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BRIEF REPORT

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Intrathecal baclofen in tetanus: four cases and a review of reported cases

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Abstract *Objective*: Spasms in patients with generalized tetanus can be suppressed by a spinal intrathecal infusion of baclofen. We report on four patients and review reported cases treated by this method elsewhere.
Design: Intrathecal baclofen infusion was started with a bolus dose (300–500 μg) and continued at a steady rate of 500–1000 μg/day. The dose was increased in daily steps as needed.
Results: Doses of baclofen of 500, 1000, or 2000 μg/day were effective in three patients, while 1500 μg/day was insufficient in the fourth. Bradycardia and hypotonia occurred in one patient at a dose of 2000 μg/day but resolved after the dose was reduced to 1500 μg/day. Another patient developed hypotonia when a bolus of 500 μg was given after a steady infusion of 1500 μg/day. Voluntary movements were preserved in one and returned in two patients when sedation, induced by initial diazepam infusions, receded. The fourth patient needed diazepam during most of the treatment with intrathecal baclofen and required mechanical ventilation while being treated with baclofen.
Conclusions: A catheter position higher than T11 would possibly have yielded better results. It may be necessary to adapt the dose during the course of the illness. The preservation of respiratory drive and voluntary movements is the main advantage of treating tetanus with intrathecal baclofen. Additionally it helps to reduce sympathetic hyperactivity. Mortality may thereby be reduced.

Key words Tetanus · Intrathecal · Baclofen · Benzodiazepine · GABA · Human

Introduction

Tetanus is still associated with a high mortality, despite treatment in intensive care units [1]. The reasons are sympathetic overactivity [2] and secondary complications due to intensive care therapy, especially pulmonary infections [3]. Different methods have been tried to improve the outcome of tetanus patients during the last decade. Immunoglobulins have been instilled intrathecally to reduce the spread of tetanus toxin in the spinal cord [4, 5], but recent reports are contradictory [6]. Suppression of the disinhibited excitatory neural mechanisms in the spinal cord and the brainstem is usually achieved with benzodiazepines, which act at the gamma-aminobutyric acid (GABA)-A/benzodiazepine receptor [7]. Peripheral muscle relaxation is achieved with pancuronium. Mechanical ventilation is mandatory in most cases. Tests with intrathecally administered benzodiazepines have shown strong sedation [8] and toxic side effects [9]. A substance that is not toxic and causes less sedation is the GABA-B agonist baclofen. GABA-B receptors are located pre- and postsynaptically. Activation of presynaptic GABA-B receptors upon sensory neurons [10] causes a reduction in transmitter release

Table 1 Data for the four patients

Patient	Age (years)	Sex	Location of injury	Incubation latency (weeks)	Period of onset (days)	Spasms and trismus	Tetanus severity score [35]	Duration of i.v. benzodiazepines (days)	Duration of artificial ventilation (days)	Start of i.th. baclofen (days after admission)	Duration of i.th. baclofen (days)	Effective dose of i.th. baclofen (μg/day)	Side effects of i.th. baclofen
1	52	F	Foot	4	4	+	2–3	12	16	12	10	500	
2	41	F	Toe	2	3	+	3	7	11	7	9	2000	
3	71	M	Finger	$1\,^1/_2$	< 2	+	3	8	9	2	17	2000	Bradycardia
4	66	F	Finger	1	1	+	3	45	54	2	52	> 1500	Bradycardia, hypotonia

[11]; activation of postsynaptic GABA-B receptors upon alpha motoneurons leads to hyperpolarization [12]. Unfortunately, baclofen does not cross the blood-brain barrier easily [13, 14]. To reach a high concentration in the spinal cord, and thus achieve a maximal therapeutic effect on muscle relaxation, the drug must be injected intrathecally, so that the blood-brain barrier can be circumvented [15]. Local subarachnoid infusions of baclofen have been used for the treatment of spinal spasticity since 1984 [16] and were introduced for treating tetanus in 1986 by Müller et al. [17]. The concentration of baclofen infused at the lumbar or lower thoracic level decreases in the cranial direction [18–20]. Therefore, relaxation is most pronounced in the lower extremities and abdominal muscles and less pronounced in the muscles of the upper extremities and the cervical muscles. The respiratory drive at the brainstem level is least depressed. The half-life of baclofen in the cerebrospinal fluid is 1–5 h after an intrathecal (i.th.) bolus injection [19]. Further, the drug is metabolized only to a small degree (less than 10 %) into a metabolite which is not active [14]. The relatively short half-life is helpful in managing i.th. baclofen therapy. The dose can be chosen so that no spasms occur while the rest of the voluntary movements are preserved. Thus, fewer secondary complications due to mechanical ventilation and immobilization should occur.

