Morphine is an arteriolar vasodilator in man

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- It has been recognized for about 10 years that morphine is a veno-dilator in man and that this effect may be related to histamine release.

WHAT THIS PAPER ADDS

- This effect also occurs in the arteriolar system, with vasodilatation at doses of morphine that may have clinical relevance in patients with heart failure, or who abuse opioids.
- The effect is mediated by histamine release and actions of nitric oxide.
- The mechanisms of this effect of morphine are unclear, but suggest an alternative therapeutic target in vascular disease.

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AIM

The mechanisms of action of morphine on the arterial system are not well understood. The aim was to report forearm vascular responses, and their mediation, to intra-arterial morphine in healthy subjects.

METHODS

Three separate protocols were performed: (i) dose ranging; (ii) acute tolerance; (iii) randomized crossover mechanistic study on forearm blood flow (FBF) responses to intrabrachial infusion of morphine using venous occlusion plethysmography. Morphine was infused either alone (study 1 and 2), or with an antagonist: naloxone, combined histamine-1 and histamine-2 receptor blockade or during a nitric oxide clamp.

RESULTS

Morphine caused an increase in FBF at doses of $30 \mu\text{g min}^{-1}$ [$3.25 (0.26) \text{ ml min}^{-1} 100 \text{ ml}^{-1}$] [mean (SEM)] doubling at $100 \mu\text{g min}^{-1}$ to $5.23 (0.53) \text{ ml min}^{-1} 100 \text{ ml}^{-1}$. Acute tolerance was not seen to $50 \mu\text{g min}^{-1}$ morphine, with increased FBF [$3.96 (0.35) \text{ ml min}^{-1} 100 \text{ ml}^{-1}$] ($P = 0.003$), throughout the 30-min infusion period. Vasodilatation was abolished by pretreatment with antihistamines ($P = 0.008$) and the nitric oxide clamp ($P < 0.001$), but not affected by naloxone. The maximum FBF with pretreatment with combined H1/H2 blockade was $3.06 (0.48)$ and $2.90 (0.17) \text{ ml min}^{-1} 100 \text{ ml}^{-1}$ after 30 min, whereas with morphine alone it reached $4.3 (0.89) \text{ ml min}^{-1} 100 \text{ ml}^{-1}$.

CONCLUSIONS

Intra-arterial infusion of morphine into the forearm circulation causes vasodilatation through local histamine-modulated nitric oxide release. Opioid receptor mechanisms need further exploration.

Introduction

Opioid drugs such as morphine are widely used in the early management of patients with acute cardiovascular events such as myocardial infarction and pulmonary oedema. The analgesic and anxiolytic effects are obvious benefits of opioids in this situation, but it is also commonly believed that, in addition, they offer important haemodynamic ben-

efits. However, there have been conflicting reports concerning the acute cardiovascular effects of opioids in man. Whereas several studies have reported reductions in blood pressure (BP) [1–3], others have shown either no effect [4] or even pressor responses [5]. Although morphine has been shown to be a vasodilator in human veins [6], surprisingly little is known about the direct effects of opioids on the peripheral arterial vasculature even though their

actions on resistance vessels could be of great importance when cardiac function is significantly impaired.

The results of animal studies examining the effects of opioids reflect the difficulty of interpreting the response to drugs that have multiple potential modes of action following systemic administration, which include agonism of opioid receptors in both the cardiovascular and central nervous system, depression of respiration and other, non-opioid receptor-mediated, effects [7].

The aim of these exploratory studies was to investigate the hypothesis that morphine is a directly acting vasodilator in human resistance vessels by observing the effects of intrabrachial infusion of morphine on forearm blood flow (FBF). Having supported this hypothesis in initial exploratory studies, we proceeded to investigate the dose-response relationship, whether the response undergoes acute tolerance, and potential mechanisms mediating vasodilatation.

Methods

Subjects

All subjects were healthy men aged between 20 and 50 years. Men were chosen to avoid any potential effects from menstrual cycle hormones. Subjects were excluded if they had known risk factors for vascular disease (e.g. hypertension, hypercholesterolaemia, diabetes and smoking), had documented evidence of vascular disease, were taking vasoactive medications or had a history of drug abuse. All subjects underwent screening for drugs of abuse before entry, and provided written informed consent to participate in the studies, which had been approved by the local Research Ethics Committee.

