Anesthesiology
1999; 91:1639–47

Rapid Opioid Detoxification during General Anesthesia

A Review of 20 Patients

Carl G. Gold, M.D., M.A., David J. Cullen, M.D., M.S.,† Scott Gonzales, M.D.,‡ Deirdre Houtmeyers, R.N.,§ Mary Jo Dwyer, A.S.‖*

Background: **Opioid addiction therapy includes successful detoxification, rehabilitation, and sometimes methadone maintenance. However, the patient may have physical, mental, and emotional pain while trying to achieve abstinence. A new detoxification technique that incorporates general anesthesia uses a high-dose opioid antagonist to compress detoxification to within 6 h while avoiding the withdrawal.**

Methods: **After Institutional Review Board approval and detailed informed consent, 20 patients, American Society of Anesthesiologists status I–II, addicted to various opioids underwent anesthesia-assisted rapid opioid detoxification. After baseline hemodynamics and withdrawal scores were obtained, anesthesia was induced. After testing with 0.4 mg intravenous naloxone, 4 mg nalmefene, was infused over 2 to 3 h. After emergence, severity of withdrawal was scored before and after administration of 0.4 mg intravenous naloxone. After 24 h, patients began outpatient follow-up treatment while taking oral naltrexone.**

Results: **All 20 patients were successfully detoxified with no adverse anesthetic events. After the first post-treatment test dose of 0.4 mg naloxone, 13 of 20 patients had no signs of withdrawal and hemodynamic changes were minimal. Withdrawal scores were always very low and similar before and after detoxification. Three of 17 patients (18%) available for follow-up have remained abstinent from opioids since treatment (≤ 18 months). Four other patients are clean after brief relapses.**

Conclusions: **Anesthesia-assisted opioid detoxification is an alternative to conventional detoxification. (Key words: Drug abuse rehabilitation; human addictive disorders; narcotic detoxification; μ-opioid receptor blockade.)**

REHABILITATION of people addicted to opioids can only begin after an initial period of abstinence. This period is variable and is associated with an extremely unpleasant "withdrawal" syndrome.[1] The character and severity of symptoms such as sweating, shivering, nausea, vomiting, diarrhea, abdominal cramping, anxiety, and muscle pain are major deterrents to patients wanting or needing to undergo detoxification. Conventional detoxification methods include tapering doses of a substitute agonist drug,[2,3] the use of μ-opioid receptor antagonists,[4] and the use of clonidine, which has been used alone and in combination with antagonists to reduce withdrawal symptoms.[5]

These techniques, requiring 3–21 days, are associated with the onset of the withdrawal syndrome described previously and may necessitate admission for inpatient monitoring. Consequently, significant initial dropout rates are seen, ranging from 30–91%.[6–8] Recently, a different approach to detoxification from opioids emerged: the administration of a high-dose μ-receptor antagonist during general anesthesia. Well-designed protocols accelerate detoxification and attenuate withdrawal symptoms. The procedure should result in 100% detoxification rates, should be safe, and should be accomplished in 4–6 h.[9,10] This concept is supported by the work of Rasmussen *et al.,*[11] which demonstrated that electrophysiologic, biochemical, and behavioral param-

* Instructor in Anesthesiology, Tufts University School of Medicine.

† Professor of Anesthesiology, Tufts University School of Medicine.

‡ Medical Director, The UniQual Network.

§ Executive Director, St. Elizabeth's Comprehensive Addiction Program.

‖Anesthesia Manager, St. Elizabeth's Medical Center.

Received from the Department of Anesthesiology and the St. Elizabeth's Comprehensive Addiction Program (SECAP), Department of Medicine, St. Elizabeth's Medical Center, Boston, Massachusetts, and The UniQual Network, Wellesley, Massachusetts. Submitted for publication December 23, 1998. Accepted for publication July 8, 1999. Supported in part by a grant from the UniQual Addiction Network (UAN), Wellesley, Massachusetts. The UniQual Addiction Network is a private company dedicated to establishing a network of anesthesia-assisted opioid detoxification programs and comprehensive rehabilitation services. Presented at the 1998 Annual Meeting of the American Society of Anesthesiologists, Orlando, Florida, October 20, 1998, and at the 1998 National Meeting of the Association for Medical Education and Research in Substance Abuse, Washington, DC, November 7, 1998.