The purpose of this article is to describe our experiences with four patients, giving an overview of reported cases, and to try to deduce which dose of baclofen is useful in treating tetanus.

Case reports

Each of the four patients had generalized tetanus and was admitted to our hospital during the last 3 years (Table 1). Each patient received 10 000 or more units tetanus immunoglobulin. Intrathecal baclofen was administered to all patients through an implanted spinal catheter that was connected to a subcutaneous port. The tip of the catheter was placed at the level of thoracic vertebra (T) 9–10. We describe the four cases with an emphasis upon muscle relaxation in the treatment of tetanus.

Case 1

A 52-year-old female farmer first developed back pain, then trismus, and finally opisthotonus 4 weeks after an open foot injury. Treatment began with diazepam. Increasing daily doses up to 1440 mg diazepam and 96 mg pancuronium were necessary for relaxation. On day 12 after admission, diazepam and pancuronium infusions were discontinued and i.th. baclofen therapy begun. A bolus infusion of 300 μg was given and then a continuous infusion of 500 μg/day. Relaxation of the neck and the extremities was good, but trismus was still observable. The patient remained somnolent and mechanical ventilation was necessary. After 3 days, 2 mg flumazenil was injected intravenously (i.v.) and immediately thereafter the patient awakened, was breathing spontaneously, and was able to move the extremities. However, she also showed increased trismus, as well as an increase in blood pressure from 110/60 to 170/80 mmHg and heart rate from 70 to 100 beats/min for 1 h. Recurrence of somnolence and decreasing respiratory drive made mechanical ventilation necessary for 1 more day. Then the effects of sedation disappeared and her respiration was sufficient. Baclofen infusion was continued for 10 days. The dose was reduced to 150 μg/day 1 day before the infusion was stopped. Spasms did not recur. Blood pressure increased 12 h after lowering the baclofen dose, from 105/60 to 140/80 mmHg. The patient was discharged from hospital after 43 days. A thrombosis of the subclavian vein, possibly caused by a local venous catheter, was observed as a complication during therapy.

Case 2

A 41-year-old female farmer developed trismus and opisthotonus 14 days after injuring her toe. Increasing doses of diazepam up to 1800 mg and pancuronium to 36 mg per day were necessary for relaxation. Therapy with i.th. baclofen was started and diazepam infusion was stopped 7 days after admission. Baclofen therapy was started with a 300 μg bolus and continued with a continuous infusion of 500 μg/day. The patient awakened the next day after being given 2.5 mg flumazenil and was able to move the extremities but still had neck stiffness and trismus. Neck stiffness disappeared after the dose of baclofen was increased to 1000 μg/day. The next day the dose was increased to 2000 μg/day in an unsuccessful attempt to reduce the trismus. The patient was mechanically ventilated for the first 4 days of i.th. baclofen therapy until the effects of sedation disappeared. Baclofen was administered at a dose of 2000 μg/day for 9 days. After stopping the infusion of baclofen, generalized tetanus spasms did not recur, though the trismus remained. The patient could swallow fluids but needed to be fed by a gastric tube for several more days. The blood pressure increased from 110/55 to 120/75 mmHg 12 h after the i.th. baclofen infusion was stopped. The

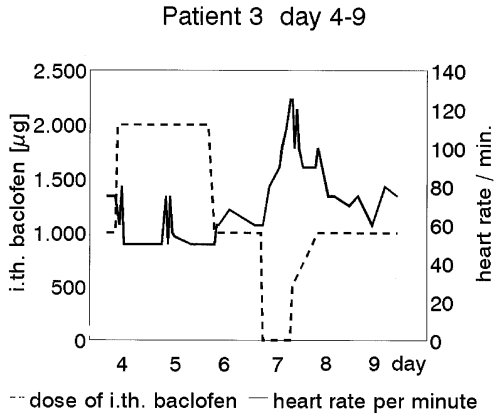

Fig. 1 Patient 3 had a slight bradycardia of 50 beats/min at a dose of 2000 µg intrathecal *i.th.* baclofen which resolved as the baclofen dose was reduced. When i.th. baclofen infusion was temporarily stopped on day 7, a gradual increase in spasms and heart rate was observed

heart rate remained at 100 beats/min during and after stopping baclofen. The patient was discharged from hospital after 31 days.

