A Single-Center, Randomized, Double-Blind, Active, and Placebo-Controlled Study of KAI-1678, a Novel PKC-Epsilon Inhibitor, in the Treatment of Acute Postoperative Orthopedic Pain

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Brief summary of article: Nociceptive properties of protein kinase C (PKC) has been studied for nearly two decades. We found that KAI-1678—a novel inhibitor of epsilon PKC—was not an analgesic for patients with postoperative pain following total hip or total knee replacement surgery. However, a different PKC inhibitor may prove to be a safe and effective analgesic.

Abstract

Objective. KAI-1678, a novel inhibitor of the interaction of the epsilon isoform of protein kinase C (εPKC) with its intracellular receptor, has demonstrated activity in countering hyperalgesia in several models of pain. In this controlled randomized trial, KAI-1678 was tested for analgesic activity in an orthopedic acute postoperative pain setting.

Design. Following hip or knee replacement surgery, subjects were treated with KAI-1678, ketorolac, or saline. Subjects recorded their pain intensity on a visual analog scale and rated their quality of analgesia. The pain intensity differences between baseline and the evaluations were summed over the first 4 hours.

Results. The analysis revealed that, while ketorolac displayed good analgesic activity, KAI-1678 was not significantly different than placebo. Analgesia quality ratings similarly did not show a difference between KAI-1678 and placebo in this pain model. A small excess of infusion site erythema was seen with KAI-1678, but otherwise the drug was safe and well tolerated.

Conclusions. We investigated the safety and efficacy of a novel inhibitor of εPKC and provide clinical evidence that inhibition of εPKC with KAI-1678 is not effective in the treatment of acute postoperative orthopedic pain.

Key Words. KAI-1678; Acute Pain; Analgesic; Epsilon Protein Kinase C Inhibitor; Postoperative Orthopedic Pain

Introduction

Under treatment of acute pain is still widely acknowledged in the medical literature. Current therapies for the management of acute postoperative pain, including opioids and nonsteroidal anti-inflammatory drugs, can be limited by side effects and inadequate efficacy [1–3]. There is a
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need for novel therapeutics with unique mechanisms of action that provide effective pain relief with reduced side effects and that can be integrated into a multimodal approach to analgesia [2].

Inhibition of protein kinase C (PKC) may constitute a novel mechanism for achieving analgesia. Early work in isolated primary afferent neurons and isolated spinal cord preparations suggested that certain PKC isozymes may mediate or modulate pain. These studies showed that 1) PKC activation could depolarize unmyelinated afferent neurons [4,5], 2) PKC activators could sensitize afferent neurons [6], 3) PKC activators could enhance currents activated by noxious thermal stimuli in afferent neurons [7], and 4) PKC inhibitors could block sensitization in afferent neurons [8,9]. Although these studies generally did not attribute activity to a specific isozyme, the expression pattern of the epsilon isoform of PKC (εPKC) suggested it as a potential candidate. Specifically, εPKC has been identified in multiple neuronal systems involved in pain processing. This enzyme is found in primary afferent neurons that transmit nociceptive signals from the peripheral site of injury to the superficial dorsal horn [10], as well as in the brain, particularly in the cerebral cortex, cerebellum, and the hippocampus [11].

KAI-1678 is a novel peptide that competes with activated εPKC for binding to its isozyme-specific docking protein, thus preventing εPKC translocation. KAI-1678 contains the peptide sequence -EAVSLKPT- that has been shown to block εPKC translocation and reduce hyperalgesia in a variety of inflammatory and neuropathic pain models [10,12,13]. These studies suggested that KAI-1678 may represent a new therapeutic approach to the treatment of pain.

The study described herein was designed to test the analgesic activity of KAI-1678 in an orthopedic model of acute postoperative pain following total joint replacement. The results of the study are described.