Address reprint requests to Dr. Gold: Department of Anesthesiology, St. Elizabeth's Medical Center, CMP2A, 736 Cambridge Street, Boston, Massachusetts 02135-2997. Address electronic mail to: cgold@tiac.net

Table 1. Dose and Duration of Opioid Use (n = 20)

Drug of Choice	Number of Patients	Dose (mg/day)		Duration of Use (mo)	
		Range	Mean ± SD	Range	Mean ± SD
Methadone	5	8–96	47 ± 28	3–36	14 ± 12
Hydrocodone	3	55–125	85 ± 29	3–50	27 ± 14
Heroin	10	50–250	112 ± 60	3–84	34 ± 21
Butorphanol tartrate	1*	25–75	50	48	N/A
Meperidine hydrochloride		300	N/A		
Oxycodone	1*	60	N/A	24	N/A
Hydromorphone		24	N/A		

N/A = not applicable.

* Chronic pain patients who predictably returned to narcotic pain medication. The last patient listed was dependent on three drugs.

eters of opioid withdrawal, primarily involving the nucleus locus coeruleus, peak and then recover to near baseline within 4–6 h after administration of high doses of opioid antagonist to morphine-addicted rats.

The purpose of this article is to report a detailed protocol for a single method of anesthesia-assisted opioid detoxification and the results of treatment for 20 patients.

Materials and Methods

Patients

The Institutional Review Board of St. Elizabeth's Medical Center approved the protocol for the procedure, which included very detailed informed consent. Twenty patients, American Society of Anesthesiologists status I–II, addicted to various opioids were screened by St. Elizabeth's Comprehensive Addiction Program (SECAP) and referred to the Department of Anesthesiology for treatment. The patients presented to the hospital at least 1 day before the procedure and were evaluated by a physician who specialized in the practice of addiction medicine and by an anesthesiologist. Screening included a detailed clinical history, physical examination, blood analysis for complete blood count, serum chemistries, and liver function tests. Urine toxicology screening was performed for opioids, benzodiazepines, methadone, phencyclidine, cocaine, amphetamine, cannabinoids, barbiturates, propoxyphene, tricyclics, and alcohol. An electrocardiogram (ECG) and chest radiograph were also obtained. The patients were then admitted to St. Elizabeth's Comprehensive Addiction Program for observation and preparation.

All patients were at least 18 yr of age (range, 27–48 yr; mean, 37.6 yr). Eleven patients reported isolated use of more than one opioid. The additional opioids used and dosage and duration of use were extremely variable and would not be expected to influence withdrawal or detoxification. All patients are described herein according to the drug used most frequently, *i.e.*, by drug of choice (table 1).

Six patients reported a history of failure to withdraw from opioids on their own, and 14 patients were unsuccessful with previous detoxification techniques. The five most common symptoms were nausea, (18 patients), diarrhea (15 patients), diaphoresis (12 patients), abdominal cramping (12 patients), and muscle aches (11 patients). All patients reported that their symptoms were relieved by administration of opioid.

Two patients with previously diagnosed chronic pain syndromes were using high doses of opioid analgesics that were not approved by their treating physicians. One patient was using nasal butorphanol tartrate, 60–75 mg/day for 48 months, for low back pain that caused a reduction in employment status to approximately 20 h per week and limited his daily activities. The second patient was using meperidine hydrochloride, 300 mg/day, oxycodone, 60 mg/day, and hydromorphone, 24 mg/day, for 30 months for neck pain that resulted from a motor vehicle accident. This patient was not able to work and was severely limited in his daily activities. No formal pain assessment was performed before detoxification. The patients were referred for detoxification to attenuate tolerance to opioids.

Comorbid conditions included hepatitis A, B, or C (nine patients), depression (nine patients), bladder cancer (one patient, postresection), bulimia (one patient), and insulin-dependent diabetes (one patient). Eight other patients showed laboratory evidence of elevated liver enzymes without an established diagnosis. No patient had evidence of compromised hepatic synthetic function. Comorbid conditions were determined to be

Table 2. Comparison of Urine Toxicology with Self-reporting of Drug Abuse

Drugs Involved	Number of Patients with Positive Urine Toxicology Screen Findings (n = 17)	Number of Patients Self-reporting Drug Abuse (n = 20)
Benzodiazepines	9	10
Tricyclic antidepressants	4	0*
Barbiturates	3	0
Propoxyphenes	1	1
Amphetamines	1	1
Opioids	14	20
Phenylcyclidine (PCP)	0	0
Cocaine	3	3
Tetrahydrocannabinol (THC)	4	4
Methadone	4	4
Ethanol	0	2

* Nine patients reported using serotonin uptake inhibitors for depression.

optimally managed and stabilized before acceptance into the program.

Eighteen patients reported abusing drugs other than opioids in various combinations (alcohol, 2 patients; marijuana, 4 patients; cocaine, 3 patients; benzodiazepines, 10 patients; propoxyphene, 1 patient; amphetamine, 1 patient). Nine patients were taking serotonin reuptake inhibitor antidepressants, as prescribed. Five patients were prescribed methadone. No patient was diagnosed as dependent on any drugs other than opioids or antidepressants. The Diagnostic and Statistical Manual of Mental Disorders,[12] fourth edition, (DSM-IV) criteria were used to define "dependence" and "abuse."

