Platelet-activating factor antagonism and streptokinase-induced hypotension in clinical acute myocardial infarction

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ABSTRACT

Continuing efforts are being made to improve thrombolytic therapy for acute myocardial infarction (AMI). The rate of streptokinase (SK) infusion is commonly limited by the hypotension that is induced. If this could be avoided, an accelerated regimen of SK could be given, analogous to that used for other thrombolytic agents such as alteplase. The mechanism of the SK-induced hypotension is unknown, but there is some evidence that platelet-activating factor (PAF) plays a role. The potent PAF receptor antagonist lexipafant (10 mg) (n = 35), or matching placebo (n = 36), was administered intravenously over 5 min, in a randomized double-blinded protocol, to consecutive patients about to receive SK for AMI; all but three had inferior MI, because of the preference for strategies other than SK therapy in patients with anterior MI. The rate of infusion of SK was set to give $1.5 \times 10^6$ units over 30 min, anticipating significant hypotension. Blood pressure fell sharply over the first 10 min of SK administration. The maximum fall in systolic blood pressure occurred between 8 and 12 min, and averaged $43 \pm 28$ mmHg (mean ± S.D.) and $40 \pm 26$ mmHg in patients given placebo and lexipafant respectively. Systolic pressure having fallen to < 90 mmHg, according to protocol the SK administration rate was reduced in 21 of 36 (58%) of patients given placebo and in 19 of 35 (54%) of patients given lexipafant. The total SK dose was given to all subjects over 40.3 ± 17.5 and 40.2 ± 13.4 min for the placebo and lexipafant groups respectively. Peak and time integrals of creatine kinase were not different in the two groups. There were no adverse effects attributable to lexipafant. It is concluded that the PAF receptor antagonist lexipafant has no significant effect on SK-induced hypotension and does not facilitate an accelerated regimen of administration.

INTRODUCTION

The earlier that thrombolytic therapy is given in acute myocardial infarction (AMI), the more effective it is in reducing morbidity and mortality [1]. There are continuing efforts to improve infarct artery patency and outcome through various adjunctive therapies and the development of better thrombolytic agents or regimes [2]. An accelerated regime of alteplase has been popularized by the results of the GUSTO I study [3], and newer agents that can be administered by bolus injection are undergoing trials [2]. Many consider the results obtained with the older thrombolytic agent, streptokinase (SK), to be inferior, but it remains widely used, largely because of

Key words: hypotension, lexipafant, myocardial infarction, PAF inhibition, platelet-activating factor, streptokinase.

Abbreviations: AMI, acute myocardial infarction; DBP, diastolic blood pressure; CK, creatine kinase; PAF, platelet-activating factor; SBP, systolic blood pressure; SK, streptokinase; VF, ventricular fibrillation.

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cost considerations. It could be advantageous to be able to administer SK by an accelerated regime. SK is commonly given over 1 h, in a dose of $1.5 \times 10^8$ units, and the major impediment to its more rapid administration is hypotension, with the magnitude of the blood pressure fall varying directly with the rate of SK administration [4]. Significant hypotension frequently ensues if an attempt is made to administer $1.5 \times 10^8$ units over 30 min. For example, in one study, when 750,000 units of SK was given to 98 patients with AMI over $30 \pm 16$ min (mean $\pm$ S.D.), systolic blood pressure (SBP) fell by $35 \pm 19$ mmHg [4]. Most early experience with SK administration was consistent with such results, leading to the prevailing regimen. Therefore, if the problem of SK-induced hypotension could be overcome, it could be beneficial to administer SK over a shorter time.

The mechanisms responsible for SK-induced hypotension remain obscure [5–7]. Hypotension does not appear to be related to complement activation [5], to the pretreatment level of anti-SK IgG antibodies or to resistance to SK [6]. However, while the platelet activation induced by SK is also complex and incompletely understood, recent detailed studies [7] support older evidence (8–10) that anti-SK antibodies contribute to the platelet activation that has been demonstrated most clearly in vitro [8–11], but for which there is at least indirect evidence in vivo [8,9]. There is some evidence for the involvement of platelet-activating factor (PAF) in these phenomena. PAF is a potently active, small-molecular-mass phospholipid that is generated from membrane phospholipids and contributes to pathophysiology in a wide variety of allergic, inflammatory and ischaemic responses [12–14]. The cardiovascular and other biological effects of PAF are many, including the induction of hypotension and platelet aggregation, which can be inhibited by PAF-receptor-specific antagonists [13,14].

