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Profound Increase in Epinephrine Concentration in Plasma and Cardiovascular Stimulation after μ-Opioid Receptor Blockade in Opioid-addicted Patients during Barbiturate-induced Anesthesia for Acute Detoxification

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Background: **Acute displacement of opioids from their receptors by administration of large doses of opioid antagonists during general anesthesia is a new approach for detoxification of patients addicted to opioids. The authors tested the hypothesis that μ-opioid receptor blockade by naloxone induces cardiovascular stimulation mediated by the sympathoadrenal system.**

Methods: **Heart rate, cardiac index, and intravascular pressures were measured in 10 patients addicted to opioids (drug history; mean ± SD, 71 ± 51 months) during a program of methadone substitution (96 ± 57 mg/day). Cardiovascular variables and concentrations of catecholamine in plasma were measured in the awake state, during methohexital-induced anesthesia (dose, 74 ± 44 $\mu g \cdot kg^{-1} \cdot min^{-1}$) before administration of naloxone, and repeatedly during the first 3 h of μ-opioid receptor blockade. Naloxone was administered initially in an intravenous dose of 0.4 mg, followed by incremental bolus doses (0.8, 1.6, 3.2, and 6.4 mg) at 15-min intervals until a total dose of 12.4 mg had been administered within 60 min; administration was then continued by infusion (0.8 mg/h).**

Results: **Concentration of epinephrine in plasma increased 30-fold (15 ± 9 to 458 ± 304 pg/ml), whereas concentration of norepinephrine in plasma only increased to a minor extent (76 ± 44 to 226 ± 58 pg/ml, $P < 0.05$). Cardiac index increased by 74% (2.7 ± 0.41 to 4.7 ± 1.7 $min^{-1} \cdot m^{-2}$), because of increases in heart rate (89 ± 16 to 108 ± 17 beats/min) and stroke volume (+44%), reaching maximum 45 min after the initial injection of naloxone. In parallel, systemic vascular resistance index decreased (−40%). Systolic arterial pressure significantly increased (113 ± 16 to 138 ± 16 mmHg), whereas diastolic arterial pressure did not change.**

Conclusions: **Despite barbiturate-induced anesthesia, acute μ-opioid receptor blockade in patients addicted to opioids induces profound epinephrine release and cardiovascular stimulation. These data suggest that long-term opioid receptor stimulation changes sympathoadrenal and cardiovascular function, which is acutely unmasked by μ-opioid receptor blockade. Because of the attendant cardiovascular stimulation, acute detoxification using naloxone should be performed by trained anesthesiologists or intensivists. (Key words: Acute opioid detoxification; cardiovascular stimulation; catecholamine plasma concentration; opioid addiction; μ-opioid receptor blockade.)**

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A MAJOR goal in the treatment of opioid addiction is to achieve abstinence from the drug. Unfortunately, classic forms of treatment are costly and not very effective, with patient drop-out rates as high as 30%.[1] These

objections have encouraged many clinicians to look for innovative forms of treatment to improve outcome. In particular, mitigation of opioid withdrawal symptoms is a desirable objective because these symptoms are thought to contribute to termination of therapy by the patient. Recently, a new approach coined ultrarapid opioid detoxification has been described, with programs starting in many hospitals worldwide.[2-6] The principle idea of this approach is to antagonize any opioid effects rapidly by the administration of large doses of μ-opioid receptor antagonists. General anesthesia is induced before the start of opioid antagonization and maintained for several hours to prevent perception of withdrawal symptoms by the patient.

This treatment represents a new clinical area of interest for anesthesiologists, and it also offers the unique opportunity to assess cardiovascular effects of opioid receptor blockade during conditions of a chronically stimulated opioid receptor system in humans. In the current study, we tested the hypothesis that μ-opioid receptor blockade by intravenous administration of naloxone (Curamed, Karlsruhe, Germany) results in significant cardiovascular effects mediated by the sympathoadrenal system, despite barbiturate-induced anesthesia, and we assessed the clinical feasibility of this method.

