

EREDETI KÖZLEMÉNY ORIGINAL ARTICLE

The effect of anesthetic blockade of greater occipital nerve during the withdrawal period of the medication overuse headache treatment

Mirac Aysen UNSAL¹, Tugrul AYDIN²

¹Sultan II. Abdulhamid Han Training Hospital, Neurology Department, Istanbul, Turkey ²Prof. Dr. Cemil Tascioglu City Hospital, Neurology Department, Istanbul, Turkey [] English | https://doi.org/10.18071/isz.77.0103 | www.elitmed.hu

Correspondent:

Mirac Aysen UNSAL, MD, Sultan Abdulhamid Han Training Hospital, Neurology Department, Istanbul, Turkey; E-mail: aysenunsal@yahoo.com Phone: +905324375070 Fax number: +905324375070 https://orcid.org/0000-0001-9991-861X

Érkezett:

2023. május 6. Elfogadva: 2023. augusztus 23. **Background and purpose** – Discontinuation of medication still remains a key element in the treatment of medication overuse headache (MOH), but there is no consensus on the withdrawal procedure. We aimed to share the promising results of anesthetic blockade of greater occipital nerve (GON), which can be an alternative to existing treatments during the early withdrawal period of MOH treatment.

Methods – This study was conducted using regular electronic medical records and headache diaries of patients diagnosed with MOH and treated with anesthetic GON blockade with 0.5% bupivacaine solution in a specialized headache outpatient clinic. A total of 86 patients who developed MOH while being followed up for chronic migraine were included in the study.

Results – The treatment schemes for MOH are based on expert consensus and withdrawal strategies are the most challenging part of treatment. In our study, numerical rating scale for headache intensity, overused medication consumption per month, headache frequency (day/month) and the duration of each attack (hour/day) decreased significantly in the first month compared to pre-treatment (p < 0.01).

Conclusion – Our study suggests that GON blockade can be used as a good alternative therapy in the treatment of MOH.

Keywords: nerve blockade, greater occipital nerve blockade, secondary headache, medication overuse headache, primary headache, chronic migraine, chronic daily headache, migraine A nervus occipitalis major gyógyszeres blokádjának hatása a gyógyszertúlhasználathoz köthető fejfájás kezelésének megvonási időszakában Unsal MA, MD; Aydin T, MD

Háttér és cél – A gyógyszerelés felfüggesztése továbbra is kulcsfontosságú elem a gyógyszertúlhasználathoz köthető fejfájás (medication overuse headache, MOH) kezelésében, azonban egyelőre nincs konszenzus a megvonási folyamat kivitelezésében. Tanulmányunk célja az volt, hogy megosszuk a nervus occipitalis major (greater occipital nerve, GON) anesztetikus blokádjának ígéretes eredményeit; e blokád alternatívát jelenthet a már meglévő terápiák mellett a gyógyszerelvonás korai szakaszában.

Módszerek – Ezt a tanulmányt elektronikus orvosi nyilvántartások és betegek fejfájásnaplói felhasználásával végeztük MOH-hal diagnosztizált és GON-blokáddal (0,5% bupivacainoldat) kezelt betegekkel egy járóbetegfejfájásklinikán. Összesen 86 olyan beteget vontunk be a vizsgálatba, akinél MOH alakult ki, mialatt krónikus migrén miatt követték őket. **Eredmények** – A MOH kezelési protokoll-

jai szakértői konszenzuson alapulnak, és a gyógyszermegvonási stratégia jelenti a kezelés legnagyobb kihívását. Vizsgálatunkban a kezelést követő egy hónapon belül a fájdalom intenzitását becslő numerikus mérőskála, a havi gyógyszertúlfogyasztás mértéke, a fejfájás gyakorisága (fejfájásnapok/hónap) és a migrénes rohamok időtartama (óra/nap) szignifikánsan csökkent a kezelést megelőző időszakhoz viszonyítva (p < 0,01).

Következtetés – Tanulmányunk azt sugallja, hogy a GON-blokád jó alternatív terápiaként alkalmazható a MOH kezelésében.

