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ORIGINAL ARTICLE

The use of opioids in children receiving intrathecal baclofen therapy

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Abstract

Purpose We hypothesized that children on chronic intrathecal baclofen therapy (ITB) may require less analgesics for postoperative pain control and are at higher risk of developing opioid-induced respiratory depression postoperatively. The aims of this study are to review children on chronic intrathecal baclofen therapy receiving opioids after major surgery and to determine the incidence complications in this population.

Method We conducted a retrospective cohort study comparing 13 children on ITB, who underwent posterior spinal fusion surgery, to 17 children with spina bifida that received the same surgery.

Results On postoperative day 0 (POD 0), four children (40%) had respiratory depression in the baclofen group compared to none in the control group. Desaturation was significantly more frequent in children in the ITB group compared to those of the control group on POD 0; oversedation was recorded in 8 (80%) children in the baclofen group vs. 3 (17.6%) in the control group. Desaturation, respiratory depression, and oversedation were significantly more frequent on POD 0 in children in the baclofen group compared with children in the control group.

Conclusions The findings of the current study suggest that children on chronic intrathecal baclofen therapy require lesser amounts of opioids for postoperative pain control and are at a greater risk of developing postoperative respiratory depression and excessive sedation compared to patients without baclofen therapy.

Baclofen · Oppioid · Children · Respiratory depression

Introduction

Intrathecal baclofen administration is considered an effective treatment for severe spasticity and dystonia due to many diseases that may affect motor function, such as infantile cerebral palsy (ICP) and traumatic brain injury [1–4]. In addition, baclofen is used to delay the development of contractures of the limbs in non-ambulatory patients [5].

In ICP, spasticity is secondary to the damage of the descending inhibitory corticospinal motor tracts, a condition characterized by an inadequate release of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) [6–8]; baclofen mimics the effects of GABA as a GABA-b receptor agonist [6–8]. The antispastic effects of baclofen seems to be related to the opening of potassium channels and to the decrease of calcium currents [8], resulting in a hyperpolarizing effect on the resting electrochemical transmembrane potential of the neuronal cell, thus decreasing the rate of neuronal discharges. Specifically, GABA-b presynaptical stimulation decreases the release of transmitters of primary afferent fibers in the spinal cord dorsal horn [8]. GABA-b receptors are widely distributed and are probably located on the spinal terminals of the primary afferent nociceptors. Opioid receptors have also been found on the same terminal spinal nociceptors [9]. Hence, the spinal cord has been suggested as a possible site for a baclofen-opioid interaction. Consequently, it is postulated that opioid-mediated analgesia may be enhanced by the co-activation of opioid receptors and GABA-b receptors at the level of the medullary dorsal horn [9, 10].

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We hypothesized that children on chronic intrathecal baclofen therapy may require less analgesics for postoperative pain control and are at higher risk of developing opioid-induced respiratory depression postoperatively. The aims of this study were to review our hospital's experience with children on chronic intrathecal baclofen therapy (ITB) receiving opioids after major surgery and to determine the incidence, if any, of the respiratory complications in this population.

Methods

Subjects

After obtaining Institutional Review Board approval, we performed a retrospective chart review of all children on ITB, who underwent surgery between April 2006 and May 2012 at the Meyer Children's Hospital. All the families provided an informed consent for surgery and management of their clinical data. Subsequently, we conducted a retrospective cohort study comparing 13 children on ITB, who underwent posterior spinal fusion for treatment of scoliosis, to 17 children with spina bifida without baclofen therapy that received the same surgery for progressive neuromuscular scoliosis. Surgery consisted in correction and fixation of thoracic and lumbar segments extended to the pelvis by means of pedicle screws and titanium rods.

The demographics data of both groups are summarized in Table 1. Data were obtained from the Hospital Acute Pain Service (APS) database and the medical charts. Only children who were receiving ITB for at least 6 months were included in the study. Children with underlying severe respiratory disease were excluded.

All patients in both group received intraoperative opioids analgesia. In our institution, we used intraoperative opioid analgesia for major surgery (intravenous, intrathecal, and/or epidural).