The evidence implicating PAF in responses to SK is as follows. The hypotension and decrease in platelet count produced by SK infusion in rabbits was reported to be completely abolished by the PAF receptor antagonists SDZ 63–675 and WEB 2170, and PAF was eluted from the heart and aorta of SK-infused rabbits, but not from those of control rabbits [15]. The same group found an increase in blood PAF levels in patients with AMI treated with SK, but not in control AMI patients [16]. Furthermore, PAF was found to be produced by cultured human endothelial cells after their exposure to SK [16]. Others found SK potentiation of human whole-blood platelet aggregation in vitro not to be inhibited by the PAF antagonist WEB 2086 [11]. However, we know of only the one study, and that in rabbits [15], which has examined PAF antagonism in relation to SK-induced hypotension. This might be partly because SK does not produce hypotension in many experimental animals, and partly because the evidence that PAF might play a role in SK-induced hypotension is indirect and inconclusive. However, the hypotension and platelet aggregation that is produced by PAF administration, the known role of PAF in pathophysiology, the involvement of anti-SK antibodies in SK-induced platelet activation and the importance of SK-induced hypotension in patient management suggested that study of the effect of a potent PAF inhibitor on SK-induced hypotension should be undertaken, since there has been no such study.

A recently developed PAF receptor blocking drug, lexipafant, has been studied extensively in experimental animals, has been subjected to clinical pharmacokinetic, pharmacological and safety studies, and has become available for clinical efficacy studies [17]. It has many times the potency of the previously frequently studied antagonist WEB 2086 (at least 10 times for various phenomena), and has a longer half-life of 0.5–1.5 h in humans [17]. After a single intravenous dose of lexipafant (10 mg), platelets harvested after 3 h showed approx. 90% inhibition of baseline PAF-induced aggregation, and similar inhibition of PAF-induced skin flare [17]. The effects of lexipafant have been studied in a range of clinical conditions, particularly acute pancreatitis, and it has been shown to have some success in the suppression of inflammatory markers, without important untoward effects [17,18]. So far as we are aware, it is the only PAF antagonist currently available for clinical trial. The main aim of the present study was, therefore, to determine whether lexipafant would reduce the hypotension produced by SK administration in patients with AMI. On the basis of the human studies, a single intravenous dose of 10 mg was chosen to immediately precede SK administration.

**METHODS**

**Protocol**

Consecutive subjects due to receive SK for AMI, with SBP > 100 mmHg, and who gave informed consent, were randomly allocated, double-blind, to receive lexipafant (10 mg) or a matching placebo. Since these were patients selected for SK therapy, they had no contraindications to SK. In addition, because of policy in the two participating hospitals (Royal Perth and Swan District), all but three had inferior AMI, since patients with anterior AMI are usually treated by other means. It was intended to recruit only patients < 75 years of age, but otherwise they were unselected and consecutively presenting over approx. 1 year. A total of 72 patients (52 male, 20 female), median age 61 years (three were > 75 years), entered the study, with 36 receiving lexipafant and 36 placebo. One additional patient did not enter the study because of the onset of ventricular fibrillation (VF) immediately before commencing the trial drug. The study
was conducted at two sites in related hospitals, and the protocol was approved by the hospital Ethics Committee. Pulse and blood pressure were recorded twice before the trial drug was given intravenously over 5 min, at completion of the trial drug and before beginning administration of SK 5 min later. It was aimed to give 1.5 × 10^6 units of SK over 30 min; temporary cessation or slowing of the SK administration, and/or other measures (head down, polygeline colloid infusion and/or atropine) were undertaken if the SBP fell by > 30 mmHg or to < 90 mmHg with signs of poor peripheral perfusion. From the commencement of SK, pulse and blood pressure were recorded at 2 min intervals for 10 min, and then at 5 min intervals for 1 h, 10 min intervals for the next 1 h, and every 1 h for 6 h.

Clinical observation, including a daily ECG, was continued for 5 days or until hospital discharge. Creatine kinase (CK), CK-myocardial band and troponin I were measured every 6 h for 30 h and daily thereafter, as were liver function tests, urea, creatinine, electrolytes, haemoglobin, white cell count and platelets.

