Intrathecally Administered High-Dose Baclofen Does Not Induce Neurotoxic Changes in Rats

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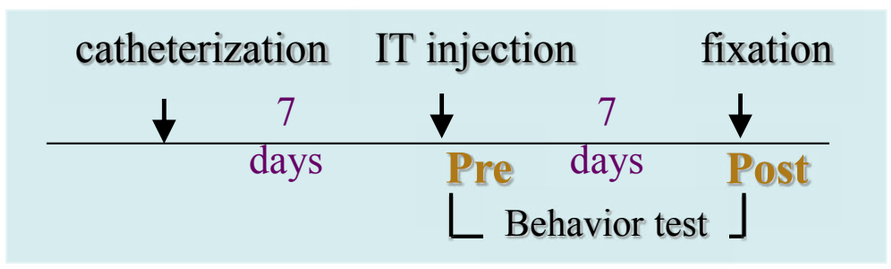
BACKGROUND and AIM

Intrathecal infusion of baclofen (ITB) is only approved for spasticity, but, it has excellent analgesic effects in neuropathic pain (e.g., central pain [1], and CRPS type 1[2,3]).

In Japan, ITB dose is allowed at less than 600 μg/day, but an increase the dose from 200 to 800μg/day was reported to improve pain, disability and quality-of-life [4]. However, the safety of high-dose ITB is unclear because histological examination is rarely to be reported.

Thus, we examined the histological and functional changes induced by high-dose ITB in rats.

MATERIAL and METHODS



Catheterization: rats were implanted an intrathecal catheter at L3 spinal cord.

IT injection: rats received one of following solutions at volume of 0.12μl/g

ITB (B) (μl/ml) :	**400B, 800B, 2000B, 3000B, 4000B, 8000B, 12000B**
Control	**: Saline**

■ Neurofunctional tests

Behavior test : we estimate at 15min, 30min, every 1hr for 4 hrs, and every 24 hrs for 7 days after the injection until rat walk normally.

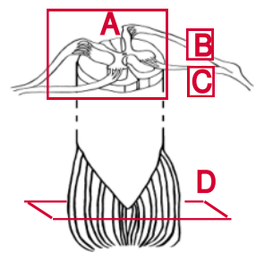
Paw stimulation test (PST) : The latency to the radiant heat stimulation was evaluated at both pre and post-injection 7 days after the injection. The data were converted to the %maximum possible effect (%MPE)

%MPE =[(post latency -pre latency) / (cut off - pre latency)]×100

■ Histological test

Spinal cord with roots were divided into 4 samples(A-D)

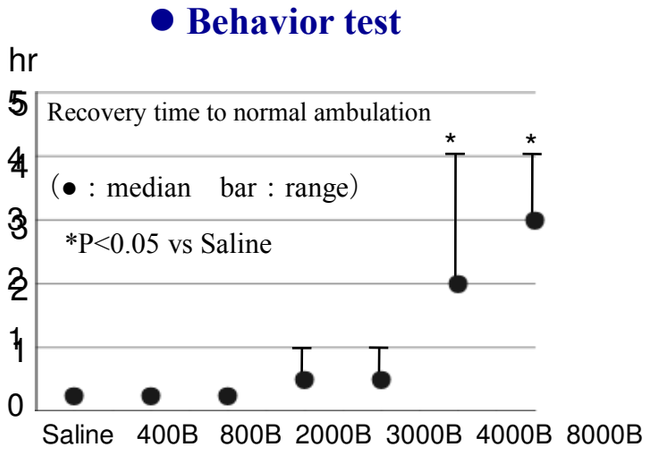
Sample A : spinal cord with both roots at L3
Sample B : posterior root just above dorsal ganglion
Sample C : anterior roots just above dorsal ganglion
Sample D : cauda equina



RESULTS

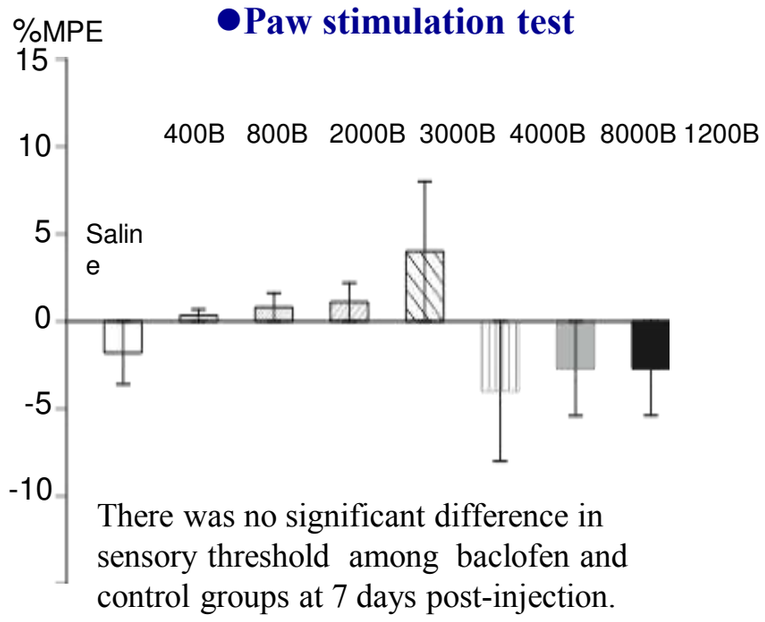
■ Neurofunctional tests

● Behavior test



Less than 800B, all rats showed normal walking behavior within 4 hrs,1200B also get normal walking at 4hrs in 3 rats, POD1 in 4 rats, respectively

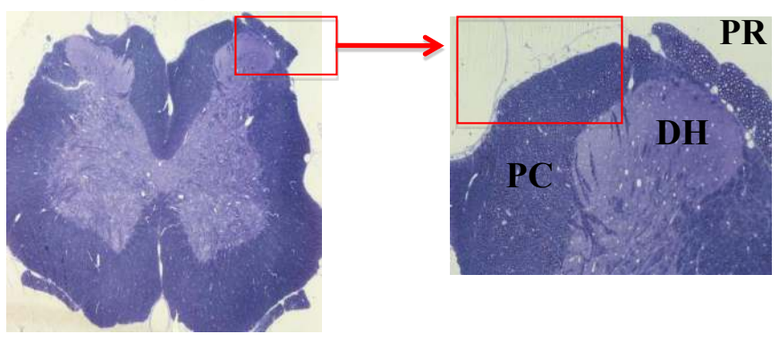
●Paw stimulation test



There was no significant difference in sensory threshold among baclofen and control groups at 7 days post-injection.

■ Histological test

12000μg B



PC: posterior column DH: dorsal horn PR: posterior root

Neurotoxic damage and inflammatory mass were not observed in all groups, even at 12000B

DISCUSSION and CONCLUSIONS

Using the same experimental protocol, we reported previously that intrathecal bupivacaine at more than 4% (i.e., 8 times higher than the clinical concentration) induced histological damage of the posterior root and posterior column in rats [5].
However, intrathecal 0.5% bupivacaine is clinically used in safety.
The present results showed that baclofen induced no histological and irreversible neurofunctional abnormality even at 12000 μg/ml (i.e., 20 times higher than the clinical concentration).

Thus, the clinical safety of ITB appears to be beyond 600 μg/ml. However, future investigation is need to confirm the effects of continuou long-term infusion of ITB.

1) Anesthesiology 2000;92:867. 2) RAPM 2002;27:90. 3) N Engl J Med 2000;343:625. 4) PAIN 2009;43:41. 5) RAPM 2005;30:464