All patients were followed in the postoperative period by the APS. The APS collects the following data: demographics, postoperative pain and sedation scores, opioid consumption, episodes of respiratory depression, episodes of oxygen saturation less than 92% as measured by pulse oximetry, administration of supplemental oxygen for desaturation or naloxone for respiratory depression, and the presence of nausea, vomiting, and pruritus. Respiratory depression is defined as apnea and/or respiratory rate less than 12 breaths/min in patients over age 10 and less than 14 breaths/min for children aged 3–7 years.

Table 1 Case-control study demographic data

	Age (years)	Weight (kg)	Male/female
Control ($n = 17$)	11.1 ± 2.9	35.7 ± 11.6	6/11
Baclofen ($n = 13$)	12.8 ± 3.1	30.7 ± 9.6	7/6
p	0.15	0.259	0.453

Pain was ascertained at rest and during activities every 4 h (except while sleeping at night) with the visual analogue scale (VAS), or the FLACC scale (Face, Legs, Activity, Cry, Consolability) depending on child's ability to self-report pain and child's developmental status.

Sedation was assessed according to a score currently used by nurses in our institution: 0 = alert; 1 = occasionally drowsy, easy to arouse; 2 = frequently drowsy, easy to arouse; 3 = somnolent, difficult to arouse [11].

Results are reported as averages mean values ± standard deviations (SD) and frequencies and percentages when appropriate. In the second arm, the two groups were compared and categorical variables were analyzed by means of chi-square test or Fisher's exact test when the expected number of subjects in any cell was < 5. The Student t test was used to test continuous variables. SPSS statistical package, version 14, for windows (SPSS Inc., Chicago, IL) was used for analysis. p-values < 0.05 were considered statistically significant.

Results

Thirteen patients were on ITB, with a mean age of 12.8 ± 3.1 years and a mean weight of 30.7 ± 9.6 kg. The group was composed of 7 males and 6 females (Table 1). These patients did not receive analgesic therapy in a period of 2 weeks before surgery.

As indicated in Table 2, the most commonly used opioid intraoperatively was sufentanil (range 0.1–0.2 mcg/kg) in bolus and continuous infusion (0.2 mcg/kg/h) for 9 patients. Fentanyl (2 mcg/kg) was used in 2 patients and a continuous infusion of remifentanil (range 0.1–0.2 mcg/kg/min) was used in 2 patients. Four patients received low-dose intravenous ketamine (average dose 0.1 mg/kg), and 1 patient received a bolus dose of intravenous morphine (0.02 mg/kg) as a second intraoperative opioid. Six children were administered 20 mcg/kg morphine intrathecally. One child received 50 mcg/kg of epidural morphine followed by a continuous epidural infusion at 4 mcg/kg/h. The epidural infusion was continued in the postoperative period.

The control group was composed of 17 children with spina bifida, without baclofen therapy, undergoing the same surgery. Children with spina bifida received intraoperatively intravenous sufentanil and remifentanil opioid analgesia, in 6 and 11 patients, respectively.

There were no hemodynamic or respiratory complications intraoperatively in both groups.

The most commonly used analgesic regimen for postoperative pain management was nurse-controlled analgesia (NCA), which was used in 8 patients (61.5%). Four patients were on patient-controlled analgesia (PCA) (30.7%), and one

Table 2 Summary descriptive study. Sex: *M*, male; *F*, female. Surgery: *PSF*, posterior spinal fusion; *PF*, analgesia modality: *NCA*, nurse-controlled analgesia; *PCA*, patient-controlled analgesia; *EPID*, epidural. PCA/NCA solution: *M*, morphine; *K*, ketamine; *B*, bupivacaine. *POD*, postoperative day. Respiratory Complications on POD 0, 1, 2: SpO_2, oxygen saturation; *RD*, respiratory depression; *Suppl* O_2, supplemental oxygen; 0 = no, 1 = yes