Methods

Patients

Eligible patients were scheduled to undergo a total hip or knee replacement surgery. In addition, on the morning after surgery and following the discontinuation of patient-controlled analgesia for at least 30 minutes, patients must have had a minimum score of 40 mm on a 100-mm visual analog scale (VAS) pain assessment. Patients for whom the joint was being replaced for the second time were ineligible. All participants were required to understand the nature of the clinical trial and to provide written informed consent prior to participation. The study was approved by the Northern Y Regional Ethics Committee (Hamilton, New Zealand).

Study Design and Treatment Procedures

This was a phase 2, single-center, double-blind, randomized, placebo- and active comparator-controlled parallel group study evaluating 4-hour subcutaneous (SQ) infusions of KAI-1678 for the treatment of acute postoperative pain in subjects following total hip or total knee replacement surgery (ClinicalTrials.gov identifier: NCT01015235). A double-dummy design was used with each subject receiving both an SQ infusion (KAI-1678 or saline) and an intravenous (IV) injection (ketorolac or saline) during the treatment period to ensure blinding.

KAI-1678 (30-mg dose) or saline placebo was administered by SQ infusion in the anterior abdominal region over 4 hours. Therefore, for KAI-1678 administration, the rate was 0.12 mg/kg/hour assuming a 65-kg subject. This dose rate of 7.5 mg/hour was the highest tolerated dose rate based on the data from phase 1 studies and was expected to result in plasma drug concentrations exceeding 45 ng/mL, i.e., the lowest plasma drug concentration associated with maximal efficacy in animal models. All infusions were to be administered at a rate of 1 mL/hour.

Ketorolac (active control) or saline placebo was administered by IV bolus injection at the start of the treatment period immediately after the start of the SQ infusion. The ketorolac dose was 30 mg, and an equal volume of saline was administered as placebo.

The treatment groups were: KAI-1678 (KAI-1678 SQ infusion plus saline IV bolus), Ketorolac (saline SQ infusion plus ketorolac IV bolus), and Placebo (saline SQ infusion plus saline IV bolus).

The planned enrollment was 110 subjects. Randomization was stratified based on surgical procedure (total hip vs total knee replacement). Subjects were randomized 2:2:1 to KAI-1678, Placebo, or Ketorolac, respectively.

As described earlier, eligible subjects had a score of at least 40 mm on a 100-mm VAS on the morning following the surgical procedure (postoperative day one) occurring at least 30 minutes after discontinuation of patient-controlled analgesia prior to commencing treatment. If epidural, spinal, or regional local anesthetics were used intraoperatively, complete resolution of local anesthesia was documented prior to commencing treatment. Pain intensity and pain relief were documented during the 4-hour SC infusions and for an additional 4 hours after the end of infusion in subjects who completed the 4-hour study drug infusion. Subjects whose infusions were stopped early were monitored for safety.

Per protocol, if the study medication did not provide adequate pain relief for the subject, rescue analgesics medication could be administered by the site investigator (in accordance with the usual medical practice). All subjects who received rescue medication were followed for safety.

Adverse events were monitored through 24 hours after the start of study drug infusion. Serious adverse events were collected through 30 days posttreatment.
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Assessments

Subjects recorded their pain intensity pretreatment and at the following time points during the 8-hour period commencing with the start of treatment: at 0.5, 1, 1.5, 2, 3, 4, 6, and 8 hours. If rescue medication was administered prior to the end of the 4-hour SC infusion, the time was noted, and the end-of-infusion pain intensity and global quality of analgesia assessments were performed.

Pain was assessed up to 4 hours following the end of infusion of study drug using a 100-mm VAS, with anchor labels of "no pain" at 0 mm and "worst pain" at 100 mm. The pain intensity difference (PID) was calculated by subtracting the pain intensity scores at each evaluation from the baseline scores, where the baseline score was the pain intensity rating made prior to the first dose of study medication. The summed PID was calculated and analyzed at 4 hours (summed PID over 4 hours or SPID4) by adding the individual weighted PID scores occurring within this interval. The weight assigned to each PID for the SPID4 score was proportional to the elapsed time in hours since the previous evaluation (the sum of the PID scores multiplied by the interval between ratings over 4 hours).

