# Intrathecal baclofen: pharmacological activities leading to innovative uses and unexpected adverse reactions

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Baclofen is a full agonist of $GABA_b$ receptors, leading to the opening of potassium channels and the inhibition of adenylyl cyclase. It hyperpolarizes neurons, suppressing monosynaptic and polysynaptic transmission through the spinal cord. This is clinically exploited to treat spastic movements and persistent hypertonicity. Baclofen administration is usually oral, but high doses are required to obtain significant concentrations in the cerebrospinal fluid (CSF). In addition, Baclofen may require up-titration to overcome tolerance. High-dose of oral Baclofen causes frequent liver toxicity, therefore intrathecal delivery (ITB) was developed to improve its safety. ITB allows higher CSF concentrations with hundred-fold lower doses, preventing toxicity and improving efficacy at the spinal level. ITB may also diffuse to the brain and cerebellum, yielding in man additional effects previously observed only in laboratory studies. We present two case reports on ITB, suggesting how high CSF concentrations may involve unusual drug targets that lead to innovative clinical uses and previously unknown safety issues.

1) Neuronal hyperpolarization due to Baclofen reduces the firing of nociceptive spinal neurons, being directly analgesic. This relatively weak effect was described in patients taking high-dose oral Baclofen. High Baclofen concentrations in the CSF may also inhibit the voltage-sensitive sodium channels of the N type (N-type VSSCs), that propagate central pain signals. This effect, not previously reported in man, may be responsible of what we observed in a patient who received a high-dose ITB for spasticity together with an extremely low dose of Ziconotide, a peptide antagonist of N-type VSSCs prescribed for pain therapy. The patient experienced good analgesic efficacy, together with an unknown ADR involving dyskinesia. Notably, N-type VSSC are found also in the cerebellum, where they control movement initiation: disrupting their signaling causes dyskinesia in mice. Therefore in our case, high-dose ITB may have significantly inhibited N-type VSSCs, facilitating both the therapeutical (in the brain) and adverse (in the cerebellum) activity of low-dose Ziconotide. This case of pharmacodynamic drug interaction suggests a novel combination therapy and warns against possible adverse effects.

2) High Baclofen CSF concentrations may also influence dopaminergic transmission in the mesolimbic and nigrostriatal circuits. Moreover, Baclofen functionally antagonizes dopamine, since $GABA_b$ receptors inhibit adenylyl cyclase activity, while D1 dopamine receptors activate it. This modulatory activity of Baclofen may be applied in psychiatry, as we observed in three patients with the Lesch-Nyhan syndrome (LN). LN is caused by a lack of dopamine that alters brain physiology since fetal development, leading to hypersensitivity of dopamine receptors. This causes movement disorders and behavioral disruption, with aggression and self-injury that are refractory to current therapies. Antipsychotics are inefficacious in patients with LN, because of dopamine oversensitivity. ITB instead showed promising clinical results in these LN patients, suppressing behavioral issues. This case series shows preliminary evidence of an innovative use of baclofen as a functional analog of antipsychotics.