No.	Age (years old)	Sex	Surgery	Intraoperative opioid	Intrathecal morphine	Analgesia modality	PCA/NCA solution	Max Sedation Score			Respiratory depression			$SpO_2 < 92$			Number desaturation			Naloxone for RD (yes/no)	Suppl O_2 (yes/no)
								POD 0	POD 1	POD 2	POD 0	POD 1	POD 2	POD 0	POD 1	POD 2	POD 0	POD 1	POD 2		
1	13	F	PSF	Sufentanil	1	NCA	M + K	3	2	1	0	0	0	1	0	0	1	0	0	0	1
2	13	M	PSF	Fentanyl + ketamine	1	NCA	M + K	3	3	0	1	1	0	1	1	0	1	1	0	0	1
3	17	F	PSF	Sufentanil + ketamine	0	NCA	M + K	1	2	0	1	1	0	1	1	0	2	1	0	1	1
4	17	F	PSF	Sufentanil	0	NCA	M	0	0	0	0	0	0	0	0	1	0	0	0	0	0
5	13	F	PSF	Sufentanil + ketamine	0	PCA	M + K	3	3	2	1	1	1	1	0	1	1	1	1	1	1
6	12	M	PSF	Remifentanil	1	PCA	M + K	0	1	0	0	0	0	0	0	0	0	0	0	0	0
7	7	M	PSF	Remifentanil	0	NCA	M + K	3	3	1	0	0	0	0	0	0	0	0	0	0	0
8	11	M	PSF	Sufentanil	1	PCA	M	2	0	0	0	0	0	0	0	0	0	0	0	0	0
9	15	M	PSF	Sufentanil + ketamine	1	NCA	M + K	3	2	1	1	0	0	1	0	0	1	0	0	1	1
10	10	M	PSF	Sufentanil	0	NCA	M + K	0	0	0	0	0	0	0	0	0	0	0	0	0	0
11	6	F	PSF	Sufentanil	0	NCA	M	2	2	2	0	0	0	0	0	0	0	0	0	0	0
12	17	F	PSF	Sufentanil	0	PCA	M	1	0	0	0	0	0	0	0	0	0	0	0	0	0
13	17	M	PSF	Bupivacaine + morphine	0	EPID	M + B	2	2	2	0	0	0	0	0	0	0	0	0	0	0

patient (7.6%) was on a continuous infusion of epidural bupivacaine 0.01% with morphine 10 mcg/mL at 0.2 mg/kg/h (Table 2).

The PCA/NCA solution consisted of either a mixture of morphine (2 mg/mL) or morphine and ketamine (MK) (both 2 mg/mL). The NCA was programmed as follows: bolus of 0.02–0.04 mg/kg of MK or M with a lockout time of 20 min. The PCA was programmed as follows: bolus of 0.02 mg/kg of MK or M with a lockout time of 8 min. As summarized in Table 3, the opioid consumption was the lowest on postoperative day 0 (10.6 ± 17.5 mcg/kg/h) compared to postoperative days 1, 2, and 3. Oversedation (sedation score of 3) was present on POD 0 and 1 in (38.4%) and (23%) of patients, respectively. The incidence of respiratory complications was higher on POD 0 and 1 (30.7%, 23%). Two of the 4 children who received intraoperative IT morphine had respiratory depression. Episodes of desaturation (< 92%) occurred in (38.4%) and (23%) on POD 0 and 1, respectively. Naloxone was used to treat respiratory depression in (23%) children on postoperative day 0, as well as the incidence of postoperative nausea and vomiting (46.1%) (on postoperative day 0). The baclofen group consisted of 13 children on stable doses of intrathecal baclofen for at least 6 months and all of them underwent posterior spinal fusion.

Five children in the ITB group received intraoperative intrathecal morphine compared to only 1 (5.9%) in the control group.

NCA was used more frequently for postoperative analgesia in the baclofen group compared to the control group (70% vs. 41%). PCA was used more frequently in the control group compared to the baclofen group (30% vs. 58.8%). Addition of ketamine to the morphine PCA/NCA was common in both groups (80% in the baclofen group vs. 76.5% in the control group).

On postoperative day 0, four children (40%) had respiratory depression in the baclofen group compared to none in the control group. Desaturation was significantly more frequent in children in the ITB group compared to those of the control group on POD 0 (50% vs. 5.9%, p value 0.02); over-sedation was recorded in 8 (80%) children in the baclofen group vs. 3 (17.6%) in the control group. Finally, naloxone was only used to treat respiratory depression in children in the ITB group (3 vs. 0, p value 0.04) on POD 0. Desaturation, respiratory depression, and oversedation were significantly more frequent on POD 0 in children in the baclofen group compared to children in the control group. The incidence of postoperative nausea and vomiting was also higher in the baclofen group (5) (50%) on POD 1 ($p < 0.01$) compared to the control group (1) (5.9%).