Study preparation and observations

Subjects abstained from alcohol and caffeine for 24 h before each study and rested recumbent in a quiet temperature-controlled room maintained at 23–25 °C for the duration of the study. Subjects were fasted and all studies began at 08.30 h. A 27-G cannula (Cooper's Needle Works Ltd, Birmingham, UK) was inserted into the brachial artery of the nondominant arm under local anaesthesia for the infusion of saline, morphine or other drugs. The intra-arterial infusion rate was maintained constant at 1 ml min⁻¹ throughout the study period. All drugs were supplied from the hospital pharmacy department of the Lothian Hospitals Trust. Morphine sulphate solutions were prepared as dilutions of morphine (Martindale Pharmaceuticals, Romford, UK) in 0.9% saline from sterile stock solutions on the day of the study.

FBF was measured in both the infused and non-infused forearms by venous occlusion plethysmography using mercury-in-silastic strain gauges securely applied around the widest part of the forearm, as previously described [8]. Measurements were made in the infused and non-infused

arms, the latter acting as a control to account for any significant change in blood flow resulting from systemic factors such as spill-over of infused drugs or autonomic activation. The hands were placed above the level of the heart throughout the study period and were excluded from the circulation during measurements through inflation of wrist cuffs to 220 mmHg. Upper arm cuffs were intermittently inflated to 40 mmHg for the first 10 s in every 15 s to prevent venous outflow temporarily from the forearm and thus obtain plethysmographic recordings. Recordings of FBF were made over 3-min periods at 10-min intervals. Venous occlusion plethysmography (dual channel strain gauge plethysmograph) was used and calibration was performed prior to the study. The mean of the final five measurements was used for analysis and all FBF results were expressed as ml min⁻¹ 100 ml⁻¹ forearm volume. BP and heart rate were measured just after each FBF measurement in the non-infused arm using a semi-automated non-invasive method.

A wheal and flare response was observed following morphine in the forearm infused, but not elsewhere. The area of flare was estimated by drawing over a translucent sheet and the area calculated by planimetry just after each BP measurement. Accurate quantification of wheal volume in the presence of the FBF monitoring system was not possible and so we do not report quantitatively on this aspect. Itching was quantified by asking subjects to express its intensity on a 10-point visual scale, ranging from no itch to irresistible itch. All skin-related measurements were done at baseline, during the morphine infusion, and during the saline wash-out up to 60 min after the end of the infusion of morphine. Subjects were asked to report spontaneously any adverse effects, including drowsiness or nausea, occurring at any time point in the study.

Assays

Histamine [lower limit 0.1 ng ml⁻¹; coefficient of variation (CV) within 4%, and between assays 6.9%], tissue plasminogen activator (tPA) (lower limit 0.5 ng ml⁻¹; CV within 7% and between assays 7%), plasminogen activator inhibitor (PAI-1) (lower limit 2.5 ng ml⁻¹; CV within 4.1% and between assays 6.3%), and von Willebrand factor (vWF) (lower limit 5% of normal; CV within 3.6% and between assays 5.0%) were all measured in plasma using commercially available enzyme-linked immunosorbent assay kits. Serum tryptase, an enzyme released by degranulating mast cells, was measured with a fluoroenzyme immunoassay (UNICAP Tryptase; Pharmacia Diagnostics, Freiburg, Germany), which detects both α - and β -tryptase (lower limit 0.1 μ g l⁻¹; CV within and between assays 5.0%).

An initial exploratory investigation was carried out in two healthy male subjects. In these subjects, after baseline measurements, incremental doses of morphine sulphate were infused at a dose of 1, 3, 10, 30, 100 and 300 μ g min⁻¹ per minute intra-arterially for a total period of 6 min each

(total dose 2.7 mg morphine). There was a 10-min wash-out between each dose, during which saline was administered. The associated wheal and flare response in these two subjects at the highest doses of morphine suggested that histamine release was likely to be involved in the vasodilator response seen. No systemic effects were observed. Following discussion with the ethics committee, the protocol was refined to that used in study 1.

Study 1: dose–response study

The full study reported here involves six subjects in whom incremental doses were given as described above, to a maximum of 100 $\mu\text{g min}^{-1}$ morphine sulphate (total dose infused 860 μg morphine), with 10-min wash-out periods between each increment, and followed by a 30-min wash-out period during which observations were also made.

