SHORT REPORT

ABSTRACT: We observed a marked prolongation of the transcranially evoked silent period during continuous intrathecal administration of high doses of the gamma-aminobutyric acid $(GABA)_B$ receptor agonist baclofen in a patient with generalized dystonia. Size of motor evoked potentials and central conduction time remained unchanged during intrathecal baclofen administration. The selective prolongation of the silent period during high-dose continuous intrathecal baclofen therapy supports the notion that $GABA_B$-ergic intracortical interneurons play a part in the generation of the transcranially evoked silent period.

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CONTINUOUS INTRATHECAL BACLOFEN INFUSIONS INDUCED A MARKED INCREASE OF THE TRANSCRANIALLY EVOKED SILENT PERIOD IN A PATIENT WITH GENERALIZED DYSTONIA

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Transcranial magnetic stimulation (TMS) of the primary motor cortex evokes an electromyographic silent period (SP) immediately after the magnetically evoked motor potential (MEP).[4] It has been suggested that intracortical gamma-aminobutyric acid $(GABA)_B$-ergic intracortical circuits participate in the generation of the transcranially evoked SP.[10] However, the intravenous administration of the $GABA_B$ receptor agonist baclofen had no effect on the SP duration.[5] Since only a small portion of baclofen penetrates the blood–brain barrier after enteral or intravenous application, a negative effect of intravenously administered baclofen on SP duration does not exclude a participation of $GABA_B$-ergic cortical interneurons in the generation of the SP.[7]

CASE REPORT

A 19-year-old patient with a severe generalized dystonia unresponsive to oral medication was treated with continuous intrathecal infusions of the $GABA_B$ receptor agonist baclofen. At the age of 8 the patient developed writer's cramp. During the following years the disorder spread to other body parts, and the patient became completely bedridden at the age of 16. After a positive testing phase with a port-catheder system, the patient received a programmable infusion pump (Synchromed, Medtronic, Minneapolis, MN). The tip of the intrathecal catheter was placed at the level of the thoracic vertebra 4/5. Since daily doses up to 700 μg baclofen per day had only a moderate effect on dystonic movements, the daily dose was stepwise increased up to 1400 μg baclofen daily. High doses of continuous intrathecal baclofen therapy resulted in a marked lasting improvement of the generalized dystonia.

INVESTIGATIONS

Before and during continuous intrathecal baclofen therapy at doses of 500, 700, 1000, and 1400 μg/day, we applied TMS to the motor cortex using a Magstim 200 stimulator (Novametrix, Dyfed, U.K., 2-T version) and a round coil with an outside diameter of

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11.6 cm. For stimulation of the primary motor hand area, the magnetic coil was placed tangentially on the scalp and centered over the vertex. Clockwise and anticlockwise monophasic currents were used for the stimulation of the right and left motor cortex, respectively.[12] Motor threshold was determined according to published International Federation of Clinical Neurophysiology guidelines.[12] The stimulus intensity was set at 80% of the maximal output of the stimulator. Five consecutive MEPs were recorded with a pair of silver cup electrodes from both first dorsal interosseous muscles during slight tonic muscle contraction with the active electrode placed over the muscle belly. All examinations were performed by the same examiner.

The electromyographic (EMG) signals were amplified and band-pass filtered between 20 and 2000 Hz, and stored at 5000 Hz on a personal computer using a CED 1401 interface. We calculated the latency and amplitude of each MEP and the duration of the SP (Signal averager, Cambridge, U.K.). The F-wave method was applied for calculation of central and peripheral conduction times.[12] The duration of the SP was defined as the time between the onset of the MEP and the time when EMG background activity reached at leat 50% of the prestimulus level. We used the nonparametric Mann–Whitney *U* test for statistical analysis. Significance level was set at $P < 0.05$.

RESULTS

Motor threshold at rest, amplitude and latency of the MEPs, central conduction time as well as the duration of the transcranially evoked SP were within the normal range before intrathecal baclofen infusion was started.[6] Up to a daily intrathecal dose of 1400 µg baclofen, motor threshold, amplitude, and latency of MEPs showed no significant changes.

In contrast, intrathecal baclofen at doses of 1000 µg and more caused a marked prolongation of the TMS-induced SP of both first dorsal interosseous muscles (Mann–Whitney *U* test, $P < 0.01$, Figs. 1 and 2). No significant changes concerning the SP duration occurred at daily baclofen doses of 500 and 700 µg (Figs. 1 and 2).