Case 3

A 71-year-old patient noticed a locked jaw 10 days after injuring his finger. He had meningism and spasms and became somnolent upon admission, developing opisthotonus the next day. Midazolam and diazepam were given for relaxation. On day 2, i.th. baclofen was continuously infused – after a bolus of 500 µg – at a rate of 1000 µg/day. The next day the dose was increased to 2000 µg/day, because relaxation was insufficient. Bradyarrhythmia and a third-degree atrioventricular block was observed after the initial 500 µg baclofen bolus and during the continuous infusion of 2000 µg/day. The heart rate and blood pressure was increased again with atropine and dopamine. The coadministration of atropine was no longer necessary after the dose of baclofen was reduced from 2000 to 1000 µg/day and the dose of dopamine could be reduced. During the first 7 days of therapy with i.th. baclofen infusion, additional spasmolytic substances were given, such as midazolam (30 mg reduced stepwise to 5 mg on day 7) together with fentanyl. Pancuronium was given until day 4. On day 7, baclofen infusion was stopped temporarily. An increase in spasms made it necessary to resume spasmolytic therapy. A bolus of 20 mg midazolam was administered and thereafter baclofen was the sole muscle relaxant suppressing spasms sufficiently at an infusion rate of 1000 µg/day. The heart rate increased when the baclofen infusion was interrupted (Fig. 1). The patient was awake from day 7 (the day after fentanyl and midazolam therapy was stopped). On day 7, mechanical ventilation was switched to self-triggered assisted support breathing, which was finally stopped on day 9. Thereafter the patient was breathing without support. The patient, who began moving his extremities on day 8, was mobilized to a sitting position and started drinking fluids on day 9. On day 14, the i.th. baclofen infusion was reduced to 700 µg/day and was terminated on day 19. Vegetative symptoms such as hyper- and hypotonia, which were treated with dopamine and urapidil, were observed primarily on day 4 and continued to a lesser degree until day 8. The patient had a transient organic brain syndrome due to tetanus for the first 3 weeks. As secondary complications pneumonia, temporary renal decompensation on the basis of pre-existing renal insufficiency without the need for dialysis, and temporary pancreatitis were observed during the first 2 weeks. The patient went home on day 36.

Case 4

A 66-year-old female developed trismus, opisthotonus, and breathing disturbances 7 days after a finger injury. She had to be intubated, and muscle relaxation was begun with midazolam, pancuronium, and fentanyl. On day 2, i.th. baclofen infusion was started with a bolus of 300 µg and was continued at a constant rate of 500 µg/day. The heart rate fell from 90 to below 50 beats/min, but increased after atropine was administered. The blood pressure dropped from 160/70 to 110/50 mmHg for 8 h after the bolus infusion. Spasms were still observable. The baclofen dose was increased to 700 µg/day without effect on the frequency of spasms on day 4. The spasms disappeared after an additional baclofen bolus of 400 µg and the increase in blood pressure, which had occurred during therapeutic maneuvers, did not recur for 7 h. The heart rate, around 70–80 beats/min, remained stable for 14 h after the bolus infusion; 0.5 mg atropine had been given before the baclofen bolus. The baclofen dose was increased to 1200 µg/day because of recurring spasms that disappeared again only after an additional 400 µg bolus was given. The dose was increased stepwise to 1500 µg/day to reduce continuing spasms in the neck and arms. Relaxation in the legs was good, but in the arms, neck, and upper trunk spasms occurred whenever nursing procedures were done. An additional 500-µg bolus led to severe hypotonia (70/40 mmHg), which was treated with dopamine. The baclofen dose was maintained at 1500 µg/day. Additional administration of midazolam 130 mg/day, pancuronium 32 mg/day, and diazepam 120 mg/day was necessary to suppress spasms in the upper extremities. When the benzodiazepine was antagonized with flumazenil, the patient immediately showed extreme opisthotonus in the neck and trunk muscles, flexion of the arms, and breathing difficulties while the leg muscles remained flaccid. Administration of midazolam was stopped on day 32 and pancuronium and diazepam on day 45. Baclofen was given in a stable dose of 1500 µg/day from day 13. On day 47, the patient became more awake but required further mechanical ventilation. Baclofen infusion was reduced to 1000 µg/day on day 48, to 500 µg/day on day 51, and was stopped on day 54. Though the patient was awake, mechanical ventilation was terminated only after stopping the baclofen infusion. The patient could eat by herself but was immobilized for 3 more days because of further increase in muscle tone and spasms in the legs. Ambulation was possible again on day 60. No complications of intensive care occurred. The patient went home on day 66.

