Methadone in the treatment of neuropathic pain

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BACKGROUND: Methadone, being an N-Methyl-D-Aspartate receptor antagonist, may have a potential role in the treatment of neuropathic pain.
OBJECTIVES: To evaluate the effect of methadone in the treatment of neuropathic pain and to estimate the possible dose ranges needed for pain control.
METHODS: Methadone was offered as a treatment option to consecutive cancer and noncancer patients with neuropathic pain. Pain intensity was measured by the visual analogue scale (VAS) (0-10 cm where 0 = no pain and 10 = worst possible pain). Mechanical allodynia and paroxysmal (shooting) pain were assessed clinically. All assessments were collected prospectively before treatment and once a stable dose of methadone was reached.
RESULTS: A total number of 18 patients met our inclusion criteria. The mean pretreatment VAS ± SD was 7.7±1.5 cm and this dropped significantly to 1.4±1.7 cm on a stable dose of methadone (P<0.0001). Nine of 13 patients (70 %) had a complete resolution of mechanical allodynia and all eight patients (100%) with shooting pain reported a complete response. The median stable dose of methadone was 15 mg per day.
CONCLUSION: Methadone at relatively low doses seems to be useful in the treatment of neuropathic pain.

Key words: *Cancer pain; Methadone; Neuropathic pain; Opioids*

La méthadone dans le traitement de la douleur névropathique

HISTORIQUE : La méthadone, un antagoniste des récepteurs N-méthyl D-aspartate, pourrait jouer un rôle dans le traitement de la douleur névropathique.
OBJECTIFS : Évaluer l'effet de la méthadone dans le traitement de la douleur névropathique et évaluer les marges posologiques éventuelles nécessaires pour contrôler la douleur.
MÉTHODOLOGIE : La méthadone a été offerte comme possibilité de traitement à des patients après un cancer ou une maladie non cancéreuse afin de soulager des douleurs névropathiques. L'intensité de la douleur a été mesurée au moyen de l'échelle visuelle analogue (ÉVA) (0 cm à 10 cm, où 0=absence de douleur et 10=pire douleur possible). L'allodynie mécanique et la douleur paroxystique (fulgurante) ont été évaluées sur le plan clinique. Toutes les évaluations ont été colligées de manière prospective avant le traitement et après l'atteinte d'une dose stable de méthadone.
RÉSULTATS : Au total, 18 patients respectaient les critères d'inclusion. Le prétraitement moyen selon l'ÉVA±ÉT correspondait à 7,7±1,5 cm, et ce chiffre a baissé considérablement à 1,4±1,7 cm une fois la dose de méthadone stabilisée (P<0,0001). Neuf patients sur 13 (70 %) ont profité d'une résolution complète de l'allodynie mécanique, et les huit patients (100 %) souffrant de douleurs fulgurantes ont fait état d'une réponse complète. La dose stable moyenne de méthadone s'élevait à 15 mg par jour.
CONCLUSION : Des doses relativement faibles de méthadone semblent utiles dans le traitement de la douleur névropathique.

Neuropathic pain is defined as "pain initiated or caused by a primary lesion or dysfunction in the nervous system" (1). This pain category encompasses a heterogeneous group of conditions that differ in etiology, anatomical location and symptoms (2-4). It is known that any process that damages the sensory pathways may cause neuropathic pain. Examples are seen in diabetes mellitus, immune deficiencies, trauma, ischemic disorders and malignant diseases.

The exact prevalence of neuropathic pain is unknown (5). It was estimated as 1% in the British population (6) but the actual figure may be far greater. In cancer patients, neuropathic pain was present in 34% of patients attending a pain clinic (7).

Neuropathic pain is often distinguished by three cardinal symptoms: constant dysesthetic pain, paroxysmal pain and allodynia (8). Each patient may have some or all of these symptoms. The usual physical signs seen in these patients are hyperalgesia, hyperpathia and in some patients, signs of autonomic dysregulation such as edema, and vasomotor and sweating abnormalities (9).