Materials and Methods

The protocol of the study, including catheterization, blood sampling, administration of barbiturates to induce anesthesia, and the use of high doses of naloxone, was approved by the ethics committee of the University GH Essen and is consistent with the Declarations of Helsinki. All patients were informed that the treatment they would receive was not an established one, and they gave written informed consent before participating in this study.

Patients

All data are presented as mean ± SD unless otherwise indicated. Ten patients (six women; 28 ± 7 yr old; range, 20–39 yr old) were selected on a voluntary basis from the local methadone out-patient care unit. All had a long history of opioid abuse (73 ± 51 months; range, 13–180 months) and were treated with orally administered methadone (96 ± 57 mg/day; range, 50–130 mg/day for 19 ± 19 months; range, 1–60 months). The patients were admitted to the hospital at least 1 day before treatment and were screened by clinical history, physical examination, laboratory examination, electrocardiogram, and chest radiography. Other than methadone, the patients reported that they did not consume other drugs, which was confirmed by repeated urine toxicology screens before inclusion in the study. Patients did not suffer from any overt disease, except five patients had serologic evidence of exposure to the hepatitis B or C virus without clinical or laboratory signs of impaired liver function.

The last dose of methadone was given 24 h before treatment with naloxone. Flunitrazepam (1 mg orally; Rohypnol®; Roche, Grenzach-Wyhlen, Germany) was administered as a premedication before the patients were transferred to our intensive care unit.

Methods

After admission to the intensive care unit in the morning, a peripheral venous cannula and an arterial and a pulmonary artery catheter were inserted using local anesthesia for fluid replacement and hemodynamic monitoring. If required, mild sedation by midazolam (Dormicum®; Roche) was provided. For prophylaxis of infection and potential development of gastrointestinal ulcers during withdrawal, 2 g ceftriaxone (Elzogram®; Lilly, Bad Homburg, Germany) and 20 mg famotidine (Pepdul®; MSD Chibropharm, Haar, Germany) were given. Heparin (Liquemin®; Roche) was administered (625 U/h) for prophylaxis of thrombosis. The infusion rate of Ringer's lactate (460 ± 98 ml/h) was adjusted to keep right atrial and pulmonary artery occlusion pressures at baseline values (central venous pressure, 7 ± 3 mmHg; pulmonary artery occlusion pressure, 8 ± 3 mmHg). Potassium chloride was infused as required (8 ± 3 mmol/h) to maintain serum concentration of potassium close to the baseline value.

After a resting period of 30–60 min, general anesthesia was induced by 2–4 mg/kg methohexital (Brevimytal®; Lilly) and a single dose (0.1 mg/kg) of piperocuronium (Arpilon®; Organon, Oberschleißheim, Germany) for muscle relaxation. The trachea was intubated, and the patients were mechanically ventilated (fractional inspired oxygen concentration, 0.21–0.3; positive end-expiratory pressure [PEEP], 3 mmHg). In addition, a gastric tube, a urinary catheter, and a rectal tube were placed. Anesthesia was maintained by continuous infusion of methohexial (74 ± 44 $\mu g \cdot kg^{-1} \cdot min^{-1}$) titrated to abolish corneal and glabella reflexes. This dose also suppressed the response to painful stimuli such as pinching of the skin, as studied in pilot patients. A mini-

mum interval of 1 h was allowed to elapse before starting administration of naloxone to achieve a cardiorespiratory and anesthetic steady state. Steady-state conditions after induction of anesthesia were assumed when heart rate, arterial pressures, and cardiac index differed by <10% between two measurements taken ≥30 min apart. Normocapnia was established and repeatedly confirmed by analysis of arterial blood gas.