Study 2: acute tolerance study

On the basis of the dose–response study, acute tolerance was investigated by observing the response to 30 min continuous intra-arterial infusion of morphine in a dose of 50 $\mu\text{g min}^{-1}$ in eight healthy male subjects (total dose 1.5 mg morphine). Potential mediators were also investigated using blood sampling from deep veins in both forearms (treated and untreated) at baseline, 10 and 30 min after starting morphine, and 60 min after discontinuing the drug. Samples were obtained for assay of plasma histamine, serum tryptase, tPA, PAI-1 and vWF from the antecubital vein in the arm infused with morphine. FBF measurements were continued for 90 min after discontinuation of the forearm infusion.

Study 3: mechanistic study

We hypothesized that there were three likely mediators involved in the effects of morphine. These were an opioid receptor, histamine release, and nitric oxide (NO) synthesis. To investigate these we undertook an open-label, randomized, four-way crossover trial in eight healthy men. A constant rate infusion of morphine sufficient to cause consistent vasodilator responses (80 $\mu\text{g min}^{-1}$) for 30 min (total dose 2.4 mg morphine) was administered. The effects of antagonists of the three mediators proposed were studied in comparison with no treatment. A wash-out period of at least 7 days was allowed between studies.

Naloxone was given at the normal therapeutic dose of 400 μg by bolus intravenously followed by an intravenous infusion of 200 $\mu\text{g h}^{-1}$ for the 90 min of the study. Naloxone was started just before commencement of the intra-arterial morphine infusion.

Histamine antagonism was achieved by combining maximum therapeutic doses of the nonsedative H_1 -receptor antagonist cetirizine (10 mg day^{-1} orally for 2 days and 10 mg 1 h before the study) and the H_2 blocker cimetidine (400 mg twice daily orally for 2 days and 400 mg 1 h before the study), as previously described [9–11].

NO effects were studied using the 'nitric oxide clamp' as previously described [12, 13]. In this technique a combination of the nitric oxide synthase (NOS) inhibitor L-N-monomethylarginine (L-NMMA) and sodium nitroprusside are co-infused. L-NMMA was initially infused at a dose of 4 $\mu\text{mol min}^{-1}$ for 12–20 min to achieve maximal inhibition of local vascular endogenous NOS activity as measured by FBF. Thereafter, sodium nitroprusside was co-infused at titrated doses (80–600 ng min^{-1}) until FBF had been restored to within 10% of baseline flow and sustained for at least two consecutive FBF measurements. Once a stable baseline FBF was obtained, the NO clamp was continued at these doses for the remainder of the study to prevent endogenous NO synthesis during the period of morphine infusion and for a further hour.

Statistical analysis

For the dose–response study the absolute FBF measurements in the infused arm were compared with those in the non-infused arm using two-way analysis of variance (ANOVA) for repeated measures. Comparison with baseline FBF and FBF in the non-infused arm was made at each drug dose using paired two-tailed *t*-tests. For the acute tolerance study the FBF measurements in the infused arm at various time points were compared with those made at baseline and in the non-infused arm as above. For the mechanistic study the FBF measurements in the infused arm during the different infusions were compared using two-way ANOVA for repeated measures.

Where significant treatment effects were observed, post hoc analysis for individual interventions was carried out using *t*-test with Bonferroni correction for multiple comparisons. Statistical significance was accepted in all cases at $P < 0.05$.

Results

The characteristics of the participants in the three study protocols are summarized in Table 1. There was no change

Table 1

Baseline characteristics of the subjects recruited into each study protocol

	Dose–response	Tolerance	Mechanistic
Number	6	8	8
Sex (M/F)	6/0	8/0	8/0
Age (years)	31.2 (1.3)	34.4 (5.2)	34.4 (4.5)
BMI (kg m^{-2})	25.8 (0.8)	25.7 (1.1)	25.7 (1.0)
Baseline systolic BP	140 (12)	141 (14)	134 (14)
Baseline diastolic BP	64 (8)	68 (7)	68 (11)
Baseline heart rate	56 (8)	61 (16)	62 (7)
Baseline FBF ratio	1.0 (0.1)	1.2 (0.1)	1.2 (0.0)

Results are presented as mean $\pm$ SD. BMI, body mass index; BP, blood pressure; FBF, forearm blood flow.