Each treatment group of 36 patients included 26 males. The median age of the placebo-treated group was 62 years, and that of the lexipafant-treated group was 60 years. In retrospect, it was considered that two placebo-treated subjects did not have AMI, one having pulmonary oedema and previous MI, and that one lexipafant-treated subject had inferior infarction 2 days earlier with ongoing angina. These three subjects completed the protocol and, hence, are included in data analysis. One lexipafant-treated female was unconscious at the time of presentation, having been found unconscious and resuscitated from VF by paramedics. She was started in the trial but, within minutes of beginning SK, review indicated SK therapy to be inappropriate; therefore SK was ceased, and trial documentation suspended. Subsequently there was no evidence of AMI, or of any other cause for her condition, at extensive investigation and autopsy. Hence the results of 36 placebo- and 35 lexipafant-treated patients are described. All but three subjects had inferior MI, with all three being in the placebo-treated group. The median time from onset of pain to the beginning of the trial drug was 188 min in the lexipafant group and 170 min in the placebo group. All 71 patients received aspirin, and 27 patients in the placebo group and 30 in the lexipafant group received heparin.

Deviations from protocol or additional complicating issues in six of the subjects were identified before breaking the randomization code. Re-analysis of the data excluding these subjects did not alter the results. The instances were as follows: one subject received only a half dose of trial drug (placebo); one in each subgroup received SK over approx. 60 min, in violation of trial protocol but consistent with previous standard administration; one patient received SK intentionally over 60 min after rapid resuscitation from VF between lexipafant and SK; one other lexipafant-treated subject was resuscitated from VF shortly after beginning SK; and one patient was given intravenous glyceryl trinitrate between lexipafant and SK to treat hypertension.

**Study data**

The primary data analysed were the maximum falls in SBP and diastolic blood pressure (DBP) from the levels recorded immediately before starting SK, the time course of changes in these pressures over 6 h, the number of patients requiring a decrease in the rate of SK administration, and the time over which the full dose of SK was given. Other data presented are peak enzyme levels and time integrals of levels over 30 h, platelet counts, clinical status, arrhythmia, evidence of recurrent infarction, cardiac failure, death and other adverse events.

Since there have been no previous clinical studies concerning SK-induced hypotension and PAF antagonism, it was not possible to carry out formal power calculations to arrive at the number of subjects to be studied. The numbers were chosen, with regard to the frequency and severity of SK-induced hypotension, as being adequate to demonstrate a substantial beneficial effect if such existed. The numbers studied, with the variation in responses observed, would have given 85% power to detect a 20 mmHg improvement in SBP, i.e. to have halved the fall observed. The randomization code was only broken after all the studies were completed.

Values are quoted as means ± S.D. Continuous variables in the two groups were compared using Student's *t* test, and discrete variables were compared using the normal approximation of the binomial distribution.

**RESULTS**

Immediately before commencing the trial drug, the heart rate was 71 ± 12 beats/min (mean ± S.D.) in the lexipafant group and 68 ± 17 beats/min in the placebo group. Blood pressure was, respectively, 134/81 ± 20/13 mmHg and 136/82 ± 29/16 mmHg. Neither heart rate nor blood pressure altered significantly during administration of lexipafant (+1 ± 12 beats/min; +4/1 ± 15/7 mmHg) or placebo (−3 ± 8 beats/min; +4/3 ± 14/11 mmHg).

Both SBP and DBP fell sharply over the first 10 min of SK administration, with the maximum falls in all subjects occurring within the relatively short time frame of 8–12 min, and the pressures had returned to approach baseline (pre-SK) levels by 25–30 min. The maximum fall in SBP averaged 43 ± 28 mmHg in the placebo-treated group and 49 ± 26 mmHg in the lexipafant-treated group (not significant). The corresponding values for DBP were 29 ± 16 mmHg and 31 ± 16 mmHg respectively. There was, therefore, no significant difference in the results between the lexipafant- and placebo-treated groups; in fact the results in the two groups were very similar.
Table 1 Blood pressure before and after SK

Note that the falls from baseline apparent at any one time during the early hypotensive phase appear less than the maximum falls quoted in the text because the nadir of pressure occurred at slightly different times in different individuals. Values are means ± S.D.

<table>
<thead>
<tr>
<th>Time after SK</th>
<th>Placebo</th>
<th>Lexipafant</th>
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<tbody>
<tr>
<td></td>
<td>SBP (mmHg)</td>
<td>DBP (mmHg)</td>
</tr>
<tr>
<td>Baseline</td>
<td>138 ± 10</td>
<td>136 ± 21</td>
</tr>
<tr>
<td>6 min</td>
<td>121 ± 22</td>
<td>125 ± 26</td>
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<tr>
<td>10 min</td>
<td>113 ± 26</td>
<td>115 ± 27</td>
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<tr>
<td>20 min</td>
<td>132 ± 25</td>
<td>138 ± 26</td>
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<tr>
<td>30 min</td>
<td>136 ± 21</td>
<td>133 ± 24</td>
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<tr>
<td>1 h</td>
<td>134 ± 22</td>
<td>128 ± 20</td>
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<td>2 h</td>
<td>129 ± 20</td>
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<td>6 h</td>
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<td>6 h</td>
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Figure 1 Mean SBP plotted from time of commencing SK infusion for the next 60 min in the placebo (▲) and lexipafant (○) groups

There are no significant differences (for S.D.s, see Table 1). Note that the falls from baseline, apparent at any one time during the early hypotensive phase, appear less than the maximum falls quoted in the text because the nadir of pressure occurred at slightly different times in different individuals.

