Multicentre evaluation of the adenosine agonist GR79236X in patients with dental pain after third molar extraction

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Background. Adenosine is analgesic in humans, and the selective adenosine A1 receptor agonist GR79236X has significant anti-nociceptive activity in an animal pain model of inflammatory pain.

Methods. Seventy-nine patients with moderate pain after third molar extraction under general anaesthesia were randomized to receive a 15 min double-blind infusion containing either GR79236X 4 μg kg⁻¹, GR79236X 10 μg kg⁻¹, diclofenac 50 mg, or saline placebo. Rescue analgesia was promptly available to all patients.

Results. Meaningful pain relief (mild or no pain) was attained by 9 (47%) patients in the placebo group, 12 (63%) patients in the GR79236 4 μg kg⁻¹ group, 10 (48%) patients in the 10 μg kg⁻¹ group, and 16 (80%) patients in the diclofenac 50 mg group. Neither dose of GR79236 produced a significant improvement over placebo, but diclofenac was superior to both placebo (P = 0.036) and GR79236 10 μg kg⁻¹ (P = 0.034). Median times to rescue or additional analgesia were 62, 100, 60, and 363 min for patients receiving placebo, GR79236 4 μg kg⁻¹, 10 μg kg⁻¹, and diclofenac 50 mg, respectively (diclofenac significantly longer than placebo, P = 0.002 log-rank test). Pain control was poor in the placebo group and in both GR79236 groups, with between 79 and 86% of patients having good pain control (i.e. mild or no pain) for <20% of the time compared with only 30% of patients who received diclofenac.

Conclusion. We found no evidence of efficacy of GR79236 compared with placebo, but the active control diclofenac was effective. It is possible that a higher dose of GR79236 might have been effective or that i.v. administration of this drug does not achieve appropriate concentrations in the brain or peripheral nerves.

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The removal of impacted third molars is a common surgical procedure, which often results in significant postoperative pain, buccal swelling, and trismus. The majority of patients require analgesics to relieve or decrease the intensity of pain, which is most severe in the first 12 h and reaches a maximum between 3 and 8 h after surgery. The factors contributing to this pain are complex, but may be related to the inflammatory process initiated by surgical trauma.

A number of analgesic drugs have been evaluated extensively to alleviate postoperative pain after third molar surgery. Salicylates and paracetamol, particularly when combined with a centrally acting analgesic, produce good dose-related analgesia in these patients. However, the most efficacious and widely prescribed compounds for the treatment of pain after dento-alveolar surgery are non-steroidal anti-inflammatory drugs (NSAIDs).
Adenosine has been shown to be analgesic in humans and, therefore, compounds with agonist activity at the adenosine receptors may have analgesic efficacy. An early selective and orally active adenosine A1 receptor agonist, 6-cyclohexyl-2′-O-methyl-adenosine (SDZ WAG 994) was effective in animal pain models, but not in humans. However, human exposure was limited to a lower dose (1 mg) than had been efficacious in rats (≥30 μg kg⁻¹), because of adverse events including headache, dizziness, fatigue, somnolence, dyspnoea, and chest pain when a 2 mg dose was used.³

The selective adenosine A1 receptor agonist N-[1S, trans]-2-hydroxycyclopentyl]adenosine, GR79236X, has significant anti-nociceptive activity in an animal pain model of inflammatory pain and has anti-inflammatory activity.⁵ Therefore, dental pain is an appropriate model to test the hypothesis that GR79236X has acute, short-term analgesic efficacy. GR79236X was well tolerated by volunteers and by patients undergoing cardiac surgery.⁶

This study was designed to evaluate the analgesic efficacy of GR79236X in the dental pain model (primarily inflammatory pain state), which has been found to be a robust model for the evaluation of NSAIDs relieving post-extraction pain. The primary objective of this study was to compare the proportion of patients with meaningful pain relief by 8 h for two doses of GR79236X with placebo.

### Methods

This multicentre, randomized, double-blind, placebo-controlled, parallel group study compared single i.v. dose of GR79236X (4 μg kg⁻¹ and 10 μg kg⁻¹) with placebo. A diclofenac group (50 mg) was used as an active control for the study. The protocol and informed consent form were approved by the local Ethics Committees. All patients gave written informed consent before participation.