Results of qualitative urine toxicology screening for 11 drugs were available for 17 patients and are listed in table 2. These are compared with the number of patients that self-reported abusing the drug listed. Three patients were not tested or the results were lost. There were 14 positive test results for opioids, 9 positive test results for benzodiazepines, 4 positive test results each for methadone, tricyclics, and cannabinoids, 3 positive test results each for cocaine and barbiturates, and 1 positive test result each for amphetamine and propoxyphene. Test results for one patient were negative for any drug, for two patients were positive for opioids only, for five patients were positive for two drugs, for five patients were positive for three drugs, and for four patients were positive for four drugs.

The use of high doses of opioid antagonist or somatostatin in children, adolescents, pregnant women, or nursing mothers has not been studied. There are no reports of anesthesia-assisted opioid detoxification performed in these patient populations. Patients with severe hepatic disease are at risk for complications associated with the use of high doses of the hepatically metabolized drugs clonidine, propofol, nalmefene, and naltrexone. Patients with known hypersensitivity to any of the medications used would be at risk for allergic complications. Therefore, these patients were excluded from treatment.

Patients with a dual addiction to opioids and alcohol are at increased risk for complications compared with patients with no other addictions. Studies suggest the involvement of the opioid system in alcohol dependence,[13] and it is well-established that acute withdrawal from alcohol is associated with significant morbidity and mortality. Although precipitating a withdrawal syndrome using an opioid antagonist in these dually addicted patients has not been reported, these patients were also excluded from treatment.

Methods

On the morning of the procedure, the patients were transported to the postanesthesia care unit (PACU). Monitors included five-lead, two-channel electrocardiography (leads II and V), noninvasive blood pressure, pulse oximetry, train-of-four neuromuscular monitoring, end-tidal carbon dioxide monitoring, an esophageal temperature probe (°C), and a Bispectral Index monitor (BIS) (Aspect Medical Systems, Inc., Natick, MA). Lactated Ringer's solution was infused through a 20-gauge peripheral intravenous catheter. Fluid loading was standardized by assuming that each patient had an 8-h deficit, based on body weight, that was replaced by infusing fluid at three to four times the calculated maintenance rate until the deficit was replaced.[14] The infusion was then slowed to the maintenance rate, also based on body weight,[15] for the duration of the procedure. Baseline hemodynamic values and withdrawal scores were

Table 3. Clinical Institute Narcotic Assessment (CINA) Scale

Abdominal changes: → Ask—"Do you have any pains in your abdomen?" 0 = No abdominal complaints, normal bowel sounds 1 = Reports waves of abdominal crampy pain 2 = Reports crampy abdominal pain, diarrheal movements, active bowel sounds	Restlessness: → Observation 0 = Normal activity 1 = Somewhat more than normal activity, moves legs up an down, shifts position occasionally 2 = Moderately fidgety and restless, shifting position frequently 3 = Gross movement most of the time or constantly thrashes about	
Goose flesh: → Observation 0 = No goose flesh visible 1 = Occasional goose flesh but not elicited by touch, not permanent 2 = Prominent goose flesh, in waves and elicited by touch 3 = Constant goose flesh over flesh and arms	Tremor: → Arms extended and fingers spread apart 0 = No tremor 1 = Not visible but can be felt fingertip to fingertip 2 = Moderate with patient's arm extended 3 = Severe even if arms not extended	Muscle aches: → Ask "Do you have any muscle cramps?" 0 = No muscle aching reported, arm and neck muscles soft at rest 1 = Mild muscle pains 3 = Reports severe muscle pains, muscles of legs, arms and neck or constant state of contraction
Changes in temperature: → Ask "Do you feel hot or cold?" 0 = No report of temperature changes 1 = Reports feeling cold, hands cold and clammy to touch 2 = Uncontrolled shivering	Nausea and vomiting: → Ask "Do you feel sick in your stomach? Have you vomited?" 0 = No nausea, no vomiting 2 = Mild nausea with no retching or vomiting 4 = Intermittent nausea with dry heaves 6 = Constant nausea, frequent dry heaves and/or vomiting	Sweating: → Observation 0 = No sweat visible 1 = Barley perceptible sweating, palms more 2 = Beads of sweat obvious on forehead 3 = Drenching sweat over face and chest
Nasal congestion: → Observation 0 = No nasal congestion, sniffling 1 = Frequent sniffling 2 = Constant sniffling, watery discharge	Lacrimentation: → Observation 0 = No lacrimentation 1 = Eyes watering, tears at corners of eyes 2 = Profuse tearing from eyes over face	Yawning: → Observation 0 = No yawning 1 = Frequent yawning 2 = Constant uncontrolled yawning

obtained before any medications were administered. All medications were administered intravenously. Withdrawal scores were determined using an adapted scoring system referred to as the Clinical Institute Narcotic Assessment (CINA) withdrawal scale[16] (table 3). The CINA scale assigns a point value (0–6), depending on the specific parameter and according to severity, to a specific set of 11 withdrawal signs and symptoms. The range of scores is from 0 to 31.