Kulcsszavak: idegblokád, nervus occipitalis major blokád, másodlagos fejfájás, gyógyszertúlhasználathoz társuló fejfájás, elsődleges fejfájás, krónikus migrén, krónikus mindennapos fejfájás, migrén

edication overuse headache (MOH) is a global health problem with a prevalence ranging from 0.5% to 7.6% in the general adult population in different countries. The prevalence is high in women and in the fourth decade of the life¹. It is defined as a headache that occurs for 15 or more days/month in a patient with pre-existing primary headache and develops as a result of regular overuse of acute or symptomatic headache medication (on 10 or more or 15 or more days/month, depending on the medication) lasting more than 3 months. It usually, though not always, resolves after overuse of the responsible drug is discontinued². In a nationwide home-based study in adults conducted in our country in 2008, the frequency of medication overuse headache in the 18-65 age group was found to be 2.1%, and this rate was found to be 8.2% in patients with a diagnosis of migraine³.

The diagnosis and treatment of MOH includes a challenging process for both the patient and the physician. It is necessary for the patient to accept the diagnosis, be aware of medication misuse and be willing to be treated. As the patient continues to overuse the medication, the exposure time to the chronic side effects of the medication will increase. In addition, associated potential complications are a burden for the patient as well as the healthcare system.

Primarily outpatient treatment is recommended for each patient. However, some complicated cases require inpatient treatment. In the treatment of MOH, the patient is recommended to discontinue the overused medication, and supportive treatment is recommended for withdrawal headaches. Optional early preventive medication therapy or symptomatic treatment using a different medication than the overused medication is recommended⁴⁻⁸.

The pre-existing primary headache which is obligatory for the diagnosis of MOH, is migraine in approximately 60% to 80% of patients. In this context, it is not surprising that migraine and MOH have similar pathophysiological mechanisms⁷. In the literature, there are not many studies on peripheral nerve blocks in the treatment of MOH⁹. However, many studies are available with almost all types of headaches and GON blockade, including the majority of migraine¹⁰.

Based on our clinical experience and past studies the most challenging period for the physician and the patient in the treatment of MOH is the withdrawal period. In this study, we included patients with MOH who had a history of chronic migraine (CM) and who had anesthetic GON blockade during the withdrawal period of the overused medication.

We aimed to share the promising results of the greater occipital nerve (GON) blockade, which can be an alternative to existing treatments during withdrawal period of MOH treatment.

Materials and methods

Study population

In the study, electronic medical records and headache diaries of patients who were diagnosed with chronic migraine (CM) and subsequently met the diagnostic criteria for MOH were examined. The data of those who underwent weekly anesthetic GON blockade during the first month of treatment were included in the study. The diagnosis of CM and MOH were made according to The International Classification of Headache Disorders, 3rd edition (ICHD-3, classification 1.3 and 8.2)². A total of 86 patients were included in the study.

Exclusion criteria

Patients who received Botulinum toxin type A (BoNT-A) treatment in the last 6 months, pregnant and breastfeeding women, patients known to be allergic to local anesthetics, patients with a history of malignancy, with a history of cranial or cervical surgery, with bleeding diathesis, patients with major psychiatric disorders, with neuromuscular dysfunction, using agents that affect neuromuscular functions, patients with uncontrolled hypertension, with hypothyroidism or hyperthyroidism, patients with a history of primary headache other than CM were excluded from the study.

Study design and procedure

Our study was designed prospectively. GON blockade was repeated at the same dose four times, every week for 4 weeks.

The following variables for each patient were recorded before the procedure and at the first month after the procedure: The Numeric Rating Scale (NRS) for the objective assessment of headache severity, the overused medication (non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol, triptan and ergotamine), the overused medication consumption per month, headache frequency (day/ month) and the duration of each attack (hour/day). NRS is a subjective measure in which individuals rate their pain on an eleven-point numerical scale. The scale ranges from 0 (no pain) to 10 (worst pain imaginable)¹¹.

No patient was offered preventive treatment for migraine in the first four weeks.

GON blockade technique

All patients were taken to the intervention room. The possible risks and complications were verbally explained to all patients before the GON blockade, then they were asked to read the procedure from the written informed material and their consent was obtained.