Figure 2 Mean DBP plotted from the time of commencing SK infusion for the next 60 min in the placebo (▲) and lexipafant (○) groups

There are no significant differences (for S.D.s, see Table 1).

SBP and DBP at selected points over the first 6 h from the time of commencing SK are shown in Table 1, and are illustrated in more detail over the first 1 h in Figures 1 and 2. In view of the measures taken promptly to counter hypotension, in accordance with the protocol and as described below, the maximum falls in blood pressure apparent at selected time points (Figures 1 and 2) are less than the individual maxima recorded above, but it can be seen that the time courses were very similar in the two groups. SBP remained below baseline at 30 min for eight of the 36 placebo-treated and nine of the 35 lexipafant-treated subjects, despite the measures described below. The numbers for DBP were similar. No significant change in heart rate accompanied the trough of blood pressure induced by SK; at this time the heart rate was 72 ± 21 beats/min in the lexipafant-treated and 70 ± 19 beats/min in the placebo-treated subjects. Individual variability was considerable, with ranges of 135–39 beats/min and 105–35 beats/min respectively.

The target infusion time of 30 min for SK was selected in anticipation of a substantial number of subjects requiring slowing of the administration according to the protocol guidelines. While the full 1.5 × 10⁶ units was given to each of the 71 subjects, the rate was reduced in 21 of 36 (58%) of the placebo group and in 19 of 35 (54%) of the lexipafant group. The time required for administration of SK in these two groups was 40.3 ± 17.5 min and 40.2 ± 13.4 min respectively, so that there was no difference between the groups in SK administration. In addition to adjusting the rate of infusion of SK, hypotension was routinely treated by putting the head into dependency. Polygeline colloid infusion was given to eight placebo-treated and 12 lexipafant-treated subjects, and intravenous atropine was given to 14 and 15 subjects respectively in the two groups.

Mean CK levels in the two groups are illustrated in Figure 3. The maximum levels reached in the placebo and lexipafant groups were 1670 ± 1630 i.u./litre and 1700 ± 1450 i.u./litre respectively, and the time integrals were 61090 ± 53600 i.u.·litre⁻¹·h and 54600 ± 47800 i.u.·litre⁻¹·h respectively. There were also no significant differences in the corresponding values for CK-MB or...
troponin I. Platelet counts obtained daily for at least 3 days. The baseline pre-therapy values were \((262 \pm 66) \times 10^9/\text{litre}\) and \((253 \pm 68) \times 10^9/\text{litre}\) in the lexipafant and placebo groups respectively (not significant). Nadirs were reached on day 2, with values of \((213 \pm 51) \times 10^9/\text{litre}\) and \((198 \pm 65) \times 10^9/\text{litre}\) respectively; these were significantly different from the baseline values (each \(P < 0.005\)), but not from each other.

Episodes of VF have been already mentioned. During their hospital stay, four placebo-treated and three lexipafant-treated patients had ventricular tachycardia documented, one who was treated with placebo had recurrent infarction, and 13 in each group had coronary angioplasty, with or without stent insertion (36% and 37% on an elective basis. All trial patients survived to leave hospital, but the patient in whom SK administration was aborted, and who did not have AMI, died without regaining consciousness.

No patient had a serious adverse event that was attributed to the trial drug. However, both of the subjects who had VF early in the trial period were found to have had lexipafant. It is also relevant that one subject had an apparent anaphylactic reaction to intravenous colloid, given to improve renal function, on the day following lexipafant and SK. One patient in each group had moderately abnormal liver function tests transiently; these were initially considered to be possibly attributable to the trial medication, but were in fact almost certainly associated with their clinical condition.