The mechanisms by which neuropathic pain is generated are complex. Nerve injury leads to alterations at the levels of both the peripheral and the central nervous system (10). At the peripheral level, these changes include ectopic and spontaneous discharge by primary afferent neurons, alterations in ion channel expression, collateral sprouting and nociceptor sensitization (11). Centrally, alterations include central sensitization, spinal reorganization and changes in inhibitory pathways (12). The N-methyl-D-aspartate (NMDA) receptor, a subtype of glutaminergic receptors, plays a key role in the development of central sensitization, as well as in the development of tolerance to opioids (13).

The successful management of neuropathic pain is a challenging endeavor. Tricyclic antidepressants and anticonvulsants are considered to be the drug treatments of choice in the setting of

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noncancer pain (2). However, these drugs only achieve clinically significant pain relief in less than 50% of patients and are usually associated with bothersome side effects. There is evidence now that opioids may be effective in certain types of neuropathic pain (14-16). This contrasts with earlier uncertainty about the role of opioids in neuropathic pain (17,18).

Methadone is a synthetic opioid that is gaining acceptance for its use in patients with difficult pain syndromes, particularly in cancer. It possesses a number of unique characteristics when compared with other opioids. It has a broad spectrum of receptor affinities, including mu and delta receptors (19). In addition, it has two important analgesic receptor activities: the prevention of monoamine reuptake in the periaqueductal gray matter and the presynaptic inhibition of NMDA receptors (20-22). It has been already demonstrated that NMDA antagonism results in pain relief in animal models of neuropathic pain (23-25). In humans, it has been shown that NMDA antagonists such as ketamine and dextromethorphan produce significant pain relief (26-28). Some observations indicate that methadone controlled pain that was unresponsive to other opioids such as fentanyl, hydromorphone and oxycodone (29-31). It is possible that the combination of mu agonism and NMDA blockade may make methadone superior to other opioids in the treatment of neuropathic pain. However, before testing methadone in a randomized control trial, more information is needed regarding its potential efficacy in neuropathic pain and the range of daily doses required to achieve pain control.

Based on the preceding arguments, we offered methadone to patients with neuropathic pain as an option for treatment and we documented prospectively the clinical response. Permission to publish these data was obtained from the local hospital ethics authority.

METHODS

Patients

For the period between May 13, 1998 and September 15, 1999, all consecutive patients assessed to have neuropathic pain by either one of two authors (Bruno Gagnon or Gil Shreier) were offered treatment with methadone. These patients were seen in the palliative care inpatient consult service or in the palliative care day hospital of a university teaching hospital. Patients were included according to the following criteria: presenting with a neuropathic pain syndrome not associated with other types of pain such as bone pain or visceral pain (mixed pain syndrome); not receiving strong opioids even though the pain was of sufficient severity to require strong opioids; or already receiving strong opioids (a daily opioid dose not exceeding 120 mg of oral morphine equivalent) but experiencing side effects, thus preventing further dose escalation and therefore requiring an opioid rotation.

We included patients who had been previously exposed to opioids, because most patients are referred after some trials with opioids. However, patients receiving higher doses of strong opioids were excluded to prevent confounding the response with central nervous system plasticity due to tolerance development (32).

Pain assessment

The diagnosis of neuropathic pain was made after a thorough assessment of history and physical examination. On history, characteristics of the pain that suggested a neuropathic origin include sensations of burning pain, dysesthesia (pins and needles), severe excruciating pain or pain that was difficult to describe with words despite fluency in English or French. On physical examination the presence of dysesthesia, allodynia or hyperalgesia suggested neuropathic pain. All available imaging tests were reviewed to document the likely etiology of pain.

The assessment of neuropathic pain was done using a visual analog scale (VAS, 0 cm to 10 cm where 0 = no pain and 10 = worst possible pain). For patients unable to fill out the VAS, a verbal rating scale of 0 to 10 was used to assess pain. Using either method, patients were asked to describe the amount of their global pain at the current moment. Specific components of neuropathic pain were assessed clinically. Patients were asked to describe whether paroxysmal (shooting) pain was present or absent. We assessed mechanical allodynia by gently stroking the skin with a cotton swab and asking the patient about the presence of a painful or unpleasant sensation. The area of allodynia was then measured and described. The response to treatment was classified as follows: complete resolution (CR) when no allodynia remained clinically detectable; partial resolution (PR) when allodynia remained present in less than 50 % of the surface area; and no response, when allodynia remained present in more than 50% of the surface area. These evaluations took place at the initial interview and at each subsequent follow-up visit. Patients were followed up on a daily basis while in hospital and at regular (biweekly/weekly) intervals as outpatients. The same physicians saw each patient on every visit (Bruno Gagnon or Gil Shreier).