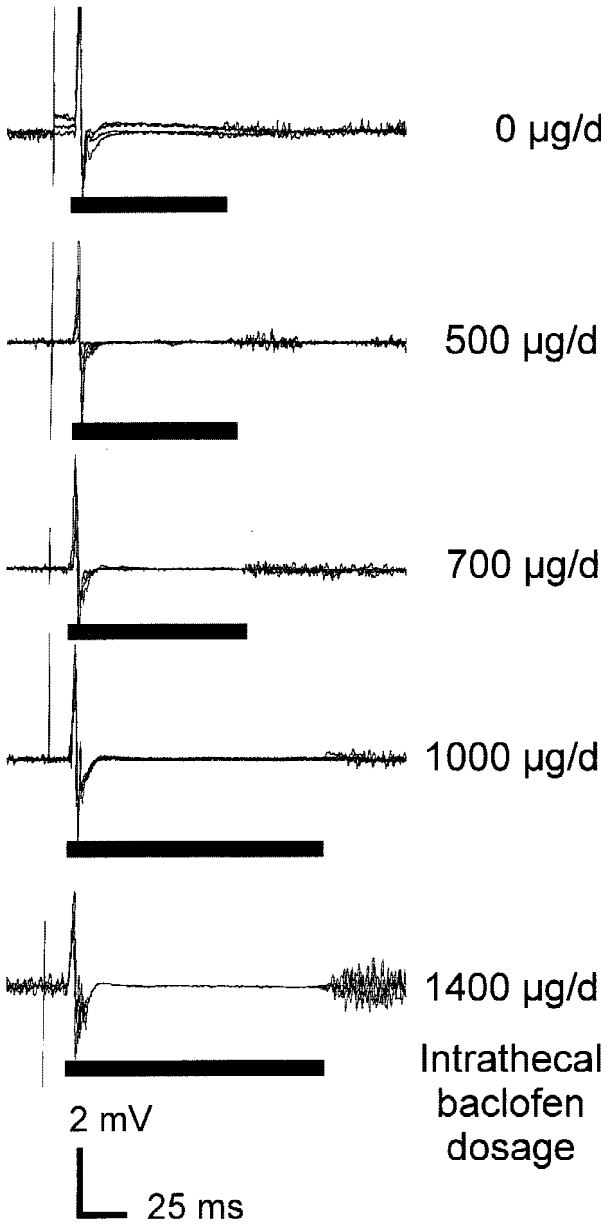

FIGURE 1. EMG responses of the right first dorsal interosseus muscle to transcranial magnetic stimulation of the left motor hand area during continuous intrathecal baclofen therapy. Note the marked prolongation of the transcranially evoked postexcitatory cortical silent period at a daily intrathecal baclofen dosage of 1000 µg or more.

DISCUSSION

Contrary to intravenous infusions, high doses of intrathecally administered baclofen caused a marked increase of the transcranially evoked SP in the patient under discussion. Motor threshold, MEP amplitude, and central motor conduction time remained unchanged, suggesting that the excitability and the conduction velocity of the monosynaptic fast-conducting corticospinal output neurons were not significantly affected by intrathecally administered baclofen.

Concerning serial SP measurements in a single subject, a recent study has shown a high degree of intraexaminer reliability over time.[3] Since magnetic stimulation was performed by the same examiner during the whole study, and the increase in SP duration was reproducible at two doses of intrathecal

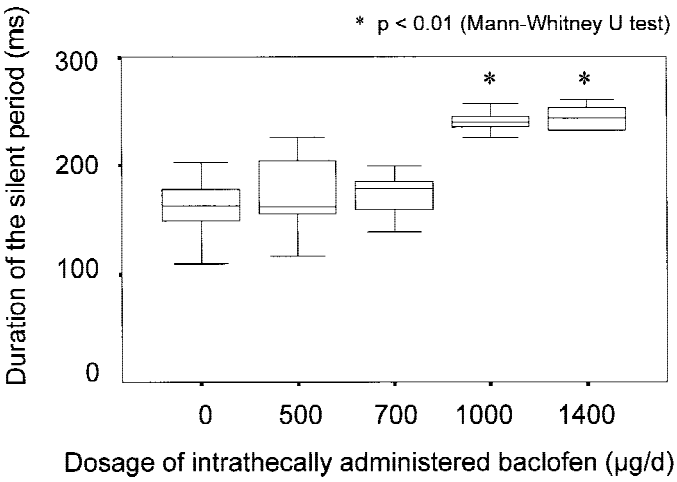

FIGURE 2. Duration of five consecutive silent periods of both first dorsal interosseous muscles after cortical stimulation during continuous intrathecal baclofen infusions. The box plot presentation shows a statistically significant increase of the postexcitatory silent periods only at high intrathecal baclofen doses of 1000 µg per day or more.

baclofen (1000 µg/day and 1200 µg/day), we suggest that the observed increase in the SP duration is a reliable finding.

Since the latter part of the SP is exclusively due to the activity of intracortical inhibitory circuits, the duration of the TMS-evoked silent period is determined by the amount of intracortical inhibition.[4,11,13] This suggests that an increase of $GABA_B$-mediated inhibition at the cortical level caused the prolongation of the postexcitatory silent period during continuous intrathecal baclofen therapy. Due to the progressive caudocranial dilution of baclofen within the cerebrospinal fluid,[8] only high doses of intrathecal baclofen administered at the midthoracal level may have reached a sufficient concentration at the convexity of the brain to induce a significant increase of intracortical GABA-mediated inhibition.

A baclofen-induced increase of spinal inhibition as the underlying mechanism seems to be less likely for the following reasons. A second period of muscle excitation terminates the transcranially evoked silent period.[9] This second increase in firing probability of the spinal motoneurons is referred to both peripheral and central sources.[9] Since baclofen reduces the excitatory peripheral afferent input to the spinal motoneuron, intrathecal baclofen may delay the onset of this second excitatory period, hereby resulting in a longer transcortically evoked silent period. However, this rebound electromyographic activity following the silent period was still well-defined at baclofen doses of 1400 µg per day (Fig. 1). In addition, maximum suppression of mono- and polysynaptic spinal reflexes like the H reflex and the flexor reflex occurs at doses well below 700 µg per day.[1,2] Hence, a prolongation of the SP visa a suppression of spinal reflexes should have already occurred at lower daily baclofen doses.

In conclusion, the prolongation of the transcranially evoked SP in a dystonic patient during high-dose continuous intrathecal baclofen therapy lends support to the notion that $GABA_B$-ergic intracortical interneurons are involved in the generation of the transcranially evoked SP.

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