GON blockade was applied 2 cm lateral and 2 cm below the palpated external occipital protuberant. After the patients were seated in a chair close to the examination table, they were asked to bend their heads in front of them by leaning on the examination table with their hands. In this way, syncope and trauma that may occur during the injection were avoided. The area to be injected was disinfected with an antiseptic before the procedure. Bilateral 2 ml 0.5% bupivacaine solutions were administered to all patients subcutaneously with a 26 gauge (G) 13 mm needle. When the periosteum was reached during the injection, the syringe was withdrawn 1 mm and the medication was given. Local pressure was applied for 2-3 minutes to spread the medication and prevent possible bleeding. All patients who underwent GON blockade were kept in the recovery room for about half an hour after the injection to confirm that there were no side effects. The sensation of the region innervated by the GON was evaluated with the pinprick test at the fifteenth minute. Post-injection numbness was achieved in all patients. GON blockade was performed on both sides. GON blockade was repeated at the same dose four times (every week for 4 weeks).

Statistical analysis

SPSS (Statistical Package for the Social Sciences) 25.0 package program was used for statistical analysis of the data. Categorical measurements were summarized as numbers and percentages, and continuous measurements as mean and standard deviation (median and minimummaximum where appropriate). Chi-square test was used to compare categorical expressions. Shapiro-Wilk test was used to determine whether the parameters in the study showed normal distribution.

The Mann-Whitney U test was used in the double group analyzes for the parameters that did not show normal distribution (parameters and genders), and the Kruskal-Wallis test was used in the analyzes of more than two groups (the type of overused drug and difference between post-and pre-GON block (Δ) NRS, headache frequency (day/month), overused medication consumption per month and the duration of each attack (hours/day). Post Hoc Tamhane's T2 test was used to determine the source of significant difference between more than two groups. Wilcoxon test was used to examine the difference between the findings before and after GON blockade treatment.

Statistical significance level was taken as 0.05 in all tests.

Results

A total of 86 patients who were diagnosed with CM, developed MOH and treated with anesthetic blockade

Table 1. Demographic data of patients (age and gen-
der), years of diagnosis of migraine and distribution of
overused medication

	Frequency (n)	Percentage (%)
Sex		
Male	20	23.3
Female	66	76.7
Overused medication		
NSAID	58	67.4
Paracetamol	12	14.0
Triptans	8	9.3
Ergotamine	8	9.3
	Mean ± SD	Med (Min- Max)
Age	37.3 ± 8.6	37 (20–64)
Migraine year	15.6 ± 7.7	15 (1–40)

NSAID: non-steroidal anti-inflammatory drug, SD: standard deviation

of GON were included in the study. Of the patients, 66 (76.7%) were female, and their mean age was 37.3 ± 8.6 years. The mean duration of migraine years of the patients was 15.6 ± 7.7 years.

The distribution of the most frequently overused medication was NSAID in 58 (67.4%), paracetamol in 12 (14.0%), triptans in 8 (9.3%), and 8 (9.3%) ergotamine respectively **(Table 1)**.

It was determined that female patients had a higher mean age and migraine duration than male patients (p = 0.003; p = 0.011, respectively). No significant difference or relationship was found between the findings of overused medication and the gender (p = 0.689) (Table 2).

Pretreatment headache frequency (day/month) and the difference between post- and pre-GON blockade treatment overused medication consumption per month were found to be higher in female patients compared to male patients (p = 0.035; p = 0.046, respectively) (**Table 3**). As shown in **Table 3**, no significant difference was found between the other parameters and the gender (p > 0.05).

It was determined that the NRS, the headache frequency (day/month), the number of overused medication consumption per month and the duration of each attack (hours/day) findings of the patients after GON blockade were significantly lower than the pretreatment parameters (p < 0.001; p < 0.001; p < 0.001; p < 0.001 respectively) (Table 4).

A significant difference was observed between the overused medication and the Δ headache frequency and Δ attack duration (hours/day) (p = 0.044; p = 0.013, re-

	Male (n = 20)	Female (n = 66)	pª
	n (%)	n (%)	
Overused medication			
NSAID	13 (65)	45 (68.2)	0.689
Paracetamol	3 (15)	9 (13.6)	
Triptans	1 (5)	7 (10.6)	
Ergotamine	3 (15)	5 (7.6)	
	Male (n = 20)	Female (n = 66)	þ
	Mean ± SD	Mean ± SD	_
Age	33.0 ± 9.1	38.6 ± 8.0	0.003**
Migraine year	12.1 ± 9.1	16.6 ± 6.9	0.011*

