Morphine Decreases Peripheral Vascular Resistance and Increases Capacitance in Man


The response of the human peripheral circulation to morphine in large doses independent of cardiac and respiratory influences has not been delineated. In 28 patients during cardiopulmonary bypass, alterations of peripheral vascular resistance (PVR) and capacitance in response to rapid arterial injection of morphine, 0.5 mg/kg or 1 mg/kg alone, or preceded by promethazine, 1 mg/kg, naloxone, 10 μg/kg, or naloxone, 20 μg/kg, were recorded over 15 min at a constant perfusion rate. Both doses of morphine decreased PVR by 46 per cent at 2 min, with values returning to control at 9 min. When promethazine preceded morphine, the decrease in PVR after morphine was 25 per cent. Naloxone did not alter the response. An increase in capacitance of 600 ml observed 5 min after morphine administration did not revert to control after 15 min, and was unaltered by prior administration of naloxone. (Key words: Anesthetics, intravenous: morphine. Antagonists, narcotic: naloxone. Atracurium, phenothiazines: promethazine. Blood pressure: peripheral vascular resistance.)

The circulatory effects of morphine in doses of 0.5 to 3.0 mg/kg in man are still not entirely clear, and the mechanism of action is still in dispute. Studies to date of the circulation in intact man have not excluded an effect of morphine on the heart or on respiration. Studies of the forearm or hand vessels of man may not reflect changes in all vascular beds. In normal man, infusion of morphine, 1 mg/kg, produces minimal hemodynamic changes.1,2 In patients with valvular heart disease, and to a lesser extent in those with coronary-artery disease, morphine, 1 mg/kg, increases stroke volume while decreasing mean arterial pressure and systemic vascular resistance. Central venous pressure and pulmonary arterial pressure, however, increase, suggesting right-sided heart failure, increased venous tone, or the effect of an increased carbon dioxide tension on the pulmonary vasculature.3 Of 20 such patients reported by Stoelting and Gibbs, six experienced hypotension, necessitating the administration of vasopressors.3 This hypotension could result from a direct action on the central nervous

system, the heart, or the peripheral blood vessels, or an indirect effect such as histamine release, or sympathetic blockade.

We have delineated the extents and durations of action of two doses of morphine sulfate (0.5 and 1 mg/kg) on peripheral resistance and capacitance vessels in man during cardiopulmonary bypass, when cardiac, pulmonary vascular, and respiratory changes were excluded. We excluded an action on central or peripheral morphine receptors by administering naloxone, and attenuated the peripheral effect on resistance with promethazine.

Methods

After obtaining informed consent, we studied 28 patients undergoing coronary-artery bypass surgery. The protocol was approved by the Human Experimentation Committee of the University of California, San Francisco. Twenty-two patients were premedicated with morphine sulfate, 0.15 mg/kg, and scopolamine, 0.4 mg, intramuscularly, one hour before operation. Six were premedicated with orally administered diazepam, 10–15 mg, one and a half hours before operation and scopolamine, 0.4 mg, intramuscularly, one hour before operation. Anesthesia was induced with halothane in nitrous oxide and oxygen by mask, and endotracheal intubation was facilitated by succinylcholine. Anesthesia was maintained with halothane, nitrous oxide, oxygen and pancuronium. During cardiopulmonary bypass, anesthesia was maintained with halothane, 0.4 per cent measured, via the oxygenator. The oxygenator was primed with 1,800 ml lactated Ringer's solution to achieve hemodilution to a hematocrit of 22–24 per cent. Esophageal temperature was maintained at 38 °C. Mixed venous blood Pco2 and pH values were within normal limits measured at 37 °C.

Venous blood from the superior and inferior vena caval canulas drained by gravity into the oxygenator reservoir. In this model, a decrease in the level of blood in the reservoir is considered to represent a capacitance increase in the patient rather than a fluid shift to the extravascular compartment, because of a rapid onset in minutes, and a concomitant decrease in venous tone.4,5 With a constant perfusion rate, a decrease in arterial pressure represents a decrease in peripheral vascular resistance, calculated as mean ar-
Fig. 1. Morphine, 0.5 mg/kg and 1 mg/kg, decreased peripheral vascular resistance in man, while the injection of saline solution or the preservatives in morphine solution did not (P < 0.01). Data points are means ± SE.

Groups I–IV were premedicated with morphine; Group V, with diazepam. The values at maximum change from control of peripheral resistance and reservoir level were subjected to analysis of variance, and the means compared by Student-Newman-Keuls test.

Results

Neither saline solution nor preservative altered peripheral vascular resistance (PVR) (fig. 1). In each group the initial value of PVR before injection was not significantly different from the control value. Morphine sulfate, 0.5 mg/kg (Group I), had decreased PVR by 46 per cent from the initial value at 2–3 min. Complete recovery to control value occurred in 9 min. Morphine sulfate, 1.0 mg/kg (Group II), produced changes similar in time and extent. In Group III (fig. 2), promethazine, 1 mg/kg, at zero time decreased PVR by 32 per cent by 1 min, with return to control at 5 min. Subsequent injection of morphine sulfate decreased PVR by 25 per cent, a significantly smaller change than the decreases in Groups I and II. In Group IV (fig. 3), naloxone, 10 μg/kg, at zero time increased PVR to 30 per cent above control by 5 min. Subsequent injection of morphine sulfate gave a decrease in PVR similar to that in Group II. Patients in Group V received diazepam (fig. 4) instead of morphine sulfate for premedication. After naloxone, 20 μg/kg, at zero time, there was no change in PVR. The increase in pressure in the morphine-premedicated patients after naloxone administration was sig-
significantly different from the effect in the group pre-
medicated with diazepam. Subsequent injection of
morphine sulfate at 5 min in Group V gave a decrease
similar to that seen in Group I.