Opioid consumption in the ITB group was lower on POD 0 (10.60 ± 17.55 mcg/kg/h) than on POD 1, 2, and 3 compared with the control group ($p < 0.01$). Pain scores were not statistically different between the two groups.

Discussion

In our institution, we used intraoperative opioids analgesia for major surgery (sufentanil, fentanyl, remifentanil, or ketamine, intravenously). In our experience, that variety has not affected the postoperative period of our group, neither the intraoperative period nor the postoperative one. Otherwise, intrathecal and epidural administrations of opioids were related to respiratory complications only in patients undergoing baclofen pump. PCA or NCA are provided depending on the mental status and age of patients during the postoperative period. However, the mixture of morphine and morphine plus ketamine is the same in terms of dosage and total quantity that patients receive in 24 h, independently from the pump PCA or NCA. Both are just "indicative" of needs of analgesia in the postoperative period. The findings of the current study suggest that children on chronic intrathecal baclofen therapy have required lesser amounts of opioids for postoperative pain control and are at a greater risk of developing postoperative RD and excessive sedation compared to patients without baclofen therapy, especially if the opioids are administrated by intrathecal way. This may be due to interaction of GABA-b receptor agonists with opioids. The intraoperative use of intrathecal morphine, which was greater in the ITB group, also can be an additional risk factor. Our impressions are that these patients should receive a lower dose of opioids and they should be monitored closely for respiratory depression in the postoperative period.

Table 3 Baclofen-control group summary of adverse events on postoperative day (POD) 0. *RD*, respiratory depression; *SpO_2*, oxygen saturation

	RD POD 0	Max sedation score POD 0	Naloxone for RD	$SpO_2 < 92\%$	Opioid consumption POD 0 (μcg/kg/h)	Postoperative nausea and vomiting	
						POD 0	POD 1
Control ($n = 17$)	0	3 (17.6%)	0	1 (5.9%)	37.08 ± 31.42	4 (23.5%)	1 (5.9%)
Baclofen ($n = 10$)	4 (40%)	8 (80%)	3 (30%)	5 (50%)	10.60 ± 17.55	5 (50%)	5 (50%)
p	0.012	0.014	0.041	0.008	0.01	0.21	− 0.01

The findings of the current study suggest that children on chronic intrathecal baclofen therapy require less amounts of opioids for postoperative pain control and are at a greater risk of developing postoperative RD and excessive sedation compared with patients without baclofen therapy. This may be due to the interaction of GABA-b receptor agonists with opioids. The intraoperative use of intrathecal morphine, which was greater in the ITB group, can be an additional risk factor. Our impressions are that these patients should receive a lower dose of opioids and they should be monitored closely for respiratory depression in the postoperative period.

When administered orally, baclofen crosses the blood-brain barrier poorly because of its low liposolubility [12]. However, when administered intrathecally, the baclofen dose is generally 1000 times smaller than the oral dose [12]. It is administered as bolus injections or continuously, via an external pump or a surgically implanted pump [5]. This route of administration is preferred in severe spasticity, because a small intrathecal dose produces a high concentration of the drug in the cerebrospinal fluid without the significant central side effects frequently observed when high doses of baclofen are administered orally [11].

Complications associated with ITB therapy in children may occur immediately after pump insertion or after abrupt cessation of use. These may be catheter-related (infections, kinking, occlusion, break) or pump-related (infections). Patients may present central side effects (sedation, lethargy, disorientation, seizures, respiratory depression, apnea, headache), cardiovascular depression (bradycardia, hypotension), nausea and vomiting, dizziness, increased salivation, urinary hesitancy, or cerebrospinal fluid-leak [1, 3, 13]. Pump programming errors are the commonest cause of overdose [14]. It may present early or be delayed and may manifest as drowsiness, respiratory depression, rostral progression of hypotonia, or loss of consciousness [14–16].

The introduction of ITB therapy in the last decade has reduced the number of children requiring orthopedic surgery [17]. Because of their progressive orthopedic deformities, ICP patients may require multiple surgeries. Orthopedic surgical interventions such us tendon releases, lengthenings, and osteotomy are the most common spasticity-reducing procedures performed in these children.

Perioperative management of these children can present specific problems related to conceptualization issues associated with intellectual disability or poor verbal communication skills and comorbidities.

It is recommended, in patients with ICP, who receive extensive surgery, to use cardiorespiratory monitoring during the postoperative period [15].