The VAS at the initial assessment served as the baseline pain score, while the VAS of the visit when the patient achieved a satisfactory level of pain control and had no further increase in the dose of methadone was used as the outcome. The other outcomes of pain assessment such as allodynia and paroxysmal pain were collected at the same time.

Medication

The initial oral methadone dose was between 2 mg and 5 mg three times a day. Patients, who were not previously exposed to strong opioids or older than 65 years of age, were started on the lower dose. Patients were allowed to use 2 mg of methadone every 4 h to 6 h if needed for breakthrough pain. The dose of methadone was usually titrated up carefully according to the clinical response and absence of side effects.

Statistical analysis

The significance of the main outcome, change in mean VAS scores for pain, was tested using a two-sided paired *t*-test. A correlation was carried out between the previous opioid doses and the stable methadone doses with all patients and including only patients previously treated with opioids. Wilcoxon matched pairs signed rank tests were performed to compare methadone stable doses to final doses for patients with and without evidence of disease progression. The other outcomes are presented with descriptive statistics.

RESULTS

The study population

A total number of 18 patients met the inclusion criteria and agreed to have a trial of methadone. All patients were followed

up until stabilization for a minimum of 16 days to a maximum of 466 days (median: 106 days). Table 1 presents the characteristics of the patients. Most patients (83%) were cancer patients. The youngest of our patients was 36 years old and some of our patients were 80 years and older. There were twice as many males as females (12:6). Amongst cancer patients, the proportion of those with loco-regional disease was approximately equal to patients with metastatic disease.

As seen in Table 2, patients suffered from a broad variety of neuropathic pain syndromes. The maximum total daily dose of opioids used before treatment with methadone was in the range of 100 mg to 120 mg of oral morphine equivalent and only five patients received it. Ten patients were either on a lower dose of a strong opioid or on a weak opioid (20 mg to 90 mg of oral morphine equivalent). Three of our patients were on no opioids before methadone. Of note, only three of our patients were using coanalgesics while on methadone. One of the patients was on methotrimeprazine, another one was on celecoxib, baclofen, methotrimeprazine, dexamethasone and amitriptyline and the last one was taking dexamethasone, naproxen, methotrimeprazine and monthly pamidronate.

The reasons for discontinuation of methadone were death in five patients, loss to follow-up in one patient, resolution of pain (post amputee pain) in one patient and dissatisfaction with pain relief in another patient (patient 9). All other patients were still on methadone and continued to be followed by our team.

Side effects were in general very mild, and none of our patients stopped taking methadone because of side effects. Patients mostly complained of mild drowsiness and nausea during the first 48 h on methadone. However, these symptoms were transient and did not require any specific treatment. Constipation was common but was easily managed with laxatives.

Change in pain

Figure 1 shows the change in the mean pain score of these patients. All patients showed an improvement in their pain scores with the treatment of methadone. The mean pretreatment VAS ± SD was 7.7±1.5 cm and dropped significantly to 1.4±1.7 cm on a stable dose of methadone (P<0.0001). Interestingly, nine of 18 patients (50%) had no pain at all (VAS of 0) when they reached a stable dose of methadone. Only two patients had a VAS score above four but both patients were satisfied with their pain control.

Change in allodynia and paroxysmal pain

Before starting methadone, 13 of 18 patients had allodynia as a component of their neuropathic pain. Once patients were on a stable dose of methadone, nine of 13 (70%) patients had

TABLE 1
Patient characteristics

n	18
Age (mean±SD) (range)	65±14 (36-85)
Male/Female	12/6
Diagnosis	
Lung cancer	6
Gastrointestinal malignancies (rectal, esophageal)	2
Urogenital malignancies (bladder, renal, prostate)	3
Hematological malignancies (lymphoma, multiple myeloma)	2
Sarcoma	1
Breast cancer	1
Diabetes mellitus	3
Extension of cancer	
Loco-regional disease	7
Metastatic disease	8