The quality of analgesia was assessed at the end of the SC infusion using a five-point verbal scale (1 = poor, 2 = fair, 3 = good, 4 = very good, 5 = excellent).

Statistical Analyses

The primary endpoint was SPID4 between placebo- and KAI-1678-treated subjects assessed with a 100-mm VAS (0 = no pain and 100 = worst possible pain). A sample size of 44 in each group was estimated to have 70% power to detect an effect size of 0.48 (calculated as the difference between the expected placebo mean of 33 mm and the expected KAI-1678 mean of 71 mm, divided by the common standard deviation of 80 mm) or an absolute difference in means of 38 mm, using a two-group t-test with a 0.05 one-sided significance level [14].

Additional endpoints included pain intensity over time, the difference between groups in pain intensity over time, and global quality of analgesia.

Two populations were defined for this study: the modified intent-to-treat (MITT) population and the evaluable population. The MITT population consisted of all subjects who were randomized and received any amount of study medication. Safety analyses were also performed on the MITT population. Randomized subjects who received study drug (i.e., KAI-1678 or placebo) for at least 30 minutes without technical problems (e.g., infusion interruption for pump failure) and had a baseline pain intensity score with at least one valid (i.e., subject did not receive rescue analgesics) postbaseline pain intensity score comprised the evaluable population. Missing data were handled using the last observation carried forward method. Efficacy analyses were performed on the evaluable population.

The difference in SPID4 and PID at the end of infusion was analyzed using analysis of covariance (ANCOVA) model, with treatment as an effect and baseline pain intensity as the covariate.

An interim analysis was predefined in the statistical analysis plan to be performed after 72 subjects had been enrolled, which was performed. The results of the interim analysis were then used to make decisions regarding continuing enrollment in the study.

Results

Patient Characteristics

Subjects were enrolled in this study between November 2008 and December 2009. A protocol-specified interim analysis was performed in November 2009. Based on the results of this analysis, it was determined that the enrollment of 110 subjects was unnecessary to meet the study objectives. Therefore, enrollment was terminated after the 90 subjects were enrolled.

All 90 enrolled subjects were randomized following total joint replacement surgery: 37 subjects were allocated to the KAI-1678 Group, 17 subjects were allocated to the Ketorolac Group, and 36 subjects were allocated to the Placebo Group. The results of the enrollment and disposition are described in Figure 1 and Table 1. Infusion of study drug was initiated in all subjects in each group. One Placebo subject was not evaluable because this subject received rescue medication prior to the first posttreatment efficacy assessment at hour 0.5. All other subjects were included in the evaluable population. All subjects completed the 24-hour follow-up period, and all 90 subjects were contacted at 30 days posttreatment per the study protocol.

Demographic characteristics were similar across the three treatment groups with the exception of gender (Table 2). A higher proportion of subjects in the Ketorolac Group were female (76.5%) compared with the KAI-1678 Group (32.4%) and the Placebo Group (22.2%); however, it is unclear that this imbalance would have a meaningful effect on study outcomes. There were no differences observed between groups in mean age, body mass index, baseline pain intensity, or the proportion of subjects undergoing hip replacement vs knee replacement. The average number of hours from the end of surgery to the start of treatment was <24 hours and was similar across groups.

Interventions

SPID4 was the primary endpoint in this trial. As shown in Table 3, the mean SPID4 for the KAI-1678, Placebo, and Ketorolac subjects were 34.7 ± 96.8, 33.0 ± 86.0, and 144.2 ± 62.9, respectively. The difference between the KAI-1678 and Placebo subjects was not significant (P = 0.924, ANCOVA analysis; Table 2). Although not part of the primary endpoint, the difference in mean SPID4 between the Ketorolac- and Placebo-treated subjects was significant (P < 0.0001).
Mean pain intensity (PI) scores, as measured by the VAS scale, over the 8-hour observation period are shown in Figure 2. The mean KAI-1678 and Placebo scores were similar throughout the 8-hour period. In contrast, the mean Ketorolac pain intensity scores were significantly lower than the Placebo and KAI-1678 Groups at the first time point (hour 0.5), and remained significantly lower for the duration of the 8-hour period.