While the role of baclofen in the treatment of spasticity is better understood, the interaction of GABA-b agonist with opioids for the treatment of pain has not been extensively studied. Results of animal and human studies are conflicting, showing that baclofen administered intrathecally or supraspinally produces antinociception [10], but currently baclofen is not specifically recommended for use as an analgesic [18–20].

A randomized double-blind placebo-controlled study, performed in adults undergoing oral surgery concluded that the administration of baclofen alone did not affect the level of postoperative pain. However, the analgesic efficacy of morphine was significantly enhanced by preoperative oral baclofen administration compared to placebo [9]. These results suggest that agonist drugs targeted at GABA-b receptors may be useful in reducing the level and frequency of dosing for μ-opioid analgesics needed in the treatment of postoperative pain. The authors of this study concluded that ITB did not add any benefit when used in combination with IT opioids for pain and muscle spasm and may interfere with the immediate postoperative assessment of motor function.

A baclofen-opioid interaction may be possible at a supraspinal site; in fact, microinjection of baclofen into the brain stem site produces antinociception [21]. Furthermore, GABA-b receptor activation may reduce the propensity to resume drug-induced heroin-seeking behavior, thus offering a possible approach in maintaining opiate abstinence [22].

Characterization of the γ-aminobutyric acid-b (GABA-b) receptor (GBR) has provided new insights into the structural composition and assembly of G protein-coupled receptors. Because GBRs are one of the many coupled to G_i and G_o, which regulate K^+ and Ca^{2+} entry into neurons and inhibit transmitter release, information on its structure, function, and pharmacology are of fundamental neurobiological and clinical importance.

From a therapeutic standpoint, the next advances in GABA-b pharmacology will be the delineation of the clinical potential of GABA-b antagonists, the identification of GBR subtypes that can be selectively manipulated for therapeutic gain, and the effect induced by μ-opioid receptor modulation on GABA-b receptor [23]. I would include here that the use of intrathecal morphine is a limitation of the study as well as the small number of patients and the issue of surgeries which are somewhat different.

In conclusion, whereas the underlying mechanism of respiratory complications in our study is as yet unknown, it seems reasonable to speculate that some of those were related to the postoperative opioid regimen.

The intraoperative use of intrathecal morphine, which was greater in the ITB group, also can be an additional risk factor. In our impression, we should treat carefully these patients under baclofen with severe regimen of opioid especially if intrathecally administered.

The findings of the current study suggest that children on chronic intrathecal baclofen therapy require lesser amounts of opioids for postoperative pain control and are at a greater risk of developing postoperative RD and excessive sedation

compared to patients without baclofen therapy. This may be due to interaction of GABA-b receptor agonists with opioids. Therefore, these patients should receive a lower dose of opioids, and they should be monitored closely for respiratory depression in the postoperative period.

