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Intrathecal baclofen: does tolerance occur?

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Concern over the development of tolerance in patients on continuous intrathecal baclofen therapy has arisen as this new form of treatment for spasticity has gained wider use. We have studied time–dose relationships in 18 spinal cord injured patients who have undergone intrathecal baclofen infusion pump implantation since February 1988 in our facility. Our data show that there was a significant increase in baclofen dosage needed to control spasticity during the first 12 months post implantation. After 12 months, however, no significant change in dosage requirement was detected. In addition, there was no significant difference between completely and incompletely spinal cord injured patients with regard to both the initial dose and the tolerance trend.

Keywords: intrathecal baclofen; spasticity; spinal cord injury; tolerance.

Introduction

Continuous intrathecal baclofen infusion has been shown to be a safe and effective treatment for severe spasticity of spinal cord origin, and has become increasingly accepted as an alternative for surgery in spinal cord injured (SCI) patients with this problem.[1–11] Nevertheless, concern over whether patients will develop tolerance remains a controversial issue affecting clinicians' decisions whether to use this modality or not.

Tolerance is defined as a phenomenon manifested by an escalation of the dose required to produce a previously obtained effect or by the decrement of the effect produced by a given dose of drug with continued administration.[12] Baclofen (Beta-4-chlorophenyl-gamma-aminobutyric acid) is an agonist of gamma-aminobutyric acid-B (GABA-B) receptors which are very superficial in the spinal cord.[13] A theory as to why tolerance develops for drugs which exert their pharmacological effects by interaction with specific receptors is that repeated administration of the agonist causes either a reduction in receptor number or an uncoupling of the receptor to effector molecules. This results, either way, in an increase in the concentration of a given agent necessary to achieve the fractional occupancy in order to evoke a given effect.[14]

In this study, we investigated the relation

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between time and the required intrathecal baclofen dose needed to keep spasticity at an acceptable level, and thereby see whether tolerance was a factor in our patients.

Materials and methods

Eighteen patients with SCI (5 complete, 13 incomplete) who had undergone continuous intrathecal baclofen infusion pump (SynchroMed, Medtronics Inc) implantation in our facility between February 1988 and May 1991 for severe spasticity were studied. All patients had temporary baclofen (Lioresal, Ciba-Geigy) infusions prior to pump implantation, in order to find a dosage of baclofen that optimally controlled spasticity without resulting in flaccidity, and which was associated with patient satisfaction. After pump implantation, patients were seen on a monthly basis for refills and clinical investigation. We documented the initial and subsequent doses of baclofen every 3 months post implantation. We also measured the intensity of spasticity using the Ashworth scale (Table I) at the same intervals.

Results

During a mean follow up period of 29.9 months (6–48 months), spasticity was kept under acceptable control (Ashworth grade 1–2). There were no significant differences between the mean Ashworth grades at the 3-monthly intervals throughout the study. Only 10 patients have been followed for more than 24 months. The data are still not sufficient for statistical analysis after 24 months because of the drop off rate of patients after that juncture. For that reason, we analyzed the data for the first 24 months only. All of the patients were followed for at least 6 months, 17 for 12 months, 16 for 18 months, 15 for 21 months and 14 for 24 months. All patients showed a significant trend to increase their dosage over the 24-month period (Fig 1) beginning with an initial dosage of 201.5 μg/day (SD = 104.9). Least squares regression analysis of the dosages on 3-monthly intervals indicated that within the first 12-month period, the patients showed a significant positive linear trend at $p < 0.0009$ (Fig 2). But additional analysis indicated that there was no trend in increase of dosage from the 12th month to the 24th month (Fig 3). We also analyzed the complete and incomplete injury groups separately. Least squares regression analysis

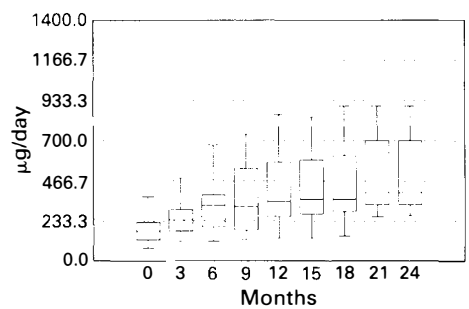

Figure 1 Box plots graphic of intrathecal baclofen doses of all patients for 3-month intervals over 24 months.

Table I Intensity of spasticity using the Ashworth scale

Grade	Degree of muscle tone
1	No increase in tone
2	Slight increase in tone, giving a 'catch' when affected part is moved in flexion or extension
3	More marked increase in tone, but affected part easily flexed
4	Considerable increase in tone, passive movement difficult
5	Affected part rigid in flexion or extension

Ashworth scale–Ashworth grade is calculated by summing grades for hip flexion, hip abduction, knee flexion and ankle dorsiflexion on each side and then dividing by 8.

indicated a significant linear increase over the first 12 months ($p = 0.0009$) with an initial dosage of 210.5 μg/day (SD = 121.9) for incompletely injured patients (Figs 4, 5) and a significant linear increase over the first 12 months ($p = 0.0009$) with an initial dosage of 180.0 μg/day (SD = 48.1) for completely injured patients (Figs 6, 7). There was no significant increasing trend between the 12th and the 24th month for either group. We compared the complete

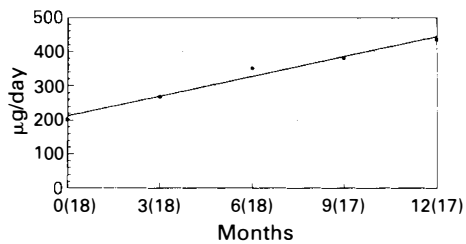

Figure 2 Time–dose relation for all patients in the first 12 months. Numbers of patients for the months are shown in parentheses.