TABLE 2
Pain characteristics and response to methadone

Patient number	Pain type	Previous opioids (total per day)	VAS T_0	VAS T_1	Allodynia T_0	Allodynia T_1	Shooting pain T_0	Shooting pain T_1	Stable methadone dose (mg per day)
1	Brachial plexopathy	None	8	5	Yes	PR	Yes	No	20
2	Lumbar plexopathy	Morphine 50 mg SC	8	0	Yes	CR	_	_	60
3	Paraneoplastic plexopathy	Anileridine 50 mg–150 mg PO	6	0	Yes	CR	_	_	7.5
4	Brachial plexopathy	Codeine 120 mg–180 mg PO	9	2	Yes	PR	_	_	9
5	Brachial plexopathy	Anileridine 300 mg PO	6	0	Yes	CR	Yes	No	30
6	Lumbar radiculopathy	Morphine 120 mg PO	6	0	Yes	CR	Yes	No	15
7	Lumbo-sacral plexopathy	Codeine 120 mg PO	9	0	Yes	CR	Yes	No	7.5
8	Brachial plexopathy	Anileridine 150 mg	7	3	Yes	CR	_	_	12
9	Paraneoplastic polyneuropathy	Morphine 60 mg PO	8	0	Yes	PR	Yes	No	12.5
10	Epigastric plexopathy	Codeine 120 mg PO	5	1	_	_	_	_	20
11	Postischemic painful myelitis	Morphine 30 mg PO	10	3	Yes	PR	_	_	20
12	Painful diabetic polyneuropathy	None	9	3	Yes	CR	_	_	9
13	Thoracic radiculpathy	Hydromorphone 24 mg PO	10	5	_	_	_	_	20
14	Phantom limb pain	Morphine 40 mg IV	8	0	_	_	Yes	No	6
15	Postherpetic neuralgia	Fentanyl 50 µg/h every 72 h	6	2	_	_	Yes	No	30
16	Lumbar plexopathy	None	9	0	Yes	CR	_	_	6
17	Lumbar radiculopathy	Morphine 30 mg–90 mg PO	7	0	_	_	Yes	No	15
18	Sacral plexopathy	Fentanyl 50 µg/h every 72 h	8	2	Yes	CR	Yes	No	15

CR Complete resolution; IV Intravenously; PO Orally; PR Partial resolution; SC Subcutaneously; T_0 Before treatment; T_1 On a stable dose of methadone; VAS Visual analogue scale for overall pain (0 cm to 10 cm, 0=no pain, 10=worst possible pain). Codeine used was a combination of acetaminpohen 325 mg and codeine 30 mg

complete resolution of their allodynia, while four of 13 (30%) patients had partial resolution. This residual allodynia was not clinically relevant, as shown by the global VAS pain score. Similarly, eight of 18 patients were found to have shooting pain as a significant component of their pain. All eight patients (100%) reported control of this symptom on a stable dose of methadone.

Methadone dose

The mean stable dose of methadone, which was required to achieve pain control, was 17.5±12.9 mg per day. The corresponding median dose was 15 mg (Q_1=9, Q_3=20). The median time required to reach this stable dose was 6.5 days (Q_1=3, Q_3=13). The methadone dosages remained constant for the 13 patients who did not show cancer progression during the follow-up period with a median stable (initial) dose of 15 mg per day (Q_1=12.5, Q_3=20) (mean=19.9 mg, SD=14.3) and a median final dose of 15 mg per day (Q_1=7.5, Q_3=30) (mean=22.7 mg, SD=19.1) (P=0.5). On the other hand, methadone dosages increased in four of five patients with evidence of cancer progression during the study period with a median stable (initial) dose of 9 mg per day (Q_1=9, Q_3=12) (mean=11.2 mg, SD=5.4) and a median final dose of 60 mg per day (Q_1=17, Q_3=75) (mean=66.6 mg, SD=67.1) (P=0.1). Correlation between previous opioid doses and stable doses of methadone was very poor (adjusted R^2=0.07, not significant) including all patients, and even poorer (adjusted R^2=0.02, not significant) when excluding patients without previous opioid use.

DISCUSSION

Our clinical experience illustrates three points. First, methadone seems to be effective for neuropathic pain. Second, methadone did not only have an impact on global pain but also affected the two other components of neuropathic pain: allodynia and paroxysmal pain. Third, the dose of methadone required to achieve a satisfactory level of pain control was relatively small.