Measurements

Arterial pressures and pulmonary artery, central venous, and pulmonary artery occlusion pressures were measured by electromanometry relative to barometric pressure with transducers referenced to the midaxillary line. Heart rate was determined from the electrocardiogram (lead two) of a five-lead electrocardiogram recording system, including ST segment analysis (Sirecust 1281; Siemens, Erlangen, Germany). Cardiac output was determined in triplicate by thermodilution, injecting 10 ml of iced saline irrespective of the respiratory phase.[7,8] Calculations were performed with variables normalized to body surface area and expressed as cardiac, stroke volume, and systemic vascular resistance indices using standard formulae.

Concentrations of Catecholamine in Plasma

Concentrations of norepinephrine and epinephrine in plasma were determined by high-performance liquid chromatography with electrochemical detection (lower detection limit, 10 pg/ml; coefficient of variation, 6.2% for norepinephrine, 6.8% for epinephrine). Mixed venous blood drawn from the pulmonary artery was sampled at specified intervals into chilled tubes with ethylenediaminetetraacetic acid, cooled to +4°C in ice water, and immediately centrifuged. Plasma was stored at −80°C until analysis.[9]

Study Protocol

Treatment with naloxone was started after achieving steady-state conditions during anesthesia (see previous section) using a first dose of 0.4 mg administered intravenously. Four additional naloxone bolus doses of increasing dose amount (0.8, 1.6, 3.2, and 6.4 mg) were injected at 15-min intervals. Accordingly, a total of 12.4 mg of naloxone was given during a 60-min period. This stepwise approach was chosen for safety reasons because complications after injection of naloxone have been described,[10–16] and effects in our patients were considered unpredictable.

Seventy-five minutes after the first dose of naloxone, an infusion of naloxone was started in a dose of 0.8 mg/h for 24 h. μ-Opioid receptor blockade was continued with 50 mg/d naltrexon administered *via* the gastric tube starting 12 h after the first injection of naloxone.

Cardiovascular variables were assessed before induction of anesthesia (patient awake), at least twice within the period before application of naloxone, and 15 min after each bolus dose of naloxone, *i.e.,* after 15, 30, 45, 60, and 75 min, and 120 and 180 min after the initial administration of naloxone. At the same time, pulmonary arterial blood was collected for determination of concentrations of epinephrine and norepinephrine in plasma.

Continuous infusion of methohexital was stopped after the 180-min observation period. To attenuate withdrawal symptoms after anesthesia, clonidine (≈2 $\mu g \cdot kg^{-1} \cdot h^{-1}$) was given intravenously until the patient was discharged to the psychiatric ward the next morning, as required.

Statistical Analysis

Differences in mean values of variables over time were determined by one-way repeated-measures analysis of variance followed by Fisher's *post hoc* test. The following *a priori* null hypotheses were tested: There is no difference in means of variables at baseline (before administration of naloxone) compared with observations (1) after administration of naloxone and (2) before induction of anesthesia. A null hypothesis was rejected, and statistical significance assumed with an α error (P value) <0.05.

Results

Concentrations of Catecholamine in Plasma

Concentration of epinephrine in plasma was 15 ± 9 pg/ml, and concentration of norepinephrine in plasma was 76 ± 44 pg/ml after achieving steady-state conditions after induction of anesthesia. Administration of naloxone induced a 30-fold increase in concentration of epinephrine in plasma (to 458 ± 304 pg/ml and a threefold significant increase in concentration of norepinephrine in plasma (to 226 ± 58 pg/ml). Peak concentrations were attained after 60–75 min and remained significantly increased compared with baseline values until the end of the observation period (fig. 1).