Figure 1

Morphine infusion rate. Effect of intrabrachial infusion of morphine, in incremental doses of 1, 3, 10, 30 and 100 $\mu\text{g min}^{-1}$ (see text) in six subjects. Post-infusion recovery is shown to 30 min. Treated (●) and control arm (○) are shown (mean and SEM)

in heart rate or BP in any study, and no other adverse events or subject withdrawals. Subjects did not report sedation or nausea at any stage. This is not unexpected since the total dose of morphine infused was maximal in the mechanistic study when a total of 2.4 mg of morphine was given over 30 min.

Dose-response study

Baseline FBF measurements in the infused and non-infused arms were similar, and there were no changes in systemic BP, heart rate or FBF in the non-infused arm throughout the study. Incremental doses of morphine led to an increase in FBF in the infused compared with the non-infused arm ($P=0.001$). FBF in the infused arm increased gradually from baseline [mean (SEM) 2.42 (0.15) $\text{ml min}^{-1} 100 \text{ ml}^{-1}$] and was significantly elevated at 10 $\mu\text{g min}^{-1}$ [3.08 (0.32) $\text{ml min}^{-1} 100 \text{ ml}^{-1}$] ($P=0.014$) and 30 $\mu\text{g min}^{-1}$ [3.25 (0.26) $\text{ml min}^{-1} 100 \text{ ml}^{-1}$] ($P=0.002$) before rising sharply at 100 $\mu\text{g min}^{-1}$ [5.23 (0.53) $\text{ml min}^{-1} 100 \text{ ml}^{-1}$] ($P=0.002$) (Figure 1). During wash-out, FBF gradually decreased but remained significantly higher than baseline up to the 30-min measurement point.

There were measurable skin effects, including flare and wheal, beginning at 30 $\mu\text{g min}^{-1}$ and increasing at the maximum dose of 100 $\mu\text{g min}^{-1}$ (Figure 2). The flare and wheal gradually decreased during wash-out, but did not disappear until 90 min after morphine discontinuation. Three volunteers recorded itching at 30 $\mu\text{g min}^{-1}$, and all reported it at 100 $\mu\text{g min}^{-1}$.

Acute tolerance study

Baseline measurements of FBF in the infused and non-infused were similar and no change in FBF occurred in the non-infused arm (Figure 3). FBF in the infused arm had increased significantly by 10 min [3.96

Figure 2

Area of flare in response to intrabrachial infusion at incremental doses of morphine at 1–100 $\mu\text{g min}^{-1} \text{ ml}^{-1}$ (see text) in six subjects during the dose ranging study (mean and SEM). Also shown is the offset of flare following cessation of the infusion

Figure 3

Forearm blood flow (FBF, $\text{ml min}^{-1} 100 \text{ ml}^{-1}$ forearm volume) in response to a continuous intrabrachial infusion of morphine in eight subjects at 50 $\mu\text{g min}^{-1} \text{ ml}^{-1}$ for 30 min followed by saline infusion alone for a further 60 min. Data are presented as mean and SEM of FBF in infused arm (●) and non-infused arm (○)

(0.35) $\text{ml min}^{-1} 100 \text{ ml}^{-1}$] ($P=0.003$) in response to 50 $\mu\text{g min}^{-1}$ morphine, and remained significantly elevated throughout the 30-min infusion period. FBF remained significantly greater than control until 30 min after discontinuation of the morphine infusion.

Mechanistic study

FBF in the infused arm increased gradually from baseline [2.90 (0.47) $\text{ml min}^{-1} 100 \text{ ml}^{-1}$] [mean (SEM)] and was elevated at 10 min after receiving 80 $\mu\text{g min}^{-1}$ and reached

Figure 4 Forearm blood flow (FBF, ml 100 ml⁻¹ forearm volume) in response to a continuous 30-min intrabrachial infusion of morphine (80 µg min⁻¹) in eight subjects either alone (○), during co-administration of naloxone (◆), after pretreatment with cetirizine and cimetidine (X), or in the presence of a nitric oxide clamp (●). The 60-min recovery period is also shown. Data are presented as mean and SEM of FBF in the infused arm