This improvement of our patients on methadone may be explained by the many additional properties that methadone possesses when compared with the conventional opioids. In particular is methadone's ability to antagonize NMDA receptors and prevent monoamine reuptake. In neuropathic pain, it has been already suggested that a drug with multiple mechanisms of action is much more likely to be superior to another drug with a single mechanism of action (33). This is due to the fact that several mechanisms may contribute to the generation of neuropathic pain in any single patient (12).

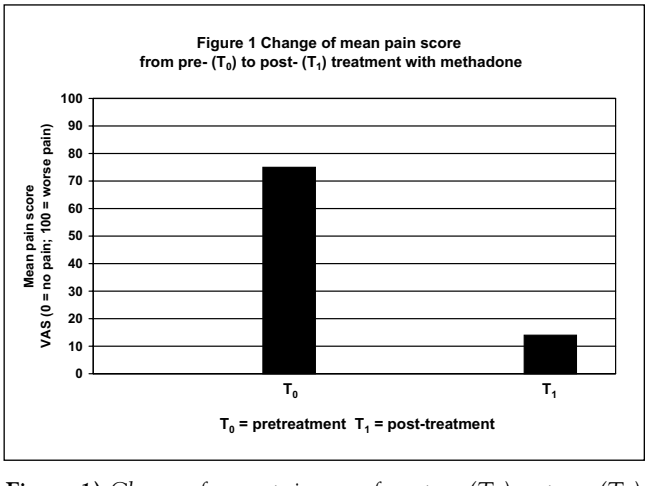

Figure 1) *Change of mean pain score from pre- (T_0) to post- (T_1) treatment with methadone. VAS Visual analog scale*

Paroxysmal pain and mechanical allodynia are both manifestations of central sensitization which is mediated by excess activity at NMDA receptor channels (34-36). The potency of methadone in relieving both allodynia and shooting pain may be explained by its NMDA antagonism. This finding is in keeping with results from experimental and small clinical studies which showed that both paroxysmal pain and allodynia can be reduced by NMDA receptor antagonists with known action on central sensitization (26,37,38). However, there may be other possible mechanisms contributing to this effect. In a trial with tramadol, it was shown that pain relief was accompanied by a concomitant and parallel relief of allodynia and experimentally induced mechanical hyperalgesia (38). Similarly, oxycodone relieved steady pain, brief pain and allodynia in patients with postherpetic neuralgia (16). In both of these studies, the presence of opioid-sensitive central sensitization may explain these findings. Additionally, in the case of tramadol, monoamine reuptake inhibition may contribute to this effect. Therefore, the effect of methadone may be explained by any of the three different mechanisms. Interestingly, it has been possible in animal studies to identify drugs with an action mainly on a single component of neuropathic pain such as allodynia-like pain or on pinprick hyperalgesia (39). However, similar data on methadone are lacking.

As opposed to other opioids that are usually required in large doses to achieve pain relief in neuropathic pain (17,40,41), methadone seems to produce satisfactory pain control at relatively smaller than expected doses. In cancer patients, it has been shown that methadone is required at a lower dose than the dose of the previous opioid agonist to maintain an analgesic effect (42-47). At present, it is believed that the dose ratio of oral morphine to oral methadone is between 2.5:1 (48-50) to 4:1 (51) at lower doses of morphine (<300 mg per day of oral morphine) and up to 14.3:1 when daily morphine doses exceed 300 mg (19,48,49). Similarly, a 10 fold increase in dose ratios has been documented when switching from hydromorphone to methadone. The dose ratio of parenteral hydromorphone to methadone is 0.17 in patients receiving a hydromorphone dose of up to 3 mg per day and 1.5 in patients on a dose of more than 300 mg per day (52) **[*ok?*]**. These dose ratios are based on studies of opioid rotation from morphine or hydromorphone to methadone. However, the dose ratio from methadone to morphine is unknown. One group reported their experience on switching methadone to another opioid and these rotations were associated with severe problems, preventing any meaningful calculation of dose ratios (53). Mercadante et al (54) found in a quasi randomized open label trial of oral morphine versus oral methadone in patients with cancer pain that the methadone starting dose was 2.5 times lower than morphine. Based on these theoretical equianalgesic dose ratios, it is hard to explain why four of our patients who were on a total daily dose of 120 mg of

oral morphine or equivalent before methadone would require between 15 mg and 30 mg daily of methadone. They should have required methadone in the dose range of 30 mg to 48 mg per day. Furthermore, it is interesting that there was no correlation between previous opioid doses and stable doses of methadone.