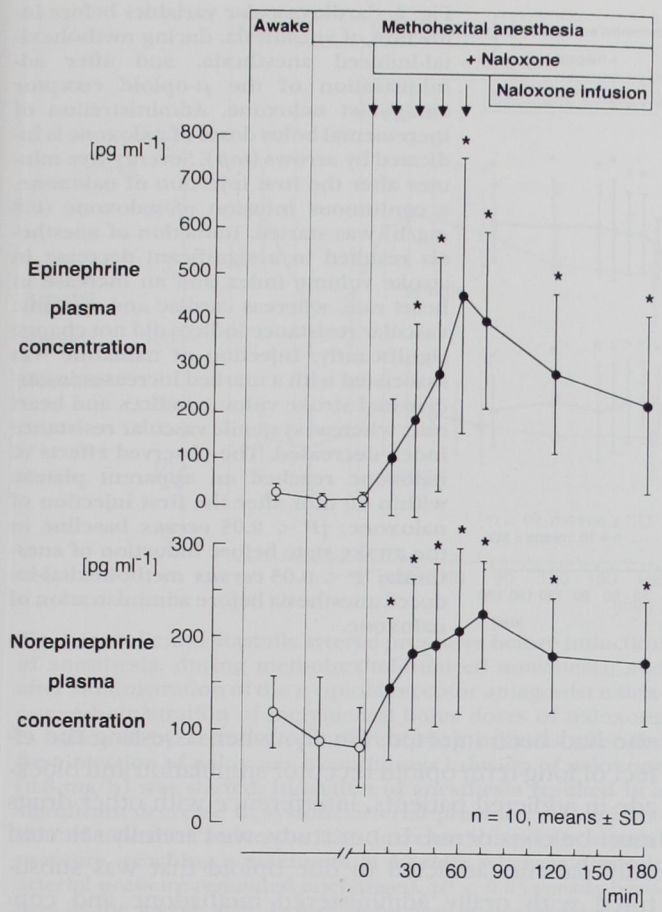

Fig. 1. Concentrations of epinephrine and norepinephrine in plasma in the awake state before induction of anesthesia, during methohexital-induced anesthesia, and after administration of the μ-opioid receptor antagonist naloxone. Administration of incremental bolus doses of naloxone is indicated by arrows (*top*). Seventy-five minutes after the first injection of naloxone, a continuous infusion of naloxone (0.8 mg/h) was started. Concentrations of epinephrine in plasma increased 30-fold after administration of naloxone, and concentration of norepinephrine in plasma significantly increased threefold. †$P <$ 0.05 *versus* baseline in the awake state before induction of anesthesia; *$P < 0.05$ *versus* methohexical-induced anesthesia before administration of naloxone.

Cardiovascular Alterations

Administration of naloxone markedly increased heart rate within 1–2 min, from 89 ± 16 to a plateau of 108 ± 17 beats/min with no further increase. Stroke volume index also increased from 31 ± 8 to 45 ± 11 $ml \cdot m^{-2}$ ($P < 0.05$) but in a more gradual fashion. Increased heart rate and stroke volume index resulted in a marked increase in cardiac index, from 2.7 ± 0.41 to 4.7 ± 1.7 $min^{-1} \cdot m^{-2}$ (+74%), reaching a plateau after ≈45 min (fig. 2). In parallel, systemic vascular resistance index decreased from 2,484 ± 762 to 1,495 ± 539 $dyne \cdot s \cdot cm^{-5} \cdot m^{-2}$ ($P < 0.05$; fig. 2).

Systolic arterial pressure significantly increased from 113 ± 16 ± 5 to 138 ± 16 mmHg, reaching maximum 15–30 min after initiation of naloxone administration, whereas diastolic arterial pressure remained unchanged (71 ± 16 *vs.* 80 ± 16 mmHg after administration of naloxone, $P = 0.13$; fig. 3).

Mean pulmonary artery pressure increased from 15 ± 5 to 20 ± 4 mmHg ($P < 0.05$) at 30 min, whereas pulmonary vascular resistance remained normal and unchanged throughout the observation period.

Clinical Observations

The clinical signs of μ-opioid receptor blockade were observed in all patients: marked gastrointestinal secretion with 500–1,000 ml of fluids draining from the gastric tube and rectal discharges of 200–500 ml during the 180-min observation period.

None of the patients moved, coughed, or vomited during the observation period after administration of naloxone. Further, all patients showed miosis and absence of the corneal and glabella reflexes during anesthesia and administration of naloxone until sedation was terminated.