Table 2. Mean age and migraine years of male and female patients, and the relationship between the overused medication and gender

*p < 0.05, **p < 0.001, a: Chi-square, b: The Mann-Whitney U test NSAID: non-steroidal anti-inflammatory drug, SD: standard deviation

spectively). When the source of the difference between the groups was examined, it was determined that the Δ headache frequency (day/month) of those using ergotamine were less likely to decrease than the patients using NSAID and paracetamol (p < 0.001; p = 0.046, respec-

Table 3. Parameters and the gender

tively). Δ attack duration (hours/day) value was found less likely to decrease in ergotamine users compared to paracetamol users (p = 0.039). As shown in **Table 5**, no significant difference was found between the other parameters and the overused medication (p > 0.05).

In our study, injection site pain lasted less than 24 hours in 14 patients after GON blockade, while it lasted 24-72 hours in 4 patients. However, none of the patients wanted to withdraw the treatment because of injection site pain. No patient needed to use analgesics due to injection site pain.

Discussion

Migraine affects an estimated 12% of the population, although it varies around the world. CM affects approximately 1% to 2% of the world's population. About 2.5% of people with episodic migraine progress to CM¹². CM, and its' possible complication,

MOH, covers 50% of patients in specialized headache centers and present a significant challenge. 30-50% of patients with headache who apply to headache clinics or tertiary care centers are diagnosed with MOH¹³⁻¹⁵. Following the chronicity of migraine, the onset of MOH oc-

	Male (n = 20)	Female (n = 66)	þp
	Mean ± SD, median, IQR	Mean ± SD, median, IQR	_
NRS, pretreatment	8.35 ± 0.9, 8.5, 1	8.67 ± 0.8, 9, 1	222
NRS, month I	3.05 ± 0.5, 3, 0	3.03 ± .6 (2-4), 3, 2	901
Headache frequency (day/month), pretreatment	23.1 ± 4.4, 20, 9	25.2 ± 3.9, 25, 9	0.035*
Headache frequency (day/month), month l	4.80 ± 1.0, 5, 0	5.35 ± 1.0, 5, 0	148
Overused medication consumption per month, pre- treatment (number)	51.0 ± 25.9, 30, 53	62.7 ± 22.8, 60, 38	55
Overused medication consumption per month, month I (number)	5.50 ± 0.7, 6, 1	5.42 ± 0.8, 6, 1	798
The duration of each attack (hour/day), pretreatment	20.40 ± 5.6, 24, 12	21.64 ± 4.8, 24, 12	333
The duration of each attack (hour/day), month l	8.70 ± 3.1, 6, 6	8.97 ± 3.2, 12, 6	808
ΔNRS	-5.30 ± 1.0	-5.63 ± 0.9	256
Δ Headache frequency (day/month)	-18.30 ± 4.7	-19.8 ± 4.1	109
Δ Overused medication consumption per month	-45.50 ± 25.8	-57.30 ± 22.7	0.046*
Δ The duration of each attack (hour/day)	-11.70 ± 7.7	-12.66 ± 5.3	996

*p < 0.05, b: The Mann-Whitney U test.

NRS: Numerical Rating Score, A: the difference between post- and pre-GON blockade, SD: standard deviation, IQR: the interquartile range

	Pre-GON blockade Post-GON blockade		р
	Mean ± SD, median, IQR	Mean ± SD, median, IQR	
NRS	8.59 ± 0.8, 9, 1	3.03 ± 0.6, 3, 0	< 0.001**
Headache frequency (day/month)	24.7 ± 4.1, 25, 10	5.22 ± 1.0, 5, 0	< 0.001**
Overused medication consumption per month (number)	60 ± 23.9, 60, 60	5.44 ± 0.8, 6, 1	< 0.001**
The duration of each attack (hours/day)	21.4 ± 5.0, 24, 0	8.91 ± 3.1, 9, 6	< 0.001**

Table 4. NRS, headache frequency (day/month), number of overused medication consumption per month and attack duration (hours/day) findings of the patients before and after GON blockade treatment

**p < 0,001, Wilcoxon rank test

GON: great occipital nerve, NRS: Numeric Rating Scale, IQR: the interquartile range

curs over a period of several months or years. Usually, MOH presents as a CM plus entity, and it is difficult to separate the present situation from CM itself unless the patient's medication overuse is questioned. MOH should be considered a complication of CM in most cases and not just a secondary headache^{15,16}. In the methodology of our study, we differentiated this specific group by including patients with CM diagnosis and those who developed medication overuse in course of time and who met the diagnostic criteria of MOH during follow-up.