Therefore, the greater potency of methadone over other opioids cannot be explained solely by equianalgesic dose ratios. The special characteristics of methadone as an NMDA antagonist together with its monoaminergic properties may play a role here. Unfortunately, despite some evidence from animal studies that NMDA antagonism is relevant to the overall mechanism of action of methadone (55,56), it is not yet clear how important this property is in clinical practice. The advantages of methadone suggested by our study may be lost when patients have been exposed to opioids for prolonged periods, especially if the patients were receiving high doses of strong opioids (57).

The fact that almost all of our patients had complete pain relief (mean decrease of the pain score of 60 mm on VAS) with methadone is in contrast with the usual limited response seen in patients treated with opioids for their neuropathic pain (usual mean decrease of the pain score of 10 mm to 20 mm on VAS)(16,58,59). This is highly suggestive of efficacy and possibly superiority of methadone to other opioids in the treatment of neuropathic pain. However, due to the open-label nature of the study, no firm conclusions can be drawn.

The safety of methadone has been confirmed recently by a large retrospective study of 3954 inpatients who were treated with methadone orally and via the epidural route for severe pain (60). None of those patients who received methadone orally developed any serious side effects. Two studies looking at switching morphine to methadone in patients with cancer pain found that the side effects profile improved with the initiation of methadone (61,62). In our study we did not look at the changes of side effects with the switch and our patients only experienced mild symptoms easily controlled with proper medications or resolving quickly with time. It is also interesting to note that in both of these studies, a stable dose of methadone was reached within three to four days. Our study found a slightly longer time probably because most of our patients were followed up twice a week. Also, as most of our patients had their pain controlled with the starting dose or after only one increase of their initial doses, it is not surprising to find a median time to stable dose of six to seven days. The great majority of our patients did not need further increases of their methadone doses.

We think that our protocol is safe and provides rapid pain relief in this patient population. The use of methadone requires, as with most other drugs, a good understanding of drug interaction, especially as methadone is metabolized by the cytochrome P450 (19). The possibility of sudden death by 'Torsade de Pointes' is to be considered, because it has been described with high doses of methadone (63). The exact mechanism has not been elucidated and a direct causality between this syndrome and methadone has not been demonstrated. In vitro data suggest a direct action of methadone on the conductivity of the cardiac cells. Another possible mechanism could be the ability of methadone to slow down the heart rate. It is known that 'Torsade de Pointes' is rhythm dependent. The likelihood of this complication through this mechanism remains to be demonstrated in advanced cancer patients, as these patients very often suffer from autonomic nervous system dysfunction that include faster resting heart rate and decreased autonomic responses to various stresses (64,65). The five patients who died during the study experienced progressive physical deterioration followed by an expected death. In our study, the doses of methadone were lower than those encountered in the documented cases of 'Torsade de Pointes'.

This prospective clinical experience could not address the possible selection bias and observer bias as it is the case with all unblinded drug trials. Furthermore, while these results could be generalized to all cancer patients with neuropathic pain, this could not be so for patients with chronic nonmalignant pain, since our study population was mainly a cohort of cancer patients. It is known that there are important differences between the two groups such as disease progression and the likelihood of having mixed pain syndromes in cancer patients (8). Our population of cancer patients included patients at an early stage of their disease and excluded patients with mixed pain syndromes. In addition, our population was heterogeneous, comprising of patients with different types of neuropathic pain. However, this heterogeneity may suggest that methadone may be useful in different types of neuropathic pain.

These results are relevant given the limited therapeutic options that are available for the management of neuropathic pain and may provide primary data in suggesting the usefulness of methadone in neuropathic pain. While this clinical experience does not provide strong evidence to support the effectiveness of methadone in neuropathic pain, it provides useful information, especially on dosage, that may be used in further randomized controlled clinical trials. Such trials may compare the efficacy and safety of methadone with morphine or other opioids in the treatment of neuropathic pain. Those trials are also justified as methadone may have a favourable safety profile when compared with other opioids (19).

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