[4.30 (0.89) ml min⁻¹ 100 ml⁻¹] in 30 min (Figure 4). The FBF response to intrabrachial infusion of 80 µg min⁻¹ morphine was significantly different between treatments ($F = 13.3$, $P < 0.001$) (Figure 4). Post hoc analysis showed that pretreatment with combined H1/H2 blockade [mean (confidence interval) difference from morphine alone -0.88 ml min⁻¹ 100 ml⁻¹ ($-0.25, -1.50$), $P = 0.008$], and inhibition of NO synthesis [-1.24 ml min⁻¹ 100 ml⁻¹ ($-0.61, -1.86$), $P < 0.001$], significantly attenuated the vasodilator effects of morphine, whereas at the dose given naloxone had no effect. Baseline data showed no significant influence of pretreatment with histamine antagonists, naloxone or NO clamp on FBF. Thus, FBF following pretreatment with combined H1/H2 blockade was [2.90 (0.17) ml min⁻¹ 100 ml⁻¹] after 30 min rest.

Flare response differed significantly between treatments ($F = 13.3$, $P < 0.001$). Post hoc analysis showed that histamine antagonists virtually abolished the flare response ($P = 0.005$). The NO clamp had no effect. Paradoxically, naloxone treatment significantly increased the flare area ($P = 0.031$) (Figure 5). There were no significant effects of any treatment on itching.

Assays

There was no increase in the ratio of histamine in the venous effluent from the infused compared with the non-infused arm during the continuous 30-min infusion of morphine at 50 µg min⁻¹ in the tolerance study (Table 2). This ratio increased (NS) at 60 min after discontinuation because of a very large increase in histamine in one subject

Figure 5 Effects of specific antagonists or no treatment on flare area following continuous intrabrachial morphine infusion (at 80 µg min⁻¹), during the infusion period and for 1 h following it. Morphine alone (○), during co-administration of naloxone (◆), after pretreatment with cetirizine and cimetidine (X), and in the presence of a nitric oxide clamp (●). All data are mean ± SEM

Table 2

Plasma measurements taken from the infused and non-infused arms at baseline, after 10 and 30 min of intrabrachial morphine (50 µg ml⁻¹ min⁻¹) and 60 min after discontinuation of morphine (90 min sample) as part of the tolerance study

		Baseline	10 min	30 min	90 min
Histamine	Infused	0.17 (0.02)	0.88 (0.48)	0.25 (0.04)	2.85 (2.16)
	Non-infused	0.35 (0.05)	0.30 (0.04)	0.17 (0.02)	0.24 (0.05)
Tryptase	Infused	5.1 (0.5)	3.85 (0.3)	4.4 (0.4)	3.8 (0.4)
	Non-infused	5.7 (0.6)	3.9 (0.3)	5.7 (0.6)	4.3 (0.4)
vWF	Infused	78.1 (33.9)	61.3 (20.5)	65.5 (21.8)	34.9 (10.4)
	Non-infused	88.5 (31.9)	42.2 (6.6)	79.5 (30.5)	56.6 (16.1)
tPA	Infused	4.0 (0.7)	4.2 (0.7)	4.2 (0.8)	4.5 (0.8)
	Non-infused	5.3 (0.9)	5.0 (0.9)	4.5 (0.8)	4.2 (0.8)
PAI-1	Infused	6.0 (1.2)	4.7 (0.9)	5.0 (1.1)	6.8 (2.3)
	Non-infused	7.1 (1.2)	5.5 (1.2)	5.0 (1.0)	4.6 (1.8)

Results are presented as mean ± SEM of eight subjects. vWF, von Willebrand factor; tPA, tissue plasminogen activator; PAI-1, plasminogen activator inhibitor.

and a smaller increase in a second. Plasma concentrations of tPA, PAI, vWF and serum tryptase levels were unchanged during the same study.

Discussion

The main finding of these studies is that intra-arterial infusion of morphine causes a dose-dependent vasodila-