Before induction, the patients were premedicated with 0.2–0.4 mg glycopyrrolate and 450–600 μg clonidine. Clonidine was administered to attenuate systemic effects of the withdrawal[17,18] that would soon occur as a result of the administration of antagonist. The dose was titrated against decreases in heart rate and blood pressure to 80% of the baseline values. If this degree of change did not occur, the maximum dose administered was 600 μg.[19]

The patients were then preoxygenated with 100% oxygen and general anesthesia was induced with 2–2.5 mg/kg propofol and 0.1–0.2 mg/kg cisatracurium. After ablation of the twitch response to train-of-four stimulation, the trachea was intubated, and the patients were mechanically ventilated with oxygen and air (fractional inspired oxygen concentration, 0.21–0.35). During the preliminary phase of

developing the protocol, general anesthesia for the first 10 patients was maintained by propofol infusion titrated to a Bispectral Index value of 40–60 and supplemental cisatracurium titrated to maintain a one-of-four twitch response. For subsequent patients, general anesthesia was maintained by propofol infusion combined with desflurane, 1–3%, titrated to a Bispectral Index value of 40–60, and cisatracurium as described. After induction, a urinary catheter, an orogastric tube, and an esophageal temperature probe were placed. Venodyne boots were applied to the patients' lower extremities and a pillow was placed under their knees. The patients' vital signs were recorded every 5 min and the Bispectral Index values and core temperature were recorded every 15 min.

Octreotide was then given intravenously as a 50-μg bolus dose followed by an infusion of 50 μg/h to a total dose of 300 μg to control gastrointestinal secretions.[20] In addition to the cited references, information in the Physician's Desk Reference[21] provided the basis for the dosing schedule.

After the patients were hemodynamically stable, a test dose of 0.4 mg intravenous naloxone was administered.[22–24] To minimize risk, we administered a single dose of 0.4 mg intravenous naloxone after general anesthesia was established. This was intended to test the degree of physiologic homeostasis achieved by premedication. The patients were observed for signs of withdrawal (piloerection, movement, lacrimation, increases in heart rate or blood pressure) for 5 min. If any response was noted, 100–200 μg clonidine was administered as needed to control the response.

At this point, detoxification was continued by starting a nalmefene infusion.[25–27] Based on published studies, we ultimately chose a dose of 4 mg intravenous nalmefene to achieve significant receptor blockade that would persist until maintenance therapy could be established after emergence and extubation by the administration of oral naltrexone.

For the first patient, nalmefene was infused at 1 $\mu g \cdot kg^{-1} \cdot h^{-1}$ for 1 h followed by infusion of the remainder of a 2-mg dose over the next 2 h. For the next 16 patients, the same schedule was followed, but the total dose was increased to 4 mg. For subsequent patients, the total dose of nalmefene (4 mg) was infused over 2 h. The dose was increased after the first patient because of the presence of moderate-to-severe withdrawal symptoms after the procedure. This suggested that the detoxification process was incomplete and therefore did not follow the time course suggested by previous studies.[4,11]

After the nalmefene infusion was complete, administration of cisatracurium was discontinued, allowing spontaneous recovery of the train-of-four twitch response over the next 1 to 2 h to avoid having to reverse neuromuscular blockade. The patient was monitored for signs of withdrawal for 30–60 min after discontinuation of the nalmefene infusion, and no patient required treatment. At this time, 8 mg intravenous ondansetron was administered, and the patient was observed for another 30–60 min. Approximately 1 h before emergence, blood was drawn and sent for analysis of serum electrolytes and osmolality. The anesthetic drugs were discontinued, and emergence followed very quickly. Before emergence and extubation, the orogastric tube, esophageal temperature probe, and urinary catheter were removed. Lidocaine jelly was placed into the patient's urethra after removal of the catheter to facilitate patient comfort. The patient's trachea was extubated when clinically indicated. After the patient was able to respond to simple questions, another withdrawal score was obtained, followed immediately by an injection of naloxone, 0.4 mg intravenous. After 5 min of observation, the withdrawal assessment was again repeated to assess any changes withdrawal signs or symptoms.

