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Reproduction of epigastric pain of duodenal ulceration by adenosine

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Abstract

Intravenous boluses of adenosine produced transient epigastric discomfort indistinguishable from spontaneous pain in five of six patients with endoscopically confirmed duodenal ulcer, an effect which was slightly but significantly antagonised by aminophylline.

These findings may be relevant to the pathophysiology of peptic ulcer pain.

Introduction

Adenosine is an endogenous nucleoside, much of which is formed as a metabolite of the nucleotide adenosine triphosphate (ATP). Adenosine exerts various pharmacological effects, including vaso-

dilatation and cardiac electrophysiological effects.¹ While investigating the respiratory stimulant effect of adenosine² one subject (a colleague who had not disclosed that he had a duodenal ulcer) reported that intravenous boluses of adenosine produced epigastric pain that did not differ from his spontaneous ulcer pain, except that it was transient.

Little attention had been paid to the capacity of adenosine to produce or modulate pain with the exception of a study of pain induced by adenosine on a human blister base preparation.³ Thus the study aimed at determining whether the adenosine induced epigastric pain observed in our subject occurred in other subjects with symptomatic duodenal ulcer, whether the pain was related to the dose given, and whether any pain that occurred was modified by aminophylline, a competitive antagonist at cell surface adenosine receptors.

Patients and methods

Informed, written consent was obtained from six patients (four men) aged 25-62 with endoscopically proved duodenal ulcers that had been symptomatic in the week before the study. Two patients with recurrent duodenal ulceration had been treated with cimetidine in the past. No patient was taking H_2 antagonists at the time of study, and no patient had taken oral antacids on the study day. It was made clear to each patient that the purpose of the study was to determine whether adenosine could mimic their spontaneous ulcer pain, that any pain was expected to last only a few seconds after any one bolus injection, and that after any injection the study would be stopped at their request. The study protocol was approved by the hospital ethics committee.

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Adenosine and saline were administered single blind as successive rapidly injected bolus doses separated by at least 90 seconds. No saline flush was given after each test injection, but appropriate allowance was made for the dead space of the intravenous cannula (0.12 ml). The initial dose of adenosine was 20 µg/kg, increasing in steps of 20 µg/kg to a possible maximum of 200 µg/kg; the effects of this regimen on respiration and heart rate have been reported previously.^{2,4} During the stepwise increase in bolus doses of adenosine saline (in a volume equivalent to an adenosine dose of 200 µg/kg) and lower adenosine doses were given to minimise any effect of anticipation by the patient on the pain score. The electrocardiogram was monitored throughout the study because of transient dose related bradycardia with this regimen.⁴

After the first adenosine series, which was stopped when a dose of 200 µg/kg was reached or earlier at the patient's request, aminophylline 250 mg was infused intravenously over 10 minutes. A further series of single blind injections of saline and adenosine (starting at a dose of 20 µg/kg) was then given.

Pain was scored using a 10 cm visual analogue scale, the left end being labelled "no pain" and the right end labelled "pain as bad as I can imagine." After each injection the patients were asked to score the peak epigastric sensations and, for the purposes of the visual analogue score, to ignore any other symptoms that adenosine might produce. Other symptoms were noted separately. After each injection patients were asked if they wanted to proceed to another bolus injection, which they understood might be at a higher dose.

Pain scores were measured by an observer who was blind to the solution administered. A pain score in mm (scale 0-100) was determined.

The relation between dose of adenosine and pain score over the dose range 60-200 µg/kg (lower adenosine doses having produced no pain) was examined for the periods before and after aminophylline was given by analysis of covariance. Threshold doses for epigastric sensations and subjective respiratory stimulation were compared using the two tailed Student's paired *t* test.

Results

Adenosine produced epigastric discomfort in five of the six patients studied (figure). Before aminophylline was given, epigastric discomfort induced by adenosine was significantly related to the dose given for all six subjects for the dose range 60-200 µg/kg ($r=0.730$, $p<0.001$). After aminophylline was given pain scores for the dose range 60-200 µg/kg were again significantly related to the dose given ($r=0.790$, $p<0.001$) but the intercept was shifted significantly to the right ($F=6.516$, $p<0.05$) without a change in slope of the relation ($F=2.240$, $p>0.20$). Adenosine produced no epigastric sensations below doses of 60 µg/kg during the periods before and after aminophylline was given. Saline injections caused little or no discomfort, the mean pain score being 0.5 (SD 1.5) for all saline injections. Pain scores for the group of six after adenosine was given were 13.8 (9.0) at a dose of 100 µg/kg and 68.2 (40.2) at a dose of 200 µg/kg.