After discontinuation of methohexital 180 min after the first dose of naloxone, patients started sweating, hyperventilating, moving, and coughing. Patients were extubated 264 ± 219 min after administration of methohexital was stopped. No complications attributable to treatment with naloxone were observed.

Discussion

This study is the first to assess concentrations of catecholamine in plasma and cardiovascular alterations after μ-opioid receptor blockade in patients addicted to opioids. These results are clinically important for evaluation of potential cardiovascular risk and for guiding care and improving patient safety during acute detoxification in those addicted to opioids. This study represents a unique setting for assessment of the effects of acute μ-opioid receptor blockade in humans with a chronically stimulated opioid receptor system.

Most important, a 30-fold increase in concentration of epinephrine in plasma, a small increase in concentration of norepinephrine in plasma, and profound cardiovascular alterations were observed after μ-opioid receptor blockade despite maintenance of general anesthesia.

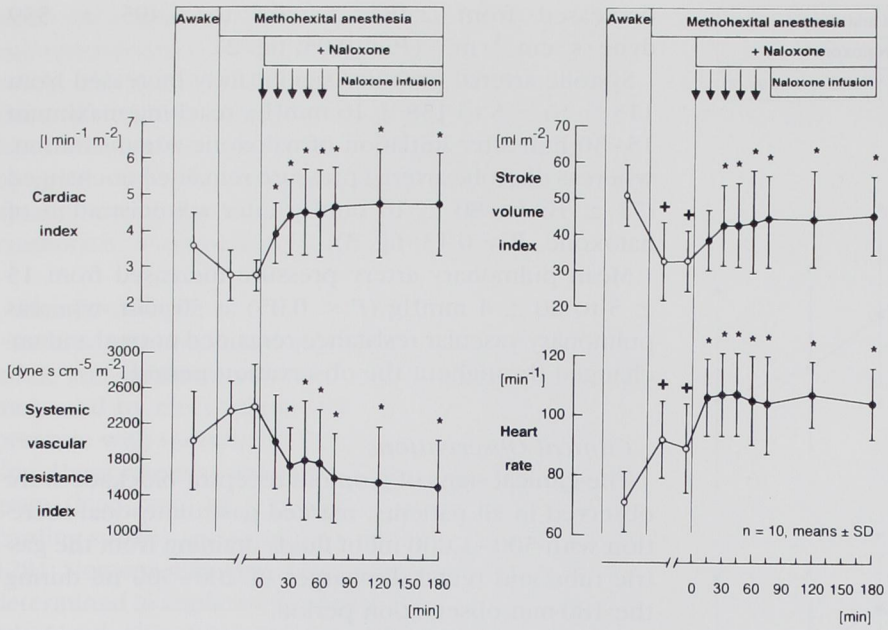

Fig. 2. Cardiovascular variables before induction of anesthesia, during methohexital-induced anesthesia, and after administration of the μ-opioid receptor antagonist naloxone. Administration of incremental bolus doses of naloxone is indicated by arrows (*top*). Seventy-five minutes after the first injection of naloxone, a continuous infusion of naloxone (0.8 mg/h) was started. Induction of anesthesia resulted in a significant decrease in stroke volume index and an increase in heart rate, whereas cardiac and systemic vascular resistance indices did not change significantly. Injection of naloxone was associated with a marked increases in cardiac and stroke volume indices and heart rate, whereas systemic vascular resistance index decreased. The observed effects of naloxone reached an apparent plateau within 60 min after the first injection of naloxone. †$P < 0.05$ *versus* baseline in the awake state before induction of anesthesia; *$P < 0.05$ *versus* methohexital-induced anesthesia before administration of naloxone.

Because of the attendant cardiovascular stimulation, we suggest that acute detoxification of patients addicted to opioids should be performed by trained anesthesiologists or intensivists.