If no signs or symptoms of withdrawal were seen or if withdrawal scores were less than 7, the procedure was deemed complete, and the patient recovered in the PACU for 1 to 2 h as indicated. Withdrawal signs and symptoms were treated with adjunct medications: ketorolac, midazolam, or clonidine, as needed. When the patient was fully stabilized and oriented, 50 mg naltrexone was administered orally. The patient was then discharged to the medical floor at St. Elizabeth's Comprehensive Addiction Program. After a total hospital stay duration of approximately 24 h, patients began outpatient aftercare. This included naltrexone maintenance therapy, counseling, follow-up examinations, and participation in a 12-step program.

Follow-up information was obtained from each patient and corroborated by at least one immediate family member. This was done by telephone interviews using a standardized set of questions concerning perceptions about the procedure, current social situation, including family and work status, and current drug use.[28]

Statistical Analysis

Values are reported as the mean values of the variable for the group ± SD. Differences in mean values of variables over time were tested by one-way repeated-measures analysis of variance followed by the paired

Table 4. CINA Withdrawal Scores (n = 20) [range 0–31]

	Mean ± SD	*P* Value
CINA before detox	2.9 ± 0.5	
CINA after emergence	3.1 ± 1.9	NS
CINA after naloxone*	2.9 ± 2.0	NS

NS = not significant.

* Naloxone administration after emergence from anesthesia.

Student *t* test. Statistical significance was assumed for a P value < 0.05.

Results

All 20 patients successfully completed detoxification without any adverse medical or anesthetic events. Detoxification was verified by documentation of no significant withdrawal response to naloxone administered just after emergence from anesthesia (table 4). Furthermore, although no CINA score was obtained at the time, all patients tolerated 50 mg naltrexone without subjective changes in withdrawal symptoms before leaving the PACU. Changes in systolic arterial pressure and heart rate during the procedure were minimal. The only statistically significant change was a slight increase in the mean diastolic blood pressure after completion of the nalmefene infusion. Core temperatures remained at baseline values (± 1°C).

At completion of the procedure, the first patient had moderate-to-severe withdrawal symptoms. He was treated by titrating doses of clonidine and midazolam intravenously until the symptoms were controlled. CINA scores decreased from 12 of 20 to 4 of 20. Six of 20 patients showed no signs or symptoms of withdrawal, and 13 had mild symptoms suggested by withdrawal scores ranging from 1 of 20 to 4 of 20. Those patients were treated with clonidine in incremental doses ranging from 100 to 400 μg and with midazolam in incremental doses ranging from 0.5 to 4.0 mg. No patient received midazolam after leaving the PACU.

Table 5 shows mean values for the total amounts of the primary anesthetic drugs used in the procedure and mean values for total intravenous fluid administration and urine output. Approximately 1 h before emergence from anesthesia, serum sodium, potassium, chloride, carbon dioxide, and plasma osmolality were all within normal ranges, suggesting that there is no clinically significant effect of detoxification on serum electrolytes, glucose, or osmolality.

No significant episodes of nausea, vomiting, or diarrhea occurred immediately after the procedure. Nausea developed in four patients in the early postprocedure period. Sixteen patients met all discharge criteria within 24 h after the procedure, of whom 6 were discharged. Patients were eligible for discharge when (1) oral intake of fluids was tolerated, (2) nausea was absent or controlled with therapy, (3) diarrhea was absent or controlled with therapy, (4) urine was voided without difficulty, (5) fever was absent, and (6) unassisted ambulation was possible. Fourteen patients remained in the hospital for more than 24 h: two for placement in a residential treatment facility, four to arrange home support, four because of a subjective sense of generalized malaise, and four for treatment of nausea. Seven patients were discharged within 24–48 h after the procedure, four patients were discharged within 48–72 h, and three patients were discharged within 72–96 h.

One patient, a 42-yr-old man, was found dead in bed at approximately 8:00 AM of the second day postprocedure, approximately 41 h after completion of the procedure. He was observed by the nursing staff 7 h before and had no complaints. At arrival of the "code team," the patient was found supine in bed, unresponsive, cyanotic, cold, and with rigor mortis.

At the time of this report, 3 of 17 patients (18%) who were expected to remain abstinent since treatment have done so (≤ 18 months). Follow-up for all patients is ongoing. Another four patients are "clean," but experienced relapse within 1 month to 1 yr after discharge. Two patients have been lost to follow-up, three transferred to methadone maintenance programs, four relapsed to active drug use, and one died of an accidental overdose of heroin in January 1999.