Underlying pathophysiological mechanism of MOH is still unclear. There is no standardized treatment protocol and no specific guidelines for MOH. The primary treatment of choice by most centers is discontinuation of the overused medication, as patients detoxify and their response to acute or prophylactic medications improve¹⁷. Abrupt discontinuation of the medication may cause severe rebound headache, nausea, vomiting, tachycardia, arterial hypotension, sleep disturbances, restlessness, anxiety and nervousness. These symptoms usually last between 2 and 10 days, but may persist for up to 4 weeks¹⁸. Withdrawal symptoms are usually relieved by taking more of the overused medication, but this also leads to continued overuse. Supportive treatments are recommended to alleviate withdrawal symptoms following medication discontinuation. Choosing a patient-specific method is the most appropriate treatment. The patient may be given a treatment protocol and recommendations that can be applied at home or in the hospital, and close observation may be required. The most commonly used treatments are fluid replacement, tranquilizers, neuroleptics, and steroids19, 20.

	NSAIDs	Paracetamol	Triptans	Ergotamine	pa	Post Hoc Tamhane's T2 p
	Mean ± SD, median, IQR	Mean ± SD, median, IQR	Mean ± SD, median, IQR	Mean ± SD, median, IQR		
∆ NRS score	-5.60 ± 1.0, -6, 1	-5.58 ± 0.9, -6, 1	-5.50 ± 0.8, -6, 1	-5.25 ± 1.0, -5, -1.75	0.812	_
∆ Headache fre- quency (day/month)	-20.2 ± 4.5, -20, 10	-18.4 ± 2.9, -19.5, 5	-19.4 ± 4.2, -20, 8.5	-15.6 ± 1.1, -15.5, 8.5	0.044*	Ergotamine vs NSAID; p < 0,001 Ergotamine vs paracetamol; p = 0,046
Δ Overused medica- tion consumption per month (number)	-58.7 ± 24.7, -54, 58	-44.7 ± 19.9, -54, 29.75	-54.3 ± 22.7, -54, 45.2	-40.0 ± 16.3, -40.5, 30.7	0.255	-
Δ Attack duration (hours/day)	-13.0 ± 5.7, -12, 6	-13.5 ± 5.2, -12, 6	-13.0 ± 4.3, -12, 4.5	-6.0 ± 7.2, −3, 12	0.013*	Ergotamine vs paracetamol; p = 0,039

Table 5. The relationship between the type of overused drug and difference between post- and pre-GON block (Δ) NRS, headache frequency (day/month), overused medication consumption per month and the duration of each attack (hours/day)

*p < 0.05, a: Kruskal Wallis test, Post Hoc Tamhane's T2 test

Δ: difference between post- and pre-GON blockade, IQR: the interquartile range

Peripheral nerve blocks are used in primary and secondary headaches. GON blockade, which was used most frequently in headaches and was first applied by Haden, is usually preferred²¹. GON blockade is very effective, safe and relatively easy to perform. The effectiveness of GON blockade in the treatment of various types of headache has been demonstrated in many studies²²⁻²⁷. It is known that the use of local anesthetics improves central and peripheral sensitization and thus disrupts the pain cycle. Local anesthetics specifically act on unmyelinated C fibers, blocking sodium channels reversibly and preventing the transmission of pain signals. However, the response observed with GON blockade cannot be explained by the direct local anesthetic effect of the injection. Because the duration of action of local anesthetics is very short, GON injections are thought to initiate widespread diffuse noxious inhibitory controls independent of the anesthetic effect. There is a functional connection between the sensory occipital segments and the trigeminal nociceptive system. Painful stimuli originating from the cranial structures are transmitted to the trigeminocervical complex and from there to the upper centers via the trigeminal nerve and superior cervical nerves. GON blockade reduces afferent input to the trigeminal nucleus caudalis, resulting in a decrease in neuronal hyperexcitability and modulation in central pain²⁸⁻³⁰. In addition to all these, peripheral and central sensitization is facilitated as a result of increased excitability in the cortex and trigeminal ganglia in excessive medication use7.