**DISCUSSION**

The results indicate that the potent PAF antagonist lexipafant has no significant effect on SK-induced hypotension in the setting of clinical AMI, or on the time over which it is possible to administer SK. The time of 30 min for the administration of \(1.5 \times 10^8\) units of SK, and the criteria for slowing administration, were chosen in the study because, from our experience and that of others [4–6, 19], substantial hypotension was likely to result. We anticipated that this would allow the efficacy of lexipafant to be assessed by determining the hypotension induced by SK, the number of subjects in whom slowing of the administration was required, and the time over which it was possible to give SK. This expectation was fulfilled and, on each of the criteria, the study demonstrated the lack of a clinically significant benefit of lexipafant. The dose of 10 mg intravenous used was such as to produce a high level of PAF inhibition. Lexipafant is many times more potent than WEB 2086, with a plasma half-life in humans of between 0.5 and 1 h. The dose would have been more than enough to produce greater than 90% inhibition of phenomena such as skin flare to PAF injection and PAF-induced platelet activation for several hours [17]. We did not study platelet activation which can result from exposure to SK in vitro [7–11] and perhaps in clinical administration [8,9]; platelet counts indicated initial and similar falls in the two groups.

Almost all the patients included in the present study had inferior AMI; for anterior AMI, in our institution and many others, there is often preference for the use of alteplase, or for primary angioplasty if that does not involve much delay. However, SK-induced hypotension does not depend upon the site of AMI [6], and the mechanism remains unknown. The patients in the two treatment groups were well matched in terms of age, sex and initial blood pressure and heart rate. They comprised a consecutive series of those with AMI who were to have SK on the usual indications [2], except that patients \(> 75\) years of age were generally excluded. In retrospect, three subjects probably did not have AMI, although two of these had recent or past MI. One subject was inappropriately started in the trial, but SK administration was aborted, and hence no result was obtained in this patient. Otherwise all subjects completed the study to hospital discharge, and there were no in-hospital deaths or episodes of intracranial haemorrhage or non-haemorrhagic stroke. The lack of any in-hospital mortality is, of no doubt, partly attributable to the great majority of the patients having inferior rather than anterior AMI and being \(< 75\) years of age, and to none being markedly hypotensive at presentation. The patients were obviously those judged suitable for SK therapy without contraindications. Although they were otherwise unselected, the in-hospital mortality for such patients should be very low. No adverse effects that could be attributed to lexipafant therapy were encountered. Two lexipafant-treated patients developed, and were resuscitated from, VF, one shortly after lexipafant administration and the other during SK. Such events are not surprising considering the nature of the patients in this study. Lexipafant has not been associated with cardiac arrhythmia in experimental animals or in clinical studies and, as mentioned below, some workers have reported PAF
antagonists to be anti-arrhythmic in experimental myocardial ischaemia [14,20].

It was not an aim of the present study to determine whether the PAF antagonist had any influence on infarct size, ventricular function, arrhythmias or prognosis. Several years ago, some considered PAF to play an important role in the pathophysiology of myocardial ischaemia. It was reported that specific PAF receptor antagonists reduced the myocardial damage and cardiac arrhythmias produced by myocardial ischaemia and reperfusion in experimental animals [14,20], although our own studies did not support that contention [21,22]. The present study was not designed to examine these questions, and we do not know of clinical studies that have done so. At the same time, it can be noted that the cardiac enzyme changes in our two treated groups were almost identical, that the only two patients who had VF following the trial drug had received lexipafant, and that the small numbers observed to have ventricular tachycardia during their hospital stay were similar in the two treated groups.

Thrombolysis with SK remains common therapy for AMI, despite the enthusiasm for alteplase generated particularly by the GUSTO I trial [3], the development of newer agents [2], and the value of primary angioplasty [23]. While there is evidence that the latter can result in greater patency rates of the infarct-related artery, higher thrombolysis in myocardial infarction (TIMI)-3 flow rates and better short-term results in clinical trials [23], long-term results when compared with newer thrombolytics and adjunctive therapies are uncertain, the logistics are difficult and the results generally may be no better than with the use of thrombolytics [24]. The superiority of the accelerated administration of alteplase proposed as a result of the GUSTO I study [3] is questioned by some [25], and there is a continuing search for safe and effective thrombolytic agents that can be given rapidly [2]. Even 30 min saved in the routine administration of SK could be clinically relevant, and would have led to further study of accelerated regimes of SK.

In conclusion, lexipafant had no significant effect on the hypotension induced by SK administration in AMI. Since lexipafant is a potent PAF antagonist, and the dose administered should have been adequate, we do not consider that the use of a different PAF antagonist, or lexipafant in higher dosage, would be likely to be beneficial in the clinical situation. Hypotension remains a major factor limiting the rapid administration of SK.

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