Critique of Methods

Sympathetic nervous system activity, concentrations of catecholamine in plasma, and cardiovascular variables are potentially influenced by anesthesia, altered cardiac filling, and changes in arterial blood gas tensions induced by mechanical ventilation.[10–12] Barbiturate-induced anesthesia abolished corneal and glabella reflexes. The absence of circulatory stress during anesthesia at baseline before administration of naloxone was indicated by constantly decreased arterial pressure and stroke volume index and by low concentrations of catecholamine in plasma.[13,14] The increased heart rate observed after induction of anesthesia by methohexital is most likely due to its parasympatholytic activity.[15,16] To minimize changes that may alter sympathetic nervous system activity, central venous and pulmonary artery occlusion pressures were maintained by administration of Ringer's lactate solution, and normocarbia was established.

Effects of receptor antagonists depend on concentrations of receptor agonist and antagonist. In our patients, μ-opioid receptor blockade induced marked gastrointestinal secretion, indicating that effective doses of naloxone had been injected. Finally, when assessing the effect of long-term opioid receptor stimulation and blockade in addicted patients, interference with other drugs must be considered. In our study, we carefully selected only patients addicted to one opioid that was substituted with orally administered methadone and confirmed the absence of intake of other drugs by repeated drug screening.

In anesthetic practice, the μ-opioid receptor antagonist naloxone is the drug of choice for reversing opioid-induced respiratory depression. Rare but serious complications have been reported after μ-opioid receptor antagonization, however, including marked arterial hypertension, pulmonary edema, and sudden death after administration of even small doses of naloxone.[17–23] The exact mechanisms responsible for these adverse effects are unknown, and no data have been reported regarding cardiovascular alterations in patients addicted to opioids. Accordingly, to minimize potential complications, we administered naloxone in a stepwise fashion.

Interpretation of Results

Conventional detoxification from long-term intake of opioids in addicted patients is accompanied by unpleasant withdrawal symptoms and drop-out rates of up to 30% during initial therapy.[1] It is widely accepted that the severity of withdrawal symptoms during detoxification is positively correlated with the frequency of un-

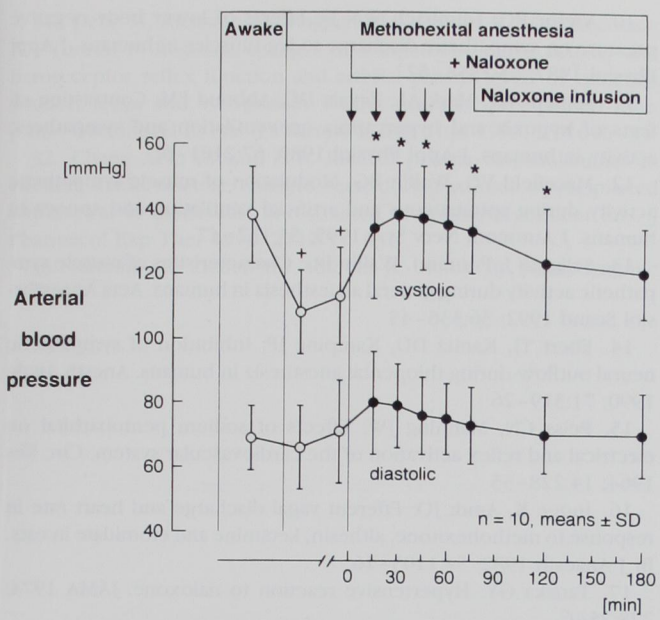

Fig. 3. Systolic and diastolic arterial pressures before induction of anesthesia, during methohexital-induced anesthesia, and after administration of the μ-opioid receptor antagonist naloxone. Administration of incremental bolus doses of naloxone is indicated by arrows (*top*). Seventy-five minutes after the first injection of naloxone, a continuous infusion of naloxone (0.8 mg/h) was started. Induction of anesthesia resulted in a significant decrease in systolic arterial pressure. Administration of naloxone induced a 22% increase in systolic arterial pressure, reaching a maximum at 30 min, whereas diastolic arterial pressure remained unchanged. †$P < 0.05$ *versus* baseline in the awake state before induction of anesthesia; *$P < 0.05$ *versus* methohexital-induced anesthesia before administration of naloxone.