Discussion

The i.th. infusion of the GABA-B agonist baclofen resulted in sufficient muscle relaxation in three of the four patients. Voluntary movements were preserved (patient 3) or reappeared after 2–4 days (patients 1 and 2). In patient 4, the 1500-µg/day dose was enough to suppress spasms in the lower extremities, but not in the upper extremities. The dose was not increased because severe hypotonia occurred after a 500-µg bolus was given during a continuous infusion of 1500 µg/day.

In all four patients, the tip of the catheter was positioned at the lower thoracic level (about T10–11). The

Table 2 Details of tetanus patients treated with intrathecal baclofen

Study	Number of patients	Bolus dose (μg)	Continuous dose (μg)	Treatment duration (days)	Improvement after treatment (h)	Complications
Müller et al. [17, 21, 22]	3	600–1000	600–2000	15–17	2	Sedation due to diazepam
Romijn et al. [23]	1	250	1200–2000			Coma at 2000 μg/day
Saissy et al. [24]	1	1000	500–2000	21		Respiratory depression at 2000 μg/day
Demazière et al. [25]	1	1000–1500		16	2	Coma after diazepam coadministration
Karp et al. [26]	1	50–100	750	24	$^1/_2$	Bradycardia and hypotonia
Saissy et al. [27, 28]	10	200–1000			$1\,^1/_2$	Coma, 5 died due to sympathetic dysregulation (3), asphyxia (1), urosepsis (1)
Pellanda et al. [29]	1	400	600–800	16	Immediate	Hypotonia, sedation due to prior administered sedatives
Sicignano and Lorini [30]	1		1000	4		Sedation due to diazepam
Brock et al. [31]	1		750–1500	15	12	Sedation due to diazepam
This study	4	300–500	500–2000	8/10 19/54	$^1/_2$–1	Sedation due to diazepam, hypotonia, and bradycardia

more effective reduction of spasms in the lower extremities than in the upper extremities is due to a decreasing concentration of baclofen in the cerebrospinal fluid correlating to the distance from the catheter tip; that the concentration of baclofen infused at T12 decreases by 60 % at T2 was demonstrated by a radionuclide technique [20]. A more cranial position at the level of T5–7 may possibly have a better effect upon suppressing spasms in the upper extremities at lower doses. This hypothesis must be evaluated in further studies.

Most of the patients in other studies started treatment with a bolus dose in the range of 50–1000 μg (Table 2) [17, 21–31]. Some patients were treated thereafter only by repeated bolus injections on consecutive days [25, 27, 28], while other patients received a continuous infusion of baclofen. Interactions with other medication and upper dose limitations with i.th. baclofen are described and are discussed below.

Baclofen and benzodiazepines

The delayed disappearance of the effects of sedation and the restoration of respiratory drive in patients 1, 2, and 3 after stopping i.v. benzodiazepines and starting therapy with i.th. baclofen might have been caused by the sedative effects of baclofen itself or by benzodiazepine accumulation from previous infusions of high doses of benzodiazepines. Baclofen in the high doses used in our patients can decrease the level of consciousness [32]. It is more likely that the delayed awakening was due to benzodiazepine accumulation, since patients 1 and 2 regained consciousness 4 days after benzodiazepine infusions were stopped, while the dose of i.th. baclofen had not yet been reduced. The prolonged awakening after therapy was changed from benzodiazepines to i.th. baclofen has also been described by other authors [17, 31, 30]. One patient became comatose 3 days after the coadministration of 120 mg diazepam with daily i.th. baclofen bolus injections of 1500 μg. The patient reawakened 1 day later and showed no reduction of consciousness after diazepam was stopped and the daily baclofen bolus dose was reduced to 1000 μg [25]. Whether this was caused by the high bolus dose of baclofen or by accumulation of diazepam is not clear. In patient 4 it is possible that i.th. baclofen had an additional depressive effect upon the respiratory drive because the mechanical ventilation was stopped when the baclofen infusion was terminated.