Although capacitance changes were more variable
than changes of PVR, in all five groups morphine
injection decreased the reservoir level from control,
and hence increased capacitance (Fig. 5). Increases in
capacitance ranged from 8 to 15 per cent of calculated
blood volume (65 ml/kg), with no significant differ-
eence among groups by analysis of variance. In Group
III, promethazine administration increased capaci-
tance significantly from control by 5 min. Subsequent
morphine administration increased capacitance fur-
ther to a level not significantly different from that
seen with morphine alone. Reservoir level had not
returned to control by 15 min.

**Discussion**

Morphine (0.5 mg/kg) produced a transient de-
crease in PVR and a sustained increase in capacitance.
No increase in response was obtained with the higher
(1 mg/kg) dosage. Preservative in the morphine solu-

**Fig. 2.** Promethazine, 1 mg/kg, attenuated the
decrease in peripheral vascular resistance pro-
duced in man by subsequent injection of mor-
phine, 0.5 mg/kg. The effect of morphine, 0.5
mg/kg, alone is shown for comparison (P < 0.01).
Data points are means ± SE.

**Fig. 3.** Naloxone, 10 µg/kg, increased peripher-
al vascular resistance in man premedicated
with morphine (P < 0.01), but failed to attenu-
ate the decrease in peripheral vascular resist-
ance on subsequent injection of morphine, 1
mg/kg, in comparison with morphine, 1 mg/kg,
alone. Data points are means ± SE.
tion played no role in the decrease in PVR. When naloxone was administered to patients who had been premedicated with morphine three hours previously, but not those premedicated with diazepam, PVR increased. Yet neither dose of naloxone attenuated the response to subsequent morphine administration. This suggests that naloxone reversed the central sedative or analgesic effects of morphine, a reversal that resulted in a catastrophic increase in arterial pressure in one reported case.7

Since our experimental approach excluded a cardiac, or respiratory, explanation for these changes, there remains only a direct or indirect effect of morphine on the vasculature, or on the central nervous system. The rapid change in resistance argues against a direct effect on morphine receptors centrally, since no measurable brain concentration of morphine is detectable 15 sec after intracarotid injection, suggesting slow penetration of the blood-brain barrier.8 Furthermore, neither changes in resistance nor changes in capacitance were blocked by naloxone, which antagonizes morphine at receptors inside and outside the brain.9,10 A central decrease in sympathetic tone as the sole mechanism is challenged also by the finding of vasodilatation in a denervated canine limb,11 and in man by vasodilatation in an arm sympathectomized by brachial plexus block.12 Lowenstein et al. did demonstrate in the dog a neurally mediated vasodilatation where initial peripheral resistance was high.11 PVR was normal in our patients. Hence there is evidence for both a neural effect and a local effect.

The published evidence for a direct local effect in man is contradictory. Zelis et al. found that intra-arterial administration of phentolamine abolished the vasodilatation produced by intravenous injection of morphine, 15 mg, but not that produced by amyl nitrite, leading them to postulate a sympatholytic rather than direct action for morphine.13 In contrast, Samuels and Dundee found that intravenously administered morphine vasodilated a sympathectomized

Fig. 4. Naloxone, 20 µg/kg, did not change peripheral vascular resistance in man premedicated with diazepam, and failed to attenuate the decrease in peripheral vascular resistance on subsequent injection of morphine, 0.5 mg/kg, in comparison with morphine, 0.5 mg/kg, alone. Data points are means ± SE.
arm, suggesting a local effect. This local effect is not alpha-adrenergic blockade, since morphine does not modify the vasconstrictor response to norepinephrine infusion in man, or to sympathetic-nerve stimulation in the dog. A local effect could also be mediated by histamine. In man, prior intra-arterial promethazine injection did not block arteriolar dilation in the forearm after intravenous administration of morphine. However, intra-arterially administered promethazine did attenuate the immediate vasodilation after intra-arterial injection of morphine in the present study. Attenuation, rather than complete block, is consistent with the fact that promethazine is an H₂ blocker only, whereas the vascular effects of histamine are mediated by H₁ and H₂ receptors. Promethazine can block a histamine effect completely, but large doses are necessary. Unfortunately, the effect of promethazine does not confirm a histamine response, since promethazine also attenuates responses to catecholamines, serotonin, and acetylcholine. Hence, promethazine itself decreased resistance and capacitance in this study.

The capacitance changes followed a slower time course, starting at 5 min. Maximum venodilatation did not occur until the resistance had returned to control. The capacitance response to intra-arterial administration of phenylephrine in the same model occurs at 30 sec, so that a local effect of morphine could be expected earlier than 5 min. Could this be a neural mechanism? When morphine is administered intra-venously in the opposite arm, venodilatation occurs at 5 min in a hand vein isolated from the circulation by tourniquet, favoring a reflex mechanism over a local or humoral effect. In the dog, morphine attenuates the venoconstrictive response to sympathetic-nerve stimulation, or norepinephrine infusion. In man, intravenously administered morphine does not block reflex venoconstriction in response to application of ice to the forehead, but decreases resting venous tone. This suggests a different mechanism or a different sensitivity from that of the resistance vessels, whose response to epinephrine or sympathetic-nerve stimulation is not attenuated.

We have shown a rapid, short-lived decrease in peripheral vascular resistance, and a slower sustained increase in capacitance in response to morphine. The lack of attenuation of these responses by naloxone argues against an effect of morphine on receptors. The attenuation of the change in peripheral vascular resistance by promethazine is consistent with, but does not confirm, a local effect mediated by histamine.

References