The two patients treated for chronic pain are continuing opioid analgesic therapy as planned. The patient previously taking 60–75 mg/day butorphanol tartrate is being treated with 30 mg/day. By patient report, this provides adequate analgesia to facilitate full-time employment and independence in daily activities. The other patient, previously treated with moderate to high doses of three agents, is treated with controlled-release morphine sulfate on a dosing schedule of 120 mg, 4 times per day. By patient report,

Table 5. Drugs/Fluids/Urine Output (n = 20)

	Mean ± SD
Propofol (mg)	2,289 ± 814
Clonidine (μg)	640 ± 139
IV fluids (ml)	2,015 ± 563
Urine output (ml)	1,507 ± 675

this provides adequate to good relief of pain and facilitates independence in activities of daily living and caring for his disabled spouse. He is not able to work.

Discussion

This is the first publication to report a detailed protocol for anesthesia-assisted opioid detoxification. Other studies have described the essential characteristics of precipitating and attenuating an acute withdrawal syndrome in patients addicted to opioids.[29–31] Clinical[4] and animal studies[11] show that withdrawal symptoms peak and return to near baseline within 4–6 h, thus establishing the expected time course for the procedure.

Patient reports of drug abuse and results of urine toxicology screening obtained at admission compare well (table 2). It is not clear why three patients showed negative screening results for any opioid. Perhaps highly motivated patients abstained long enough before testing that the amount of drug remaining in the blood was below minimum detectable levels. The rates reported for false-negatives in our laboratory for these tests are 0% for specimens containing 300 ng/ml or more of the drug.

Although electrocardiography or chest radiography findings for any patient before admission were not significant, they might be useful to establish baseline information.

Prophylaxis for gastrointestinal symptoms of withdrawal included H_2-receptor antagonist therapy administered the night before and again on the morning of the procedure. Antidiarrheal therapy was never prescribed. No patient experienced adverse gastrointestinal events in the interval between admission and the time of the procedure.

A major concern about this procedure has been the safety of general anesthesia when combined with opioid addiction and comorbid conditions.[32] No data specifically address the influence of the conditions described in this report of the extent of withdrawal precipitated by an opioid antagonist. However, patients with comorbid depression can be detoxified with opioid antagonists during general anesthesia without adverse outcomes or specific drug interactions.[33,34] Profound increases in plasma catecholamine levels during anesthesia-assisted opioid detoxification associated with significant cardiovascular changes have been shown.[35] Yet, we saw no significant changes in systolic arterial pressure or heart rate. Although this does not exclude the possibility of cardiovascular stimulation, any of the indices based on heart rate or systolic arterial pressure should show a lesser degree of stimulation than that observed in the study referenced previously. We did not analyze plasma samples for catecholamine levels, but using our protocol, no end-organ effects were seen. Presumably, this was caused in part by the noradrenergic stabilizing effects of clonidine and the use of different anesthetics.

A recent study showed significant increases in respiratory rate, minute ventilation, oxygen consumption, and carbon dioxide production in patients undergoing anesthesia-assisted opioid detoxification who were allowed to breathe spontaneously.[36] We maintained deep anesthesia, muscle relaxation, and controlled ventilation during the procedure to hold end-tidal carbon dioxide at 28–38 mmHg associated with oxygen saturation measured by pulse oximetry at more than 97%. Whether the patient benefits from this approach is not clear and necessitates further investigation. In our study group, as muscle relaxation diminished, several patients exhibited spontaneous and random-appearing muscle activity, perhaps reflecting effects of the antagonist on receptors in the spinal cord.[37,38]

We believe detoxification was complete because CINA withdrawal scores after emergence were always low for all patients, suggesting a significant decrease in withdrawal physiology. Furthermore, the scores did not change significantly after administration of a final intravenous test dose of 0.4 mg naloxone (table 4). Finally, all patients tolerated 50 mg naltrexone before leaving the PACU without subjective changes in withdrawal symptoms, a clinical end point in previous studies of antagonist-induced opioid detoxification.[5,39,40]

Patients were administered appropriate doses of adjunct medications as indicated, such as ketorolac, midazolam, or clonidine. For two patients, subsequent doses of naltrexone were unable to be administered until nausea was controlled (up to 3 days). This allowed blood levels to decrease and minimized receptor blockade, increasing the risk for immediate relapse. In response, the initial dose was increased for the twentieth patient (and all subsequent patients) to 150 mg, providing a sufficient level of receptor blockade for 3 days.[41]

The occurrence of mild-to-moderate withdrawal symptoms for 3 to 4 days after a rapid detoxification procedure is expected.[4,11] Studies of anesthesia-assisted detoxification published in the peer-reviewed literature report the severity and character of withdrawal symptoms as relatively minor after this type of treatment.[9,10,29,31] Our results support these conclusions.