Patients, male or female, aged 18–45, requiring removal of one or more third molar teeth under general anaesthesia were eligible for the study. Patients were required to be within 30% of their ideal body weight and classified as ASA I or II. Women of child bearing potential were required to have a negative pregnancy test immediately before study entry. Exclusion criteria included history or presence of organ disease or mental illness, drug or alcohol abuse, or contraindication to NSAIDs. In addition, exposure to analgesics (NSAIDs and aspirin) and psychoactive drugs (including sleeping preparations) within 48 h before surgery, or exposure to caffeine (including caffeine-containing food and beverages) within 8 h before surgery was prohibited.

No premedication was given. After application of standard monitoring, anaesthesia was induced with propofol and fentanyl 200 μg and maintained with isoflurane (as required) and nitrous oxide 66% in oxygen. Nasotracheal intubation was facilitated by a neuromuscular blocking agent and reversed, if necessary, with neostigmine 2.5 mg and glycopyrronium 1 mg.

In the postoperative period, patients notified the study nurse if they began to feel pain and rated their pain using the pain verbal rating scale (VRS) (Table 1). Patients who experienced moderate pain were randomized into one of four treatment groups and received a 15 min infusion containing either GR79236X 4 μg kg⁻¹, GR79236X 10 μg kg⁻¹, diclofenac 50 mg, or saline placebo in a volume of 1 ml kg⁻¹. The treatment allocation was determined by a computer-generated randomization schedule and drug administration was double-blinded with all study infusions prepared in the pharmacy. Patients not achieving minimum pain criteria of moderate pain on the VRS by 3 h after surgery were not randomized into the study.

Rescue medication (i.v. morphine in 5 mg increments) was immediately available to patients for first rescue (i.e. if the patient had failed to attain meaningful pain relief). In addition, further analgesia was made available to any patient who requested it at any time during the study. Patients could withdraw from the study for any reason or could be withdrawn from the study by the investigator at any time.

Pain assessments were recorded using the pain VRS and the pain visual analogue scale (VAS; Table 1) immediately before and at 15, 30, and 45 min and 1, 1.5, 2, 3, 4, 6, and 8 h after the start of the 15 min infusion, and at discharge. In addition, immediately after study drug administration, patients were given two stopwatches, which were started simultaneously by the investigator. The patient was instructed to stop one timer when ‘perceptible pain relief’ was achieved and the other timer when ‘meaningful pain relief’ was achieved.

The time to first additional analgesic medication was recorded together with a pain assessment at that time. Subsequent analgesic medication was also recorded. Safety was assessed by recording vital signs, 12-lead ECG, clinical laboratory tests (haematology and clinical chemistry), and spontaneous reporting of adverse events.

Data were recorded on a trials database with appropriate validation procedures.

### Table 1 Efficacy assessments and outcome measures

<table>
<thead>
<tr>
<th>Efficacy assessments</th>
<th>Outcome measures</th>
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<tbody>
<tr>
<td>Pain VRS. Patients were asked to respond to the question ‘What is the intensity of your pain?’ with one of the following responses: none (0), mild (1), moderate (2), severe (3), and intolerable (4)</td>
<td></td>
</tr>
<tr>
<td>Visual analogue scale. A 100 mm ungraded line ranging from ‘no pain’ to ‘worst pain imaginable’</td>
<td></td>
</tr>
<tr>
<td>Time to maximum effect measured as the time to minimum pain score on the VAS before additional analgesic use during the first 8 h after dosing</td>
<td></td>
</tr>
<tr>
<td>Time to onset of ‘perceptible pain relief’</td>
<td></td>
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<tr>
<td>Time to onset of ‘meaningful pain relief’</td>
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</table>
A total of 128 patients were to be randomized with the intention of achieving 28 evaluable patients in each treatment group, giving a power of 87% to detect an increase from 30% (placebo group) to 70% of patients with meaningful pain relief (a score of 0 or 1 on the pain VRS, Table 1) by 8 h using two-sided significance tests at the 5% level.

All patients randomized to the study drug and who received the dose were included in the efficacy and safety analysis. Patients who withdrew from the study prematurely had their missing data imputed using the ‘last observation carried forward’ principle.

All significance tests and confidence intervals were two sided. The proportions of patients achieving meaningful pain relief were compared using Mantel–Haensel $\chi^2$ tests. Weighted mean pain intensity differences\textsuperscript{7} were subjected to analysis of covariance (ANCOVA) using the baseline score as a covariate. Treatment groups were compared using $t$-tests from the ANCOVA model. Survival times (for duration of effect), and times to onset of effect were compared using Kaplan–Meier life-table estimates and log-rank tests.

