flexibility in dosage.

Results

Of the thirty-six patients with MS, one had a relapse during the trial and was excluded. The results in the other thirty-five patients are shown in Table 1. The effects of treatment were assessed in the following groups.

(1) Ambulant patients whose speed and distance of walking were impaired by spasticity. A careful watch was kept for patients in whom a degree of spasticity was required to support the legs when walking, and the dose of baclofen was reduced or treatment stopped if there was any deterioration of gait due to reduction of the spasticity. Such deterioration was not classified as a side effect of baclofen, but indicated that the reduction of spasticity was inappropriate in these cases;

(2) patients largely confined to a wheelchair in whom spasticity interfered with active and passive movements;

(3) patients with muscle spasms in both the above groups, irrespective of their other disabilities.

Overall benefit from the drug in each case was recorded as nil, slight or considerable.

In sixteen patients there was a reduction of spasticity on treatment with baclofen. Benefit was graded as considerable in eight and slight in eight patients. Of the twenty-one ambulant patients, benefit was slight in five and considerable in only four, whereas the drug helped a higher proportion of the fourteen patients confined to a wheelchair, four deriving considerable benefit in their day-to-day care, and three slight benefit. When dummy tablets were substituted for the baclofen in the sixteen patients who improved, ten deteriorated and after a week were restarted on baclofen. The other six patients maintained their improvement during the week on dummy tablets, and when the dummy tablets were stopped, two then deteriorated and four remained unchanged.

TABLE 1. Progress of thirty-five patients on baclofen

	Ambulant	Wheelchair	Muscle spasms*
Improvement			
Considerable	4	4	9
Slight	5	3	4
No benefit			
Increased weakness	7	2	4
Intolerable side effects	5	5	4
Total	21	14	21

* Includes patients in ambulant and wheelchair groups.

Of the twenty-one patients with troublesome muscle spasms, thirteen were relieved when treated with baclofen, nine completely and four partially. When dummy tablets were substituted in these thirteen patients, the spasms increased again in eight. In the other five there was no deterioration during the week on dummy tablets, but when these were stopped the spasms increased again in two, but were no worse in three.

One patient suffered from painful spasms involving the psoas muscles. This was a woman of 40 who had undoubted MS and for the last 10 years had been largely confined to a wheelchair with a spastic paraparesis and intermittent incontinence of urine. In May 1973 she started to complain of bouts of severe cramp-like pains in the lower part of her abdomen on both sides and centrally in the perineal and pelvic region. Detailed urogenital investigations failed to reveal any cause, and it was then suspected that her pains were due to psoas spasms. Neither analgesics, diazepam or carbamazepine had helped but when she was treated with baclofen 10 mg t.d.s., there was dramatic relief of the spasms and of the abdominal pain. Further increase in dosage was associated with increased weakness and urinary retention. She has been maintained on baclofen 10 mg t.d.s. with considerable relief of her spasms and spasticity.

In twelve patients the optimum dose was 15–40 mg/day. Only four patients tolerated between 60 and 80 mg daily. Seven patients became weaker as the dosage was increased, but recovered following adjustment in the amount and frequency of doses so that treatment could be continued and worthwhile improvement of gait was achieved.

Patients intolerant of baclofen

In nine patients withdrawal was necessary because of deterioration due to diminution of the support given by the spasticity. In these patients the reduction of spasticity was required to provide support for the legs while walking. This occurred with a dose of baclofen as small as 5 mg t.d.s. but the spasticity and ability to walk returned within a week of stopping the drug.

Side effects as listed in Table 2 were encountered in fifteen of the thirty-five patients. In five patients, these were transient or could be abolished by reducing the dose of baclofen without loss of benefit, but in the other ten, the side effects necessitated stopping the drug.

The average age of the ten patients with intolerable side effects was 48 years, only two being under 40. In all cases, the side effects soon disappeared after reduction or cessation of therapy, suggesting that the symptoms were unlikely to have been manifestations of the disease, although we could not always

TABLE 2. The side effects occurring in fifteen of thirty-five patients on baclofen

Side effects	No. of patients*
Dizziness	7
Drowsiness	3
Depression	1
Confusion	2
Agitation	1
Nightmares	1
Headache	1
Incoordination	1
Blurring of vision	2
Nausea	3
Diarrhoea	1
Constipation	1
Impotence	1
Incontinence of urine (worse)	2

* Some patients had more than one side effect.

be sure about this. For example, one patient developed impotence and constipation while on treatment with baclofen 30 mg daily. This dose produced considerable relief of spasticity and of his painful muscle spasms; when reduced to 15 mg daily his impotence recovered within a few days. He still suffers from muscle spasms during the day, but these are less troublesome. He remains slightly constipated on the reduced dose of baclofen but this is easily managed with aperients.

Discussion

In this study we have attempted to assess the overall benefit from baclofen in patients with MS, in whom spasticity was considered to be a prominent factor in their general disability. The preponderance of males in this series, contrasting with the usual female preponderance in MS in this country, was probably due to chance selection.

Of the sixteen patients who appeared to benefit when treated with baclofen, the use of dummy tablets confirmed that the reduction of spasticity could be attributed to the pharmacological effects of the drug in ten patients, as they deteriorated on the dummy tablets. Of the other six, two deteriorated only after the dummy tablets had been stopped, suggesting that the apparent benefit on baclofen was a placebo effect. The remaining four patients maintained their improvement on dummy tablets and after they were stopped, suggesting that the apparent benefit on baclofen might have been due to coincidental remission of the disease, or possibly that the improvement on baclofen had broken a vicious cycle so that benefit could be sustained when the drug was withdrawn.

Reduction of spasticity in sixteen out of thirty-five patients (45.7%) was less than expected from reports of previous series, but with the relief of troublesome muscle spasms in thirteen of twenty-one patients

was of considerable value. The patients who improved were more comfortable and nursing was easier, but this was not accompanied by significant functional improvement, for example in the ability to walk. No tenotomies or intrathecal phenol were required, but on the other hand none of the patients in the wheelchair group benefited to the extent of becoming ambulant. The occurrence of increased weakness in nine patients requiring withdrawal of the drug indicates the functional role of spasticity in some patients and the difficulty in predicting it before starting treatment.

The incidence of side effects (ten of thirty-five patients, 28.6%) was higher than in previously reported series. However, these side effects were dose-related and rapidly subsided on stopping the drug. In view of Paesleck's report (1972) that five out of nine of his patients intolerant of the drug were over 40 years old, it is of interest that the average age of the ten patients in our series with intolerable side effects was 48 years and only two were under 40. As the average age of all our patients was 47 years, this may have contributed to the frequency of side effects in our series.

It has been suggested that baclofen may be beneficial in relieving some bladder disturbances such as frequency and urgency. We were not able to confirm this in our series; on the other hand two patients complained of worsening incontinence and one of constipation while on baclofen and one patient developed urinary retention while on dummy tablets. None of our patients had priapism but one patient developed impotence on the drug which rapidly subsided on reduction of the dosage. Although we could not be sure whether this was due to the drug or the disease, it seems possible that baclofen might precipitate impotence in patients with MS.

We can conclude that baclofen has been of value in the relief of spasticity or of muscle spasms in about 50% of the patients with MS in this series, although the relatively high incidence of side effects and increased weakness is a significant limiting factor in its use. The average dose tolerated was less than in previous reports and it is clear that each patient requires his or her individualized dose regime. The importance of starting with small doses in patients with MS needs further emphasizing.

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