Pain scores after adenosine injections. ●=Before aminophylline. ○=After aminophylline.

Each of the five subjects who experienced transient epigastric pain after adenosine injections was unable to distinguish the peak effect of adenosine at higher doses from spontaneous ulcer related pain. Discomfort induced by adenosine differed from spontaneous pain, however, in that adenosine it was transient, lasting 10-15 seconds.

Respiratory stimulation was reported by all six subjects. In the subjects who experienced epigastric pain the threshold dose for respiratory stimulation (48 (11) µg/kg) was significantly ($p<0.01$) lower than the threshold dose (85 (10) µg/kg) producing even the mildest epigastric sensations. In none of the subjects did bradycardia induced by adenosine cause the study to be stopped. Other subjective sensations reported after adenosine injections were facial flushing and neck discomfort. No subject reported retrosternal discomfort. No subjective sensations were reported after saline injections other than occasional minor epigastric discomfort scored on the visual analogue scales.

Discussion

This study shows that in patients with endoscopically proved symptomatic duodenal ulcer intravenous adenosine boluses above a dose of 40 µg/kg produce dose related epigastric discomfort, which patients were unable to distinguish from spontaneous ulcer related pain other than by the transient nature of discomfort induced by adenosine. This dose related discomfort was slightly but significantly antagonised by pretreatment with aminophylline, a competitive antagonist at cell surface adenosine receptors.⁵

The mechanisms of spontaneous pain related to peptic ulceration are not clear. The two possible mechanisms that have received most attention are smooth muscle spasm and low intraluminal pH, which is now more widely accepted. The theory that smooth muscle spasm may cause ulcer related pain⁷ was not supported by the findings of Bonney and Pickering,⁸ who performed studies showing a poor correlation between pain and increases in intraluminal pressure. Spontaneous ulcer pain in patients with active ulcers is commonly associated with low intragastric pH, and as pain is frequently alleviated by alkali and precipitated by intragastric acid⁹ the concept of acid as a cause of ulcer pain has become widely accepted. When acid is administered by nasogastric tube into the stomach of patients with ulcers there is a delay for both gastric and duodenal ulcers before pain results, possibly due to either hydrogen ion (H^+) diffusion or production of an intermediate metabolite in sufficient concentrations to stimulate sensory nerves.¹⁰ The identity of such a metabolite, if it exists, is unknown.

The release of adenosine has been associated with high acid production in the gastric mucosa.¹¹ Secretion of gastric acid stimulated by histamine and methacholine¹² is inhibited by adenosine, thus providing a possible adenosine mediated feedback control loop for the control of acid production.

Adenosine can produce pain on a human blister base preparation.³ Many effects of adenine nucleotides depend on prior conversion to adenosine,^{13,14} and so the capacity of these nucleotides to produce pain may also at least in part depend on the conversion of the adenine nucleotides to adenosine.¹⁵

The mechanism of the transient epigastric discomfort produced by adenosine in this study is not clear. One possibility is that adenosine causes transient smooth muscle spasm in foregut structures, but this seems unlikely as adenosine has been reported to relax intestinal smooth muscle.¹⁶ Alternatively, adenosine may increase production of acid by a vagally mediated mechanism, as has been reported at very high doses in the rat.¹⁷ Even if stimulation of secretion of gastric acid did occur in our patients, however, the occurrence of pain perhaps 20 seconds after the bolus injection of adenosine and lasting about 15 seconds is unlikely to be explained by a fall in intragastric pH as local instillation of acid takes several minutes to initiate pain.^{10,18}

Another possibility is that adenosine concentrations in the tissues near the ulcer are raised before adenosine is given, possibly because of access of acid to the tissue secondary to mucosal damage. When exogenous adenosine carried in the bloodstream reaches this abnormal tissue the sum of endogenous and exogenous local concentrations of adenosine might be raised sufficiently to stimulate sensory nerves and so generate pain. To our knowledge the capacity

of adenosine to stimulate afferent nerves in the foregut has not been defined, but in cutaneous nerves adenosine stimulates sensory neural discharges with a threshold concentration of 1-3 mM.³ Our suggestion that adenosine stimulates sensory nerve endings in the tissues near the duodenal ulcer seems plausible but has yet to be confirmed experimentally.