Results

Owing to slow recruitment, the planned number of patients was not achieved. A total of 95 patients were screened; of whom, 79 were randomized to receive the study drug: 19 received placebo; 19 received GR79236 4 $\mu$g kg$^{-1}$; 21 received GR79236 10 $\mu$g kg$^{-1}$, and 20 received diclofenac 50 mg (Table 2). Patients and surgery were comparable across the four groups (Table 3). None of the patients recruited had chronic pain conditions, and none were taking either amitriptiline or gabapentin. In total, three patients withdrew from the study after receiving study medication (placebo). One patient withdrew consent and two patients discharged themselves from hospital at the 6-h assessment.

Meaningful pain relief (i.e. mild or no pain) was attained by 9 (47%) patients in the placebo group, 12 (63%) in the GR79236 4 $\mu$g kg$^{-1}$ group, 10 (48%) in the 10 $\mu$g kg$^{-1}$ group, and 16 (80%) in the diclofenac 50 mg group (Fig. 1). Neither dose of GR79236 produced a significant improvement over placebo, but diclofenac was superior to both placebo ($P = 0.036$) and GR79236 10 $\mu$g kg$^{-1}$ ($P = 0.034$).

The median times to rescue or additional analgesia were 62, 100, 60, and 363 min for patients receiving placebo, GR79236 4 $\mu$g kg$^{-1}$, GR79236 10 $\mu$g kg$^{-1}$, and diclofenac 50 mg, respectively. This was significant for diclofenac over placebo, $P = 0.002$, log-rank test.

Pain control was poor [i.e. having good pain control (mild or no pain) for >20% of the time] in the placebo and both GR79236 groups, with between 79 and 86% of patients compared with only 30% of patients who received diclofenac.

The median times to onset of ‘perceptible pain relief’ were 18, 14, 10, and 8 min for patients receiving placebo, GR79236 4 $\mu$g kg$^{-1}$, 10 $\mu$g kg$^{-1}$, and diclofenac 50 mg, respectively. Onset was quicker with diclofenac than with placebo, $P = 0.002$, log-rank test.

VAS scores are presented graphically using last observation carried forward in Figure 2. After calculation of weighted mean change from baseline, the estimated

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<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo</th>
<th>GR79236 4 $\mu$g kg$^{-1}$</th>
<th>GR79236 10 $\mu$g kg$^{-1}$</th>
<th>Diclofenac 50 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation (randomized to treatment), $n = 79$</td>
<td>19</td>
<td>19</td>
<td>21</td>
<td>20</td>
</tr>
<tr>
<td>Allocated to intervention</td>
<td>19</td>
<td>19</td>
<td>21</td>
<td>20</td>
</tr>
<tr>
<td>Received allocated intervention</td>
<td>16</td>
<td>19</td>
<td>21</td>
<td>20</td>
</tr>
<tr>
<td>Did not receive allocated intervention</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Reasons</td>
<td>Prematurely discontinued</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Follow-up</td>
<td>19</td>
<td>19</td>
<td>21</td>
<td>20</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Analysis</td>
<td>Analysed</td>
<td>19</td>
<td>19</td>
<td>21</td>
</tr>
<tr>
<td>Not analysed</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
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</table>
treatment effects relative to placebo were 0.1 \((-11.8-12.0)\) and 5.9 \((-15.1-8.6)\) mm for GR79236 4 µg kg\(^{-1}\) and 10 µg kg\(^{-1}\), and 18 \(6.3-29.8\) mm for diclofenac 50 mg, mean (95% confidence interval). Diclofenac was significantly more effective than placebo, \(P=0.003\).

Haematology and clinical chemistry, ECG measurements, and vital signs were comparable across treatment groups. No persistent or unexpected adverse events were reported. Adverse events were typical of a post-anaesthesia patient population and included nausea, vomiting, headache, dizziness, and drowsiness with no substantial between group differences. The most common adverse events were headache in 2 (11%), 3 (16%), 0, 3 (15%), and ‘nausea and vomiting’ in 1 (5%), 0, 1 (5%), 2 (10%) of placebo, GR79236 4 µg kg\(^{-1}\), GR79236 10 µg kg\(^{-1}\), and diclofenac recipients, respectively.