tation in the human forearm. A number of investigators have also previously demonstrated the direct vasodilator action of opioids in animal vessels [14–16]. This response was not subject to acute tolerance and persisted for a period of at least 1 h after the end of the morphine infusion. An important question is the clinical relevance of these studies at the doses of morphine administered. Morphine levels were not measured in the venous effluent. However, based on the known baseline FBF in man of 50 ml min^{-1} [8], which doubled at a morphine dose of around $80\text{--}100 \mu\text{g min}^{-1}$, we estimate that the concentration of morphine in the arterial circulation in this experiment was of the order of 800 ng ml^{-1} . This is 5–20 times the morphine concentration seen in healthy individuals receiving 10 mg of morphine intravenously [17, 18]. However, it is well within the range experienced by recreational drug users [19] and likely to be seen acutely during bolus injection of 10 mg morphine in patients clinically. Whereas some have suggested that therapeutic doses of morphine and nalbuphine cause histamine and catecholamine release with no haemodynamic response [20], others have shown clear effects of peri-anaesthesia on systemic vascular resistance following 1 mg kg^{-1} morphine and protective action of histamine antagonists [21]. We were able to measure effects at infusion rates as low as $10 \mu\text{g min}^{-1}$, which adds further support to the clinical relevance of these data.

Morphine-induced vasodilator effects seen involve the actions of two natural vasodilator compounds, histamine and NO, since treatment with antagonists of both these systems significantly impaired vasodilatation. A number of *in vitro* studies support the potential interaction between opioids and NO and histamine mechanisms. Human studies on hand veins have shown similar patterns of response to those described here [6]. The issue is whether histamine releases NO, or NO histamine in this model. Two previous studies of sufentanil and remifentanil, relatively specific synthetic μ -opioid agonists, have shown vasodilator responses after intrabrachial infusion into the human forearm circulation [22, 23], with dose–response curves showing a maximal response at an infusion rate of $0.8 \mu\text{g min}^{-1}$ [24, 25]. These agents did not release histamine. In contrast, there is widespread evidence for histamine release in response to various other opioids [2, 20–23], and that morphine effects on NO are due to histamine release [26–28]. The mechanism for this effect is not understood. Others have suggested that there may be a receptor on endothelial cells that is specific for opioids and coupled to NO release [29].

In our study design we are unable to determine a direct relationship between opioid receptors and NO. Histamine antagonists blocked both wheal and flare and vasodilator effects, whereas the NO clamp inhibited only vasodilatation, suggesting histamine may be a more important factor here than any direct interaction between morphine and NO.

Study limitations

As in all studies of this type, a relatively small number of volunteers can be studied, and the design of this study was necessarily exploratory and is therefore underpowered to refute the possibility that there were no changes in some of the vasoactive mediators we studied. In addition, these mediators were studied in plasma, and this may not reflect local concentration in the arterial tissues. We have previously used the assay techniques applied here and shown effects [30]. The presence of a wheal and flare response could potentially alter the forearm flow measurement, but the technique used by us should not have been markedly affected by this response. Changes in forearm flow were detectable in all studies before a wheal and flare was seen.

Failure to antagonize the effects of morphine by naloxone was almost certainly due to an inappropriate low dose of naloxone. Morphine is not a pure μ agonist and it is therefore possible that some of the effects observed may not be due to μ agonism, but to effects on other subclasses of opiate receptors.

The effects could in theory result in part from systemic or central effects of morphine. At higher doses morphine causes carbon dioxide retention if it suppresses respiration. We did not specifically measure end tidal CO_2 concentrations in the volunteers we studied, but in other experiments we have conducted such changes were not seen until the total dose of 8 mg of morphine had been infused [31]. This is almost four times more than the maximum dose used in the studies described. Furthermore, systemic pulse rates and BP were unaltered, and blood flow in the non-infused arm was stable throughout the experimental period, suggesting that a systemic vascular response was not observed.

Conclusions

These studies have clearly demonstrated that intra-arterial morphine is an arterial vasodilator in man and that its effects occur at local doses of morphine that are equivalent to plasma concentrations potentially seen in clinical practice. The effects appear to be due to a combination of actions involving histamine and NO, as they are antagonized by specific pharmacological tools that block these receptor systems. The role of opioid receptors *per se* in the response remains to be elucidated using higher doses of opioid antagonists. These effects of opioids on the vasculature are of relevance to the management of cardiovascular disease, but also, perhaps more importantly, to the understanding of anaphylactoid reactions to opioids [32, 33] and to the management of patients with opioid poisoning, in whom noncardiac pulmonary oedema may occur [34].

The clinical relevance of our experiments would appear to be that morphine is a vasodilator in both arteries and veins and that, at concentrations observed in man, these

effects may be relevant for doses used in the management of cardiac failure. This raises the possibility of using locally vasoactive opioid analogues as a potential new investigative tool for the treatment of cardiovascular disease.

Competing interests

None declared.

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