In this retrospective study, we did not report the preoperative pain of patients because there were no notes in the medical chart of assumptions of analgesic opioids other than analgesic in the last 3 months before surgery. The control group was undergoing baclofen because of spasticity only. Prospective studies are needed to further evaluate the incidence of side effects related to the use of opioids in combination with intrathecal baclofen therapy in children.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Gilmartin R, Bruce D, Storrs BB, Abbott R, Krach L, Ward J, Bloom K, Brooks WH, Johnson DL, Madsen JR, McLaughlin JF, Nadell J (2000) Intrathecal baclofen for management of spastic cerebral palsy: multicenter trial. J Child Neurol 15:71–77. https://doi.org/10.1177/088307380001500201
2. Albright AL, Barry MJ, Painter MJ, Shultz B (1998) Infusion of intrathecal baclofen for generalized dystonia in cerebral palsy. J Neurosurg 88:73–76. https://doi.org/10.3171/jns.1998.88.1.0073
3. Armstrong RW, Steinbok P, Cochrane DD, Kube SD, Fife SE, Farrell K (1997) Intrathecally administered baclofen for treatment of children with spasticity of cerebral origin. J Neurosurg 87:409–414. https://doi.org/10.3171/jns.1997.87.3.0409
4. Buonaguro V, Scelsa B, Curci D, Monforte S, Iuorno T, Motta F (2005) Epilepsy and intrathecal baclofen therapy in children with cerebral palsy. Pediatr Neurol 33:110–113
5. Butler C, Campbell S, Adams R, Abel M, Chambers H, Goldstein M, Leach J, Darrah J, Msall M, Edgar T, McLaughlin J, Damiano D, Stott NS, Samson-Fang L, Logan L, Albright L, Armstrong R, O'Donnell M (2007) Evidence of the effects of intrathecal baclofen for spastic and dystonic cerebral palsy. Dev Med Child Neurol 42:634–645. https://doi.org/10.1111/j.1469-8749.2000.tb00371.x
6. Bucholz R (1994) Management of intractable spasticity with intrathecal baclofen. Phys Med Rehabil 8:565–577
7. Albright AL (1996) Intrathecal baclofen in cerebral palsy movement disorders. J Child Neurol 11(Suppl 1):S29–S35. https://doi.org/10.1177/0883073896011001S05
8. Belelli D, Pistis M, Peters JA, Lambert JJ (1999) General anaesthetic action at transmitter-gated inhibitory amino acid receptors. Trends Pharmacol Sci 20:496–502
9. Gordon NC, Gear RW, Heller PH, Paul S, Miaskowski C, Levine JD (1995) Enhancement of morphine analgesia by the GABAB agonist baclofen. Neuroscience 69:345–349
10. Dickenson AH, Brewer CM, Hayes NA (1985) Effects of topical baclofen on C fibre-evoked neuronal activity in the rat dorsal horn. Neuroscience 14:557–562. https://doi.org/10.1016/0306-4522(85)90310-0
11. Merkel SI, Voepel-Lewis T, Shayevitz JR, Malviya S (1997) The FLACC: a behavioral scale for scoring postoperative pain in young children. Pediatr Nurs 23:293–297
12. Bowery NG, Enna SJ (2000) γ-Aminobutyric acid (B) receptors: first of the functional metabotropic heterodimers. J Pharmacol Exp Ther 292:2–7
13. Gooch JL, Oberg WA, Grams B, Ward LA, Walker ML (2003) Complications of intrathecal baclofen pumps in children. Pediatr Neurosurg 39:1–6. https://doi.org/10.1159/000070870
14. Anderson KJ, Farmer JP, Brown K (2002) Reversible coma in children after improper baclofen pump insertion. Paediatr Anaesth 12:454–460. https://doi.org/10.1046/j.1460-9592.2002.00844.x
15. Dressnandt J, Weinzierl FX, Tolle TR et al (1996) Acute overdose of intrathecal baclofen. J Neurol 243:482–483
16. Nolan J, Chalkiadis GA, Low J et al (2000) Anaesthesia and pain management in cerebral palsy. Anaesthesia 55:32–41. https://doi.org/10.1046/j.1365-2044.2000.01065.x
17. Perry HE, Wright RO, Shannon MW, Woolf AD (1998) Baclofen overdose: drug experimentation in a group of adolescents. Pediatrics 101:1045–1048
18. Gerszten PC, Albright a L, Johnstone GF (1998) Intrathecal baclofen infusion and subsequent orthopedic surgery in patients with spastic cerebral palsy. J Neurosurg 88:1009–1013. https://doi.org/10.3171/jns.1998.88.6.1009
19. Dapas F, Hartman SF, Martinez L et al (1985) Baclofen for the treatment of acute low-back syndrome: a double-blind comparison with placebo. Spine (Phila Pa 1976) 10:345–349. https://doi.org/10.1097/00007632-198505000-00010
20. (1994) Geigy Pharmaceutical Lioresal. In: Physicians' Desk reference. pp 1063–4
21. Franek M, Vaculín S, Rokyta R (2004) GABA(B) receptor agonist baclofen has non-specific antinociceptive effect in the model of peripheral neuropathy in the rat. Physiol Res 53:351–355
22. Levy RA, Proudfit HK (1979) Analgesia produced by microinjection of baclofen and morphine at brain stem sites. Eur J Pharmacol 57:43–55. https://doi.org/10.1016/0014-2999(79)90102-X
23. Spano MS, Fattore L, Fratta W, Fadda P (2007) The GABAB receptor agonist baclofen prevents heroin-induced reinstatement of heroin-seeking behavior in rats. Neuropharmacology 52:1555–1562. https://doi.org/10.1016/j.neuropharm.2007.02.012