Figure 1 Subject enrollment and disposition. The number of subjects enrolled, randomized, and their treatment group allocation are shown. The disposition of subjects at follow-up and analysis is described. MITT = modified intent-to-treat.
Mean PID scores over the 8-hour treatment period are shown in Figure 3. Mean PID scores for the KAI-1678 and the Placebo Groups were similar and were generally less than 10 mm, whereas the mean PID for the Ketorolac Group was significantly higher than both the KAI-1678 and Placebo Groups at all time points.

Global quality of analgesia was assessed at the end of study drug infusion, regardless of when the infusion was terminated. The proportion of subjects reporting good, very good, or excellent analgesia was 23%, 38%, or 88% for Placebo, KAI-1678, and Ketorolac subjects, respectively (Figure 4). Consistent with the lack of efficacy demonstrated on the primary endpoint, the proportion of subjects requiring rescue medication was similar between subjects in the Placebo and KAI-1678 Groups, and significantly higher than observed in the Ketorolac Group.

Plasma concentrations of KAI-1678 were assessed at the end of the SC infusion, regardless of when the infusion was terminated. All KAI-1678-treated subjects had detectable KAI-1678 in their plasma, with concentrations consistent with pharmacokinetic simulations based on prior phase 1 SC infusion studies (data not shown). Mean KAI-1678 plasma concentration at the end of infusion was 115 ng/mL, well in excess of plasma concentration of KAI-1678 associated with efficacy in preclinical models (data not shown), suggesting that the lack of efficacy observed in this study with KAI-1678 was not related to inadequate systemic exposure.

Adverse Events

KAI-1678 was well tolerated in this study. Treatment-emergent adverse events (TEAEs) are presented in Table 4. In the KAI-1678 treatment Group, 70% subjects experienced at least one AE, while in the Ketorolac and Placebo Groups 53% and 61% of subjects experienced at least one AE, respectively. This was primarily attributable to infusion site erythema in the KAI-1678 Group, which was reported by 10 subjects (27%) compared with 1 subject (6%) in the Ketorolac Group and no subjects in the Placebo Group. This was the main difference in safety observed through TEAEs for KAI-1678 vs the other groups.

The severity of the AEs across the three treatment groups was similar and was predominantly mild. During the study, no subjects experienced severe or maximal/life-threatening TEAEs. Four subjects in the KAI-1678 Group

### Table 1  Subject disposition

|                        | KAI-1678 (N = 37) | Ketorolac (N = 17) | Placebo (N = 36) |
|------------------------|-------------------|--------------------|-----------------|
| Infusion completed      |                   |                    |                 |
|                        | Yes               | No                 |                 |
| Reason for infusion     |                   |                    |                 |
| stopped early           |                   |                    |                 |
| Adverse event           | 0                 | 0                  | 0               |
| Rescue medication used  | 21/37 (56.8%)     | 2/17 (11.8%)       | 26/36 (72.2%)   |
| Median duration of infusion (minutes) | 124               | 240                | 103             |

Mean PID scores over the 8-hour treatment period are shown in Figure 3. Mean PID scores for the KAI-1678 and the Placebo Groups were similar and were generally less than 10 mm, whereas the mean PID for the Ketorolac Group was significantly higher than both the KAI-1678 and Placebo Groups at all time points.

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### Table 2  Demographics and baseline clinical characteristics