**Discussion**

The primary objective of this study was to evaluate the effect of GR79236 at two doses in achieving meaningful pain relief at or before 8 h after treatment. We have not shown any significant analgesia with either dose of GR79236. For example, neither dose showed a significant improvement over placebo with respect to meaningful pain relief, whereas diclofenac was significantly better than placebo (\(P=0.036\)). The lower dose of GR79236 was associated with a non-significantly larger percentage of patients with analgesia, but other measures suggest that this does not indicate a significant analgesic effect. For example, pain control was poor in the placebo and both GR79236 groups; 79–86% of these patients reported good pain control (defined as mild or no pain) for <20% of the time compared with only 30% of patients who received diclofenac. We have been unable for find any evidence in
the literature suggesting a bell-shaped analgesic response curve for adenosine agonists.

Our study was terminated before we recruited the planned number of patients described in our statistical power calculation (eight to nine patients less in each group). This raises issues with respect to the negative findings of our study. However, the data in our primary outcome measure clearly show that only diclofenac was significantly superior to placebo \( (P = 0.036) \), and that diclofenac was significantly superior to the highest dose of GR79236 \( (P = 0.034) \). The confidence intervals of the mean change from baseline in the VAS scores confirm that we did not miss any clinically significant differences in pain relief (20 mm on the VAS scale) compared with placebo; the confidence intervals for the difference were \(-11.8 \text{ to } -12.0 \text{ mm for GR79236} \, 4 \mu \text{g kg}^{-1}\), and \(-15.1 \text{ to } -8.6 \text{ mm for GR79236} \, 10 \mu \text{g kg}^{-1}\).

Studies of analgesia may be confounded by treatment effects. Our double-blind design with an active control demonstrated both the power of placebo and the efficacy of diclofenac (Figs 1 and 2). We can therefore be confident that the study drug lacked efficacy, in this pain model, at the doses tested. The higher dose of GR79236 was selected, because it had been well tolerated in earlier studies\(^6\)\(^8\) and this was confirmed in our patients. It is possible that a higher dose of GR79236 might have been effective, but safety data were not available to support such a dose.

As yet, early work on the analgesic effects of adenosine and its agonists has not led to agents with proven, reliable efficacy in humans. It may be that because the likely site of action is spinal, i.v. administration fails to deliver the drug in sufficient concentrations. For example, a double-blind, cross-over study investigating the effect of i.v. and intrathecal adenosine 2 mg in patients with neuropathic pain showed that only intrathecal administration reduced allodynia and hyperalgesia; i.v. injection was ineffective.\(^9\)

It is generally accepted that adenosine plays a significant role in the modulation of the nociceptive pathways.\(^10\) Our study investigated the efficacy of an adenosine A1 receptor agonist. Three more types of adenosine receptors have been described and cloned (i.e. A2A, A2B, and A3).\(^11\)\(^12\) A recent study has elucidated the role of A1, A2A, and A3 receptors in spinal nociceptive transmission in the rat formalin model.\(^13\) The investigators described responses in the early (up to 10 min) and late (10–60 min) stages of the formalin test. The data suggest that all three receptors were involved in the modulation of pain transmission, but A1 and A3 receptors suppressed only the late stage response. Our A1 agonist may not have penetrated the central nervous system sufficiently to have an effect; in addition, if an early and late response occurs in man, it might be that failure to modulate the early response in our model was another factor. However, this remains speculative. When adenosine was infused during gynaecological surgery\(^2\) at an average dose of 161 mg kg\(^{-1}\) min\(^{-1}\) for 171 min, intraoperative analgesia was equivalent to remifentanil 0.2 mg kg\(^{-1}\) min\(^{-1}\), and postoperative morphine consumption was lower. However, both heart rate and systolic arterial pressure were decreased in patients receiving adenosine. The 2129 mg average total dose of adenosine required in this study was enormous, and at current UK cost (£4.63 for 6 mg) would have averaged £1643 per patient. Thus, a combination of cost and concern about haemodynamic disturbance are likely to prevent further development of adenosine as an analgesic. Whether alternative selective agonists may be usefully efficacious remains unclear.

We found no evidence of efficacy of GR79236 compared with placebo, but the active control diclofenac was effective. Similar findings emerged from the analyses of secondary endpoints: changes in pain intensity, duration of effect, and onset of pain relief.

Acknowledgement

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References

8 Kelion AD, Webb TR, Gardner MA, Ormerod OJ, Shepherd GL, Banning AP. Does a selective adenosine A(1) receptor agonist protect against exercise induced ischaemia in patients with coronary artery disease? Heart 2002; 87: 115–20
10 Sawynok J. Adenosine receptor activation and nociception. Eur J Pharmacol 1998; 347: 1–11
11 Klotz KN. Adenosine receptors and their ligands. Naunyn Schmiedebergs Arch Pharmacol 2000; 362: 382–91