successful therapy. Accordingly, general anesthesia is induced before μ-opioid receptor blockade in the approach described here of acute opioid detoxification to prevent perception of withdrawal symptoms by the patient. The purpose of administering high doses of naloxone is to terminate μ-opioid receptor stimulation rapidly and to prepare maintenance of prolonged μ-opioid receptor blockade by naltrexone while minimizing withdrawal symptoms, *e.g.*, by administration of the α_2-receptor agonist clonidine. Studies with this new approach have been aimed mainly at psychiatric variables, and,[2-6,23-25] to our knowledge, the cardiovascular effects of high-dose naloxone in patients addicted to opioids have not been described previously.

Although naloxone, even when injected in high doses (0.15 mg/kg) in healthy volunteers, does not increase concentrations of epinephrine in plasma,[26-28] heart rate, arterial or central venous pressures, or efferent sympathetic nerve activity to calf muscle in the absence of opioid receptor agonist stimulation,[29,30] we observed a 30-fold increase in the concentration of epinephrine in plasma and a threefold significant increase in the concentration of norepinephrine in plasma. Maximum concentrations of catecholamine in plasma were attained 45-60 min after the initial injection of naloxone with a total dose of 2.8-6.0 mg naloxone administered. In parallel, cardiac output (+74%), heart rate (+24%), stroke volume (+44%), and systolic arterial pressure (+22%) increased, whereas systemic vascular resistance decreased (−40%).

It is noteworthy that a similar pattern of changes in the concentrations of catecholamine in plasma was observed earlier in awake morphine-dependent rats after administration of naloxone and was abolished by removal of the adrenal glands, suggesting that the increase in concentration of epinephrine in plasma is due to increased adrenal release of epinephrine.[31,32]

Cardiovascular changes observed in our study are in line with β-adrenoceptor effects of epinephrine and, accordingly, may be mediated by the determined alterations in concentrations of catecholamine in plasma. This hypothesis is supported by other data.

Infusion of epinephrine in awake volunteers increased concentration of epinephrine in plasma from 50 to 480 pg/ml, *i.e.*, to concentrations very similar to those observed in our study after μ-opioid receptor blockade by naloxone; increased heart rate by 24%, cardiac output by 74%, and stroke volume by 40%; and decreased systemic vascular resistance by 31%.[33] Most of these cardiovascular changes were attained at plasma concentrations of 260 pg/ml, with few additional changes when the concentration of epinephrine in plasma was further increased.[33] Concentrations of norepinephrine in plasma also increased (by 60%) during infusion of epinephrine, possibly secondary to the decrease in systemic vascular resistance induced by epinephrine, and this increase in concentration can be considered hemodynamically important.[33] Accordingly, these data taken together support the assumption that cardiovascular stimulation observed in our study after μ-opioid receptor blockade is mediated to a major extent by increased concentrations of epinephrine in plasma.

Although our study design does not allow us to pinpoint responsible mechanisms for the profound increase in the concentration of epinephrine in plasma after μ-opioid receptor blockade by naloxone in patients addicted to opioids, potential mechanisms in-

clude direct effects of naloxone, μ-opioid receptor antagonization on the adrenal medulla,[34] and neurally mediated changes of central sympathetic outflow, *e.g.*, by disinhibition and resetting of cardiopulmonary baroreflexes.[35] The 30-fold increase in the concentration of epinephrine in plasma in the absence of a quantitatively similar increase in that for norepinephrine is rather atypical for a generalized activation of the sympathetic nervous system.

Despite maintenance of general anesthesia, μ-opioid receptor blockade in patients addicted to opioids undergoing methadone substitution induces a profound increase in the concentration of epinephrine in plasma and cardiovascular stimulation in a pattern similar to that observed with infusion of epinephrine in healthy volunteers. Because of the attendant cardiovascular changes, we suggest that acute detoxification of patients addicted to opioids should be handled by trained anesthesiologists or intensivists.

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