|                        | KAI-1678 (N = 37) | Ketorolac (N = 17) | Placebo (N = 36) |
|------------------------|-------------------|--------------------|-----------------|
| Mean age, years (SD)   | 59.7 (8.66)       | 63.35 (8.04)       | 61.58 (9.96)    |
| Sex                    |                   |                    |                 |
| Male                   | 25/37 (67.6%)     | 4/17 (23.5%)       | 28/36 (77.8%)   |
| Female                 | 12/37 (32.4%)     | 13/17 (76.5%)      | 8/36 (22.2%)    |
| Mean baseline body mass index, kg/m² (SD) | 29.76 (4.49) | 31.05 (5.57) | 29.9 (4.32) |
| Surgery type           |                   |                    |                 |
| Total hip replacement  | 21/37 (56.8%)     | 10/17 (58.8%)      | 20/36 (55.6%)   |
| Total knee replacement | 16/37 (43.2%)     | 7/17 (41.2%)       | 16/36 (44.4%)   |
| Mean time from end of surgery to start of infusion, hours (SD) | 20.4 (2.29) | 21 (2.91) | 20.3 (2.16) |
| Mean baseline pain intensity, mm (SD) | 51.1 (9.29) | 51.7 (12.55) | 52 (13.49) |

SD = standard deviation.
and three subjects in the Placebo Group experienced at least one serious adverse event (SAE) during the study. There were no SAEs in the Ketorolac Group. None of the SAEs was considered related to the study drug, whether KAI-1678 or placebo. All SAEs were of moderate severity, except one, which was considered mild.

The SAEs in the KAI-1678 Group included two subjects with wound infections and one subject with postprocedure hip pain. These events were considered procedure related. Other SAEs in this group included tachycardia and syncope occurring concurrently in one subject 17 days postprocedure, and bronchitis secondary to postoperative atelectasis that occurred in the fourth KAI-1678 subject.

**Table 3**  Primary endpoint—summed pain intensity difference at 4 hours in the evaluable population

| Treatment Group | SPID4       | P Value   |
|-----------------|-------------|-----------|
| KAI-1678        | 34.7 ± 96.8 | 0.924*    |
| Ketorolac       | 144.2 ± 62.9| <0.0001   |
| Placebo         | 33.0 ± 86.0 |           |

* P value for linear contrasts of KAI-1678 Group vs Placebo Group.

SPID4 = summed pain intensity difference over 4 hours.

**Figure 2** Pain intensity over 8 hours. The mean pain intensity for each group at each evaluation (±standard error of the mean [SEM]) is shown. The dependent variable is the position on the visual analog scale (VAS) in millimeters; the independent variable is the time of evaluation.

**Figure 3** Pain intensity difference (PID) over 8 hours. The mean PID for each group at each evaluation (±standard error of the mean [SEM]) is shown. The dependent variable is the position on the visual analog scale (VAS) in millimeters; the independent variable is the time of evaluation.
The SAEs in the Placebo Group included a left knee joint hematoma in one subject and wound infection in the right hip with cellulitis in another subject. These SAEs were considered procedure related. The third SAE in this group was thrombus formation in the peroneal vein, which responded to thrombolysis therapy.

Discussion

In this study, a 4-hour SC infusion of KAI-1678, a novel peptide inhibitor of ePKC, did not have obvious analgesic efficacy in subjects with moderate to severe postoperative orthopedic pain following total hip or total knee replacement surgery. This was assessed by evaluating pain scores over time, global quality of analgesia at the end of the treatment, and by the proportion of subjects requiring rescue medication. In contrast, the active treatment, 30 mg ketorolac administered by IV bolus, provided robust analgesic responses, indicating that the study design used was able to detect an analgesic effect had it occurred with KAI-1678.

Initially, enrollment was planned for 110 subjects to achieve demonstration of the endpoint. An interim analysis was designed into the trial to allow assessment of the success or failure against the primary endpoint prior to complete enrollment. This planned analysis revealed that the primary endpoint demonstrating superiority of KAI-1678 over placebo for analgesia in this setting would not be achieved; therefore, enrollment was capped at 90 subjects.