This protocol provides another alternative to traditional techniques for detoxification from opioids. Long-term abstinence rates (*i.e.*, 12–18 months) appear to be comparable with rates for conventional therapies, which range from

20–30%.[42] Assuming similar long-term abstinence rates, the major value in the anesthesia-assisted procedure is the 100% success rate in achieving detoxification. Therefore, a larger absolute number of patients will begin rehabilitation and achieve long-term abstinence.

Overall function improved with lower effective doses after return to opioid analgesic therapy for both patients with chronic pain, who received high doses of single or multiple agents. However, no data specifically address the effects of detoxification on tolerance to opioids in patients with chronic pain.

The death of one patient on the second day postprocedure shows a possible risk of rapid detoxification from opioids. At the bedside, no information was apparent about the cause of death, and no autopsy was performed, at the family's insistence. Analysis of blood samples showed the presence of medications, prescribed according to protocol, in concentrations reflecting appropriate dosing. The presence of illicit drugs was not found in the analysis. Preoperative evaluation revealed only a remote history of hypertension that was not being treated at the time of admission. Blood pressure was not elevated before the procedure. In the absence of any further information, we cannot know whether this death was a result of the detoxification procedure. Certainly, it shows the need for continuous monitoring of these patients during their hospital course and may suggest the need to observe selected patients beyond the first 24 h after the procedure.

Patients paid approximately $6,000 for professional and hospital services. This is a comprehensive price and includes preadmission testing, a bed on the addiction medicine service ward, the detoxification procedure, and all follow-up rehabilitation services for 6 months. Other programs charge $2,500–$7,500,[9,42] which often does not include comprehensive rehabilitation.

Anesthesia-assisted opioid detoxification followed by naltrexone maintenance may be more cost-effective than long-term methadone maintenance.[43] A recent survey reported the average annual cost for "standard methadone treatment" to be between $3,750 and $4,400,[44] not including counseling services. This cost is cumulative. Naltrexone costs $4.50–$5.00 per 50-mg tablet, or $1,642–$1,825 per yr for a 50-mg/day dosing regimen. Combined with the $6,000 cost of the detoxification procedure, the cost for the first year would be between $7,642 and $7,825. However, naltrexone maintenance is discontinued as the patient adopts behavior consistent with long-term abstinence. Therefore, the cost decreases progressively.

As the role for anesthesia-assisted opioid detoxification evolves, experts in addiction medicine debate issues of safety, effectiveness, and cost-effectiveness. Essentially, all agree on the importance of establishing comprehensive psychologic and psychosocial aftercare programs and long-term outcome data.[31,32,42]

In summary, anesthesia-assisted opioid detoxification is an alternative to conventional techniques. Using an appropriate protocol of premedication and supportive treatment during the procedure, we observed no significant hemodynamic or physiologic derangement. The initial detoxification rate is 100%. Eighteen percent of patients remained abstinent since discharge (≤ 18 months), which is comparable with 20–30% for traditional methods of detoxification.[42] Because all patients are successfully detoxified by the procedure, the absolute number of patients beginning rehabilitation is greater, compared with traditional techniques. Assuming similar rates of achieving a specific long-term abstinence end point, compared with traditional detoxification techniques, the absolute number of patients achieving that end point also is greater. This feature may prove to be a significant advantage in the treatment of opioid-addicted patients. The procedure may prove to be cost-effective as well. Long-term outcome studies and large, multicenter studies using standardized protocols and appropriate controls will further define the value of anesthesia-assisted opioid detoxification.

The authors thank Magda Bishai, M.D., Richard Eng, M.D., Kenneth MacDonnell, M.D., Andrew Menard, Esq., Harry Barnett, Esq., Kathy Kiley, R.N., and the staff of the postanesthesia care unit and St. Elizabeth's Comprehensive Addiction Program at St. Elizabeth's Medical Center.

Editor's Note:

The use of nalmefene for rapid narcotic detoxification as described in the preceeding article may be covered entirely or in part by US Patents 5,783,583 (April 12, 1996) and 5,922,705 (April 13, 1998) assigned to David Simon and Intensive Narcotic Detoxification Centers of America, LLC (Toland, CT).