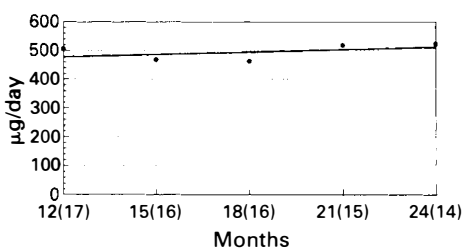

Figure 3 Time–dose relation for all patients between the 12th and 24th month. Numbers of patients for the months are shown in parentheses.

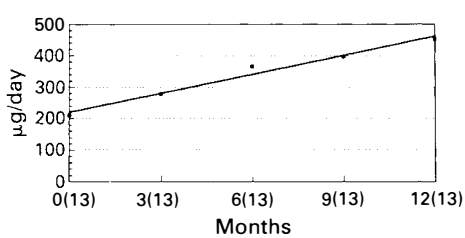

Figure 4 Time–dose relation for incomplete injury patients in the first 12 months. Numbers of patients for the months are shown in parentheses.

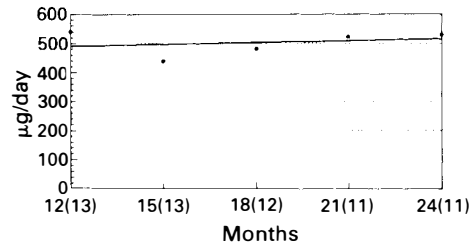

Figure 5 Time–dose relation for incomplete injury patients between the 12th and 24th month. Numbers of patients for the months are shown in parentheses.

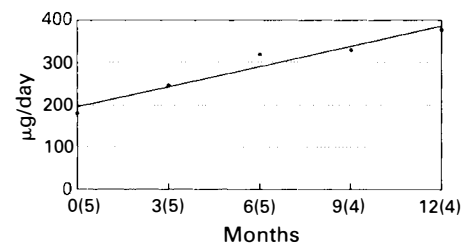

Figure 6 Time–dose relation for complete injury patients in the first 12 months. Numbers of patients for the months are shown in parentheses.

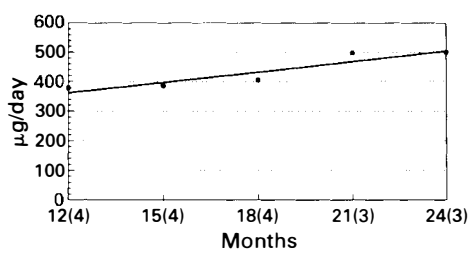

Figure 7 Time–dose relation for complete injury patients between the 12th and 24th month. Numbers of patients for the months are shown in parentheses.

and incomplete injury groups with regard to initial dosages and found no significant difference. Similarly, we tested the null hypothesis that there was no significant difference in the slopes between the linear fit of dosages for both groups for the first and second 12-month periods, by incorporating an indicator variable representing slopes. The analysis indicated no significant difference between the slopes.

Discussion

Penn and Kroin, the first authors who proposed intrathecal baclofen therapy for spinal spasticity,[15] were also the first authors who pointed out the problem of tolerance.[1] In their series of 7 patients with spinal spasticity (due to SCI and multiple sclerosis), they reported a gradual increase in dose during the first 3–4 months in 6 patients, which extended up to 2 years in 2 patients. Ochs *et al*, on the other hand, reported that most of their patients reached a stable dose in 3 months except for a few patients who had experienced an increasing number of spasms even after one year, in their study with 28 patients, 10 of whom had SCI.[6] Lazorthes *et al* stated that they had not observed any case of pharmacological tolerance in their series of 18 patients, 7 of whom had SCI, with an average follow up of 18 months.[8] Sahuquillo *et al* suggested that tolerance was observed only in complete SCI patients, based on their series of 9 patients (5 complete, 4 incomplete) with an average follow up of 18 months.[10] They also reported that dosage increases were statistically significant in the first 12 months, but not between 12 and 24 months. Recently, Meythaler *et al* reported the occurrence of tolerance in their 12-month follow up study in their series, including 5 SCI patients.[11]

Our data with 18 SCI patients, 5 complete and 13 incomplete, clearly show that tolerance to baclofen administered intrathecally is observed within the first 12 months, but after the 12th month patients reach a stable dose and do not require further dosage increases. Further, there is no difference between completely and incompletely injured patients with regard to dosage over time. None of our patients discontinued treatment due to side effects or from complications with high doses, thus safety of this modality was not a problem in our series. We suggest that tolerance per se should not dissuade one from choosing intrathecal baclofen pump implantation in SCI patients with severe intractable spasticity refractory to traditional modalities.

Acknowledgement

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