All the enrolled subjects had the respective surgeries, initiated infusions of study drug, completed the 24-hour

| Number of subjects (%) fulfilling the following parameters | KAI-1678 (N = 37) | Ketorolac (N = 17) | Placebo (N = 36) |
|-----------------------------------------------------------|-------------------|-------------------|-----------------|
| At least one TEAE (%)                                     | 26 (70%)          | 9 (53%)           | 22 (61%)        |
| At least two TEAEs (%)                                    | 16 (43%)          | 5 (29%)           | 8 (22%)         |
| TEAEs caused by study drug                                | 17 (46%)          | 5 (29%)           | 9 (25%)         |
| Severe or maximal/life-threatening TEAEs                   | 0                 | 0                 | 0               |
| At least one serious TEAE                                 | 4 (11%)           | 0                 | 3 (8%)          |

TABLE 4  Adverse event summary

TEAE = treatment emergent adverse events.
follow-up, and were contacted 30 days posttreatment per protocol. Only one subject in the Placebo Group was ineligible for the evaluable population because the subject received rescue medication prior to the first posttreatment efficacy assessment at hour 0.5. No subjects were lost to follow-up, and there were no protocol deviations that would influence the outcome of the trial.

The dose evaluated in this study (30 mg KAI-1678 administered at a rate of 7.5 mg/hour) was selected based on data from phase 1 studies, and as expected the plasma concentrations of KAI-1678 at the end of the infusion exceeded the plasma concentrations associated with maximal efficacy in the preclinical pain models, thus indicating that the selected dose of KAI-1678 provided adequate exposure to produce analgesia based on the preclinical models. Most subjects who withdrew from the study for lack of efficacy did so after more than 60 minutes of treatment, providing sufficient time for a clinical response to acute pain had it occurred.

Analysis of AEs that were reported in this study revealed that KAI-1678 was generally well tolerated and safe. There was an excess of infusion site erythema in the KAI-1678 Group relative to the Ketorolac and Placebo Groups, but these events were all mild in intensity, did not lead to discontinuation of study medication, and resolved without intervention. Otherwise, the type and severity of AEs seen with KAI-1678 were similar to those recorded for ketorolac-treated and placebo-treated subjects.

There were six SAEs in the KAI-1678 group vs three in the Placebo Group and none in the Ketorolac Group; however, all were judged to be unrelated to the study drug. There were no severe or life-threatening AEs in this study.

Several aspects of the study may limit the interpretations that can be drawn from it. First, we assessed the effect of KAI-1678 at a single dose rate over a short time frame of 4 hours in patients with acute postsurgical orthopedic pain. It is possible that longer treatment periods may be required for ePKC inhibition to demonstrate clinical analgesic activity, despite the apparent rapid onset of action in preclinical models. However, this is not practical in an acute pain setting, but longer treatment periods are feasible in chronic pain models. Second, in addition to the short time frame chosen, postsurgical orthopedic pain may not be the optimal model for ePKC inhibition to demonstrate clinical analgesic activity, as suggested by some nonclinical studies. It is possible that chronic or neuropathic pain models may allow a better model for demonstration of an analgesic effect. Thus, we cannot exclude the possibility that KAI-1678 may be analgesic in chronic pain. Third, we were unable to develop an assay to directly assess if KAI-1678 inhibited the activity of ePKC. In preclinical studies, KAI-1678 was shown to block the translocation of ePKC and to reduce pain responses. The ePKC amino acid sequence that is mimicked in KAI-1678 is identical in rat and human, suggesting that similar pharmacology should occur in both species. Finally, as mentioned earlier, numerous preclinical studies have suggested a role for ePKC in inflammatory (e.g., carrageenan and acetic acid) and neuropathic (e.g., alcohol and chemotherapy) pain models [12,15,16]. In these studies, local injection of peptide inhibitors of ePKC at or near the site of injury resulted in rapid improvements in pain responses. Consistent with these results, SC infusion of KAI-1678 in the carrageenan model resulted in rapid reversal of pain responses [17]. However, the failure to demonstrate clinical benefit with KAI-1678 in this study may reflect the limitations of these preclinical models to predict human pain responses.

Conclusions

The study results showed activity for the active comparator, ketorolac, similar to that previously reported. Therefore, the study was able to accurately detect analgesic activity if the test compound possesses it. However, KAI-1678 did not display analgesic activity in this pain model. The safety profile of KAI-1678 revealed that the compound is safe and well tolerated.

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