Baclofen and flumazenil

In one report, patients who had had an overdose of baclofen became more awake after flumazenil was administered [27]. Another report describes the ineffectiveness of flumazenil in bringing a patient out of a coma who had received an overdose of i.th. baclofen during treatment for spasticity [33]. Sicignano and Lorini reported a patient, who, after treatment was changed from diazepam to i.th. baclofen, remained comatose even after 2 mg flumazenil was administered 3 days after the diazepam infusion had been stopped. Only neck and face spasms were observed after flumazenil, and these disappeared after 400 μg baclofen was additionally given [30]. Brock et al. described a patient in whom muscle relaxant therapy with midazolam and vecuronium was changed to i.th. baclofen therapy, which was more effective in a dose range of 750–1500 μg/day. The patient was still comatose 2 days after all muscle relaxing drugs except baclofen had been stopped, and therefore 2 mg flumazenil was given. He became conscious immediately but also developed severe muscle spasms. The authors discuss a possible antagonizing effect of flumazenil on the spinal effects of baclofen [31]. Though this cannot be ruled out, it is more probable that spinal GABA-A receptors were blocked. A constant inhibitory GABA tonus exists at the spinal level, which is transmitted through GABA-A receptors [34]. It may be that the antagonism of accumulated benzodiazepines acting at spinal GABA-A receptors led to the spasms. In patient 4 the administration of flumazenil led to increased spasms in the arms and the neck but not in the legs, which remained flaccid. This demonstrates that flumazenil blocked the coadministered benzodiazepines but not the baclofen.

Overdoses of baclofen

In a group of ten patients with tetanus treated by repeated i.th. baclofen bolus injections, five patients developed respiratory depression within 1 1/2–6 hours after the first, second, third, or fourth bolus. Of these five patients, three required mechanical ventilation and two became alert after flumazenil was administered [28]. Temporary bradypnea and sedation occurred when a bolus of 500 μg baclofen was administered with a continuous infusion of 1000 μg baclofen per day [22]. Bolus injections of baclofen may lead to coma, because the concentration of baclofen will temporarily be higher at more cranial levels than during a continuous infusion. It is probable that significant depression can occur more easily at the brainstem level. Additionally, the half-life in the myelon may be longer than in the cerebrospinal fluid, and thus, even though the dose is not increased, repeated bolus injections might lead to a stronger depressive effect.

Coma without spontaneous respiration and absent pupillary reaction to light was observed in one patient in whom the dose was increased from 1200 μg/day (at this dose the patient was alert but still had some muscle spasms) to 2000 μg/day [23]. A dose below 2000 μg was not sufficient to reduce spasms. Another patient whose spasms were effectively controlled within a dose range of 1000–2000 μg/day required mechanical ventilation. After the dose was reduced to 500 μg/day on day 13, mechanical ventilation was stopped [24]. Patient 2 breathed sufficiently by himself at a dose of 2000 μg/day. This demonstrates that some patients need mechanical ventilation at a dose range of 1000–2000 μg/day, while other patients can breathe unaided. There seem to be different interindividual responses for the same dose of i.th. baclofen. Different responses to baclofen 500 to 2000 μg/day could have different causes (a) Catheter position: a higher position might have yielded better results in suppressing spasms in the arms and neck of patient 4. (b) Severity of the tetanus: patient 4, with the highest severity score [35] and the fastest developing symptoms of tetanus responded least. (c) Time between the first symptoms of tetanus and the start of i.th. baclofen: therapy was started in patient 1 on day 12 after tetanus symptoms appeared and only 500 μg/per day was needed, while in patients in whom baclofen treatment was started earlier, higher doses of 1000–2000 μg/day were needed. (d) Different interindividual dose responses, possibly due to a different quantitative distribution of GABA-B receptors. As interindividual doses vary greatly in spastic patients who are treated with i.th. baclofen [36], it is not unlikely that patients with tetanus have different interindividual dose responses.