Considering the studies in the literature, the number of patients treated with GON blockade is relatively high (n = 86) in our study. Similarly to the previous studies, the number of female patients is high (n = 66 vs n = 20)and female patients had a higher mean age and migraine duration than male patients $(38.6 \pm 8.0 \text{ vs. } 33.0 \pm 9.1, \text{ p} =$ 0.003; 16.6 ± 6.9 vs. $12.1 \pm 9,1$, p = 0.011, respectively). Theoretically, female patients have longer migraine duration and more neuromodulation, and we would expect them to have a worse response to treatment as they have a longer evolution in migraine. However, in our study, only the difference in headache frequency before treatment (day/month) and overused medication consumption per month before and after GON blockade treatment was found to be higher in female patients than in males (p =0.035; p = 0.046, respectively). There was no significant difference between other parameters and gender.

There are limited studies in the literature between MOH and peripheral nerve blockades. In a recent study, bilateral GON blockade was applied to 41 patients with a diagnosis of MOH, and bilateral GON and supraorbital nerve blockade were applied to 41, and both methods were reported to be effective in the treatment of MOH³¹. Karadas et al. in a multi-centre study of 105 patients who had triptan overuse headache, achieved significant improvement in patients with repeated GON blockade³².

Similar to these studies, in our study, anesthetic blockade of GON gave us promising results during the early withdrawal period of MOH treatment. The most striking point of our study is that in the first month following the GON blockade NRS, overused medication consumption used monthly, headache frequency (day/month) and the duration of attacks (hour/day) decreased significantly compared to pre-treatment (p < 0.001).

As another important point determined in our study, in patients using ergotamine, headache frequency (day/ month) difference before and after the GON blockade was less likely to decrease than in the patients using NSAID and paracetamol, and the difference on attack duration (hours/day) was found to be less likely to decrease in ergotamine users compared to paracetamol users. While ergotamine is not preferred by physicians due to its side effects, it is still used because of its easy access and low price. Severe withdrawal symptoms often occur after discontinuation of ergotamine. These may include increased headache, nausea, and vomiting. Although various treatments are recommended for the management of ergotamine withdrawal symptoms, intravenous fluid therapy and anti-nausea medications are essential if withdrawal is rapid. The usual practice is to use narcotic analgesics and tranquilizers to counter the withdrawal symptoms³³⁻³⁵. In our study, migraine preventive treatment was not recommended for patients during the first four-week GON blockade treatment period. We made agreement to discontinue medication overuse to restore the natural course of the patient's headache. These results suggested that patients experienced more difficulty with ergotamine withdrawal than other overused drugs. Therefore, it should be considered that GON blockade alone may not be sufficient during the withdrawal period in patients using ergotamine.

Generally, GON blockade is a fairly safe treatment. Although the frequency of reported adverse events in open-label studies ranged from 2.4% to 99.6%, most were mild and transient. The three most frequently reported consistent adverse events were local pain, vasovagal syncope attacks, and vertigo³⁶. In our study, after GON blockade, 14 patients reported pain lasting less than 24 hours, and 4 patients reported pain lasting 24-72 hours at the injection site which was found in the acceptable limits for most patients.

Our study suggests that GON blockade can be used as a good alternative therapy in the treatment of MOH, with very low cost. When applied by an experienced clinician, the procedure takes minutes. With appropriate patient selection, the rate of side effects is low. Since patients will be invited for injection at frequent intervals, it allows the physician to follow up the patients' withdrawal compliance closely.

The biggest limitation of our study is the absence of a placebo group. However, our clinic serves a large num-

ber of patients for headaches and is therefore specialized. Since MOH patients are a special group of patients with intense pain, it was not offered in our previous experience with the assumption that they would not accept placebo therapy. Undoubtedly, our study shows that GON blockade therapy is beneficial in the treatment of MOH, similar to other therapeutic treatments.

In conclusion, physicians should keep in mind that GON blockade can be a good alternative to existing treatments, especially in headache centers dealing with MOH. However, randomized, placebo-controlled studies are needed to determine how long this improvement can be sustained, how to schematize the treatment, how to identify potential patients, and to evaluate the efficacy of treatment.

DATA AVAILABILITY – The data that support the findings of this study are available from the corresponding author upon reasonable request.

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