Analgesic effect of adenosine on ischaemic pain in human volunteers

C. P. Rae, M. D. Mansfield, C. Dryden and J. Kinsella

University Department of Anaesthesia, Glasgow Royal Infirmary University NHS Trust, 8–16 Alexandra Parade, Glasgow G31 2ER, UK

Present addresses: 1Department of Anaesthesia, Western Infirmary, Dumbarton Road, Glasgow G11 6NT, UK. 2Department of Anaesthesia, Ipswich Hospital NHS Trust, Heath Road, Ipswich IP4 5PD, UK. 3Department of Anaesthesia, Royal Liverpool Hospitals NHS Trust, Alder Hey, Eaton Road, Liverpool L12 2AP, UK

This study was designed to measure ischaemic pain during and after infusion of adenosine. In a double-blind, placebo-controlled, crossover study, eight ASA I male volunteers received infusion of adenosine 100 µg kg⁻¹ min⁻¹ or placebo for 10 min. This was repeated 1 week later with the alternate infusion. Pain measurements were made during tourniquet-induced ischaemia in an exercising arm before infusion, during infusion and for 24 h afterwards. Pain was reduced significantly in the adenosine group compared with the saline group during infusion (median difference 20.8; 95% confidence interval 2.0–40). There was no significant difference in pain after infusion and there were no significant changes in cardiovascular variables. During infusion of adenosine, transient mild chest discomfort, shortness of breath and facial flushing occurred. We conclude that adenosine had measurable effects on ischaemic pain which were not sustained after discontinuation of infusion.

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Adenosine is an endogenous purine acting on A1 and A2 receptors. Activation of A1 receptors results in cardiac and muscular ischaemic-type pain.1 Activation of A2 receptors produces vasodilatation.2 Adenosine reproduces the pain of cardiac ischaemia when given by the i.v. or intracoronary route.3 Limb pain occurs when adenosine is injected into peripheral arteries.1 In contrast, studies in humans have suggested central analgesic actions mediated by A1 receptors and a reduction in anaesthetic and analgesic requirements.4 In a volunteer study, adenosine 70 µg kg⁻¹ min⁻¹ had essentially the same analgesic effect as morphine 0.1 mg kg⁻¹ but subsequent pain was not measured.5 This study used a different ischaemic pain test in which maximal or intolerable pain was induced, and different exercises were used to induce pain in men and women.

Therefore, we have investigated the effects of i.v. infusion of adenosine 100 µg kg⁻¹ min⁻¹. The primary end-point of the study was a comparison of ischaemic pain scores during adenosine and saline infusions using paired data from each subject. The secondary end-point was the sum of pain scores in the 24 h after infusion. Tolerability and side effects were also assessed.

Methods and results

After obtaining approval from the Local Ethics Committee and written informed consent, we studied eight ASA I male volunteers. A 12-lead ECG was performed and subjects were not permitted caffeine-containing beverages for 12 h before and 24 h after infusion. Two investigators and resuscitation equipment were present throughout. Electrocardiography, non-invasive arterial pressure (Finapres) and pulse oximetry were measured continuously. Venous access was established in the non-dominant hand. Ischaemic pain was induced using an orthopaedic tourniquet applied to the opposite upper arm. The ischaemic pain test consisted of elevation of the arm for 1 min and inflation of the tourniquet to 300 mm Hg. The arm was lowered and the forearm exercised by maximally squeezing a rolled up bandage for 2 s, followed by relaxation for 3 s, repeated for 2 min.
Subjects then rated pain in their forearm (not tourniquet pain) on a 100-mm visual analogue scale (VAS).

Three baseline ischaemic pain tests were carried out at 10 min apart. Subjects then received an infusion of adenosine (Adenocor, Sanofi-Winthrop) 100 µg kg⁻¹ min⁻¹ over 10 min, or saline, made up to an identical volume, in a double-blind manner. After 7 min of infusion, the arm was raised for 1 min, after which the tourniquet was inflated for 2 min, the arm exercised and a VAS performed. Further ischaemic pain tests were carried out at 15 min, 1, 4 and 24 h after the end of infusion. Monitoring was maintained for 15 min after infusion. One week later, the procedure was repeated with the alternate solution.

The Wilcoxon matched pairs rank sum test was used to compare pain scores at the end of infusion of adenosine and saline in the same subject. The sum of pain scores in the subsequent 24 h was also compared. *P* < 0.05 was taken as significant.

Pain, measured by VAS, was significantly reduced in the adenosine group compared with the saline group at the end of infusion (median difference 20.8; 95% confidence interval 2.0–40) (Fig. 1). There was no significant difference in the sum of pain intensity difference in the 24 h after infusion between the two groups, or at any of the individual times at which pain scores were measured.

There were no significant cardiovascular changes in either group. In the adenosine group, the greatest decrease in heart rate was 15.6% from baseline. There was no significant decrease in arterial pressure in either group. During infusion, brief, self-limiting side effects of facial flushing and mild chest tightness were experienced. The symptoms were never sufficient to require cessation of infusion. Symptoms occurred in all subjects during infusion of adenosine; there were no symptoms during infusion of saline. No discomfort was felt at the site of infusion.

Comment
We have demonstrated that infusion of adenosine 100 µg kg⁻¹ min⁻¹ produced a significant reduction in visual analogue pain scores in healthy volunteers at the time of infusion. This effect was not maintained when the infusion was stopped, but a larger study would be required to see if a small effect was missed.

The induced muscular ischaemic pain we used has been described previously and has been compared with postoperative deep somatic pain. Although the study was double-blind, volunteers experienced side effects with adenosine, including facial flushing and mild chest tightness. This may have had an influence on the recording of pain experienced, but as adenosine may also induce pain, we are unable to conclude if subjects would have tended to score pain as more or less severe as a result. These side effects would preclude its use in the perioperative period as the effects in patients with cardiovascular or respiratory disease would be unpredictable.

The mechanism by which adenosine produces antinociception is unknown. Both central and peripheral mechanisms have been proposed. In this study, adenosine was unable to reach the limb in which the pain was being assessed when the tourniquet was inflated. This is consistent with a central mechanism of antinociception.

In summary, adenosine appeared to have measurable central effects on ischaemic pain but side effects may limit clinical usefulness in the conscious patient and probably precludes further studies of this type.

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References
2 Sollevi A. Cardiovascular effects of adenosine in man; possible clinical implications. Prog Neurobiol 1986; 27: 319–49