Side effects of baclofen on the sympathetic system

Patients with tetanus often show excessive sympathetic nervous activity [2], which accounts for the high mortality despite intensive care treatment [1]. There are reports that sympathetic overactivity subsided when a continuous i.th. baclofen infusion was given [22, 29, 37]. Hypotonia and bradycardia occurred in patient 3 after the dose was increased from 1000 to 2000 μg/day but resolved after the dose was reduced to 1000 μg/day again. Patient 4 developed hypotonia and bradycardia after an initial bolus of 300 μg on day 2, while boluses of 400 μg during continuous infusions of 700 or 1200 μg baclofen per day did not cause hypotonia, but they did bring about a normalization of blood pressure from hypertensive measurements before the boluses. Some days later severe hypotonia was observed in patient 4 after a bolus of 500 μg was given in addition to a continuous infusion of 1500 μg/day. The bolus infusion may have led to a significant increase in the baclofen concen-

tration at the brainstem level, leading to sympathetic depression. Pellanda et al. reported hypotonia after the first i.th. baclofen bolus of 400 μg, which was treated with dopamine and volume expansion. The subsequent continuous infusion of 600–800 μg baclofen per day did not cause hypotonia [29]. Interestingly, the same authors also described the reappearance of dysautonomic signs after terminating the i.th. infusion of baclofen after 16 days [29].

In experiments with rats, it was demonstrated that administration of i.th. L-baclofen can decrease diastolic and systolic arterial pressure and heart rate [38, 39]. Thus, attenuation of the sympathetic system, especially that regulating heart rate and blood pressure in humans who receive high doses of i.th. baclofen, is not unlikely. The doses used to treat patients with tetanus are high (500–2000 μg/day) compared to doses used to treat patients with spasticity (100–300 μg/day) [36]. Therefore, it is not unlikely that significant amounts of baclofen will reach supraspinal structures. Thus, depression can also occur at the brainstem level. Reducing sympathetic overactivity by this means is possible. As patient 2, who was also treated with 2000 μg baclofen/day, showed only a moderate reduction in blood pressure, there seems to be an interindividual variation of the dose that attenuates sympathetic activity. Attenuation of sympathetic activity which can be reduced with atropine and dopamine, may prohibit a sufficient dose increase needed to suppress spasms in cervical and arm muscles as in patient 4.

Changing response to baclofen

A change in the sensitivity to baclofen when tetanus symptoms are developing and diminishing can be deduced from the fact that the dose of i.th. baclofen was reduced stepwise in patient 3 without spasms recurring. Further, Saissy et al. reported a patient in whom the dose was reduced stepwise from 2000 to 50 μg/day without spasms recurring, though they did recur when the infusion was stopped. The patient was then treated with benzodiazepines for several days [24]. Adapting the dose to the duration of the illness may be necessary.

Another reason for a change in response might be that some of the suppressive effects of the tetanus toxin on the endogenous inhibitory system diminish and the endogenous inhibitory GABA tonus starts to work again, at least partially, over the duration of the illness. Thus, the same baclofen dose produces a stronger suppression than initially.

In conclusion; patients with severe tetanus benefit most from i.th. baclofen infusion if therapy is started early, before large amounts of benzodiazepines are given. The respiratory drive is less depressed because the primary distribution of .th. baclofen is in the spinal cord, with a decreasing concentration in the cranial direction. It may be better to place the catheter at the mid-thoracic level to obtain proper muscle relaxation in the upper extremities. We think that therapy with i.th. baclofen infusion in a dose range of 500–2000 μg/day can be helpful in patients with tetanus, not only to reduce spasms but also to normalize blood pressure and heart rate as such patients often have increased blood pressure and tachycardia due to central disinhibition. When doses of 2000 μg or more are used, one should be aware of potentially dangerous reductions in heart rate, blood pressure, and respiratory drive possibly caused by the action of baclofen at the brainstem level. Therefore, we recommend that this therapy be used only in intensive care units where continuous monitoring and intervention are possible.

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