If adenosine does directly stimulate afferent nerves in tissues other than the skin the possible role of adenosine in the pathophysiology of pain in other conditions where concentrations of adenosine in the tissues are increased—for example, ischaemia—would merit further investigation. Moreover, Sylven *et al* have recently reported transient angina-like sensations in apparently healthy volunteers and have proposed that adenosine stimulates sensory nerves in the heart.¹⁹ It is unlikely that these sensations are caused by myocardial ischaemia as we found adenosine boluses to double coronary blood flow while causing similar retrosternal sensations in nine of 10 patients with chest pain but normal coronary arteries.²⁰ It is uncertain from which anatomical site such retrosternal sensations arise. The neck, arm, or epigastric sensations that are sometimes associated with retrosternal sensations²¹ also occurred during intra-aortic infusion of adenosine²¹ into the aortic arch or descending thoracic aorta, which, in view of the fact that the half life of adenosine in human blood is less than 10 seconds,²² suggests that sensations in those areas can arise from non-cardiac structures. Interestingly, the only patient in which the intra-aortic infusion study could not be completed was one with a hiatus hernia, who suffered epigastric pain. This may suggest that duodenal ulceration is not the only gastrointestinal inflammatory condition with a predisposition to epigastric discomfort induced by adenosine, and so the association between adenosine and pain may be of greater importance. If our hypothesis that adenosine, in sufficiently high concentrations, directly stimulates pain receptors is subsequently proved a suitable selective antagonist at such adenosine receptors may provide a new method of pain relief in appropriate painful conditions.

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100 YEARS AGO

Under an impression that the authorities may be induced to reconsider the position they have taken up on the question of relative rank, we have a suggestion to offer which we venture to hope they will entertain, a suggestion which, if not new, is one they may accept without loss of dignity. Over and over again the assurance has been given that in abolishing relative rank, Mr. Secretary Stanhope did not mean to strike a blow at the Medical Staff of the army. We have placed before the authorities abundant evidence that this measure, whatever its intention was, has deeply wounded the *amour propre* of the service, and has sensibly lowered its position in the estimation of all branches of the army. We have pointed out that this impression can never be removed by explanatory words in a warrant, still less by politely worded letters to the Chairman of the Parliamentary Bills Committee of the British Medical Association, letters never seen or heard of outside that Association. After all is said and "explained," one patent fact remains, relative rank is abolished, and no other is given or promised; and this is felt to be a grievous wrong by those who are directly affected, as well as a gratuitous affront to a great and liberal profession, second to none in usefulness to the community and devotion to the public weal.

We venture, in the name of the great Association we represent, to ask Mr. Secretary Stanhope and his advisers, is it a wise and statesmanlike proceeding, all other considerations apart, to leave this wrong without a remedy? There can be but one answer to this question. It is not wise, it is not statesmanlike. Is it good to lower the self-respect of the Service? Is it good for the health and efficiency of the most costly army in the world, so to treat its officers as to scare from its ranks the very men a wise Minister should do all he reasonably can to attract into it?

The Royal Commission which, at the close of the Crimean war, inquired into the health of the army, was composed of men the most competent of their day, presided over by a statesman and "man of affairs," who, more

than any other of his time, had the well-being of the soldier at heart. The Commissioners saw that to maintain the health of the army at the high standard to which they aspired, it was above all things necessary to place the Medical Department in a position of rank and authority beyond the reach of cavil or dispute. This determination, submitted to the War Minister in a series of recommendations, was by that Minister embodied in the famous Warrant of 1858. This warrant was from the first viewed with great disfavour by the military branch of the army administration; and, as was pointed out to Mr. Stanhope by the deputation he so courteously received, they never rested until, after the lamented death of Lord Herbert, with the connivance of weak-kneed Ministers, they whittled it away, a proceeding which ever since has caused discontent, and has at last culminated in the unhappy crisis, brought to a head by the unwise measure under discussion. Do the authorities really wish to give evidence of their desire to give satisfaction to the Army Medical Service? If so, let them restore this Warrant in its integrity, and let future War Ministers set their faces firmly against the insidious attempts on the part of those who have more regard for their own class privileges and prejudices than for the best interests of the public service.

We know it is our misfortune to differ on this question from the able and popular officer who deservedly presides over the Medical Staff of the Army. Sir Thomas Crawford, as he has a perfect right to do, does not regard this question from the same standpoint as his brother officers; but, even so, we cannot think the healing measure we, in this article, press on the attention of the authorities, can be otherwise than pleasing to him. No man living knows better than the Director-General does the good done by the Warrant of 1858, and the evil wrought by its suppression an evil which, in this its latter-day development, bodes ill for the health and consequent efficiency of the army. (British Medical Journal 1887;ii:29.)