References

1. O'Connor PG, Kosten TR: Management of opioid intoxification and withdrawal, Principles of Addiction Medicine. Edited by Miller N. Washington DC, American Society of Addiction Medicine, 1994, pp 1–6

2. Dole VP: A medical treatment for diacetylmorphine (heroin) addiction. JAMA 1965; 193:646–50

3. Bickel WK, Amass L, Higgins ST, Badger GJ, Esch RA: Effects of adding behavioral treatment to opioid detoxification with buprenorphine. J Consult Clin Psychol 1997; 65:803–10

4. Resnick RB, Kestenbaum RS, Washton A, Poole D: Naloxone-precipitated withdrawal: A method for rapid induction onto naltrexone. Clin Pharmacol Ther 1977; 21:409–13

5. O'Connor PG, Carroll KM, Shi JM, Schottenfeld RS, Kosten TR,

Rounsaville BJ: Three methods of opioid detoxification in a primary care setting. A randomized trial. Ann Intern Med 1997; 127:526–30

6. Mattick RP, Hall W: Are detoxification programmes effective? Lancet 1996; 347:97–100

7. Gold ML, Sorensen JL, McCanlies N, Trier M, Dlugosch G: Tapering from methadone maintenance: Attitudes of clients and staff. J Subst Abuse Treat 1988; 5:37–44

8. Azatian A, Papiasvilli A, Joseph H: A study of the use of clonidine and naltrexone in the treatment of opioid addiction in the former USSR. J Addict Dis 1994; 13:35–52

9. Simon DL: Rapid opioid detoxification using opioid antagonists: history, theory and the state of the art. J Addict Dis 1997; 16:103–22

10. Seoane A, Carrasco G, Cabre L, Puiggros A, Hernandez E, Alvarez M, Costa J, Molina R, Sobrepere G: Efficacy and safety of two new methods of rapid intravenous detoxification in heroin addicts previously treated without success. Br J Psychiatry 1997; 171:340–5

11. Rasmussen K, Beitner-Johnson DB, Krystal JH, Aghajanian GK, Nestler EJ: Opiate withdrawal and the rat locus coeruleus: Behavioral, electrophysiological, and biochemical correlates. J Neurosci 1990; 10:2308–17

12. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th edition. Washington, DC, American Psychiatric Association, 1994, pp 175–82

13. Catafau AM, Etcheberrigaray A, Perez de los Cobos J, Estorch M, Guardia J, Flotats A, Berna L, Mari C, Casas M, Cario I: Regional cerebral blood flow changes in chronic alcoholic patients induced by naltrexone challenge during detoxification. J Nucl Med 1999; 40:19–24

14. Tonneson AS: Crystalloids and colloids, Anesthesia, 4th Edition. Edited by Miller RD. New York, Churchill Livingstone, 1994, p 1611

15. Prough DS, Mathru M: Acid-base, fluids, and electrolytes, Clinical Anesthesia, 3rd edition. Edited by Barash PG, Cullen BF, Stoelting RK. Philadelphia, Lippincott–Raven Publishers, 1997, p 165

16. Fultz JM, Senay EC: Guidelines for the management of hospitalized narcotics addicts. Ann Intern Med 1975; 82;815–8

17. Gold MS, Redmond DE Jr, Kleber HD: Noradrenergic hyperactivity in opiate withdrawal supported by clonidine reversal of opiate withdrawal. Am J Psychiatry 1979; 136:100–2

18. Gold MS: Opiate addiction and the locus coeruleus. The clinical utility of clonidine, naltrexone, methadone, and buprenorphine. Psychiatr Clin North Am 1993; 16:61–73

19. Lin SK, Strang J, Su LW, Tsai CJ, Hu WH: Double-blind randomised controlled trial of lofexidine versus clonidine in the treatment of heroin withdrawal. Drug Alcohol Depend 1997; 48:127–33

20. Buchanan KD: Effects of sandostatin on neuroendocrine tumours of the gastrointestinal system. Recent Results Cancer Res 1993; 129:45–55

21. Physician's Desk Reference, 51st edition. Montvale, NJ, Medical Economics Company, 1997, pp 2421–3

22. Tanaka GY: Hypertensive reaction to naloxone. JAMA 1974; 228:25–6

23. Andree RA: Sudden death following naloxone administration. Anesth Analg 1980; 59:782–4

24. Johnson C, Mayer P, Grosz D: Pulmonary edema following naloxone administration in a healthy orthopedic patient. J Clin Anesth 1995; 7:356–7

25. Kaplan JL, Marx JA: Effectiveness and safety of intravenous nalmefene for emergency department patients with suspected narcotic overdose: a pilot study. Ann Emerg Med 1993; 22:187–90

26. Gal TJ, DiFazio CA: Prolonged antagonism of opioid action with intravenous nalmefene in man. ANESTHESIOLOGY 1986; 64:175–80

27. Dixon R, Howes J, Gentile J, Hsu HB, Hsiao J, Garg D, Weidler D, Meyer M, Tuttle R: Nalmefene: Intravenous safety and kinetics of a new opioid antagonist. Clin Pharmacol Ther 1986; 39:49–53

28. San L, Torrens M, Tato J, Castillo C, de la Torre R, Arranz B: Monitoring patterns of substance use in drug-dependent patients. J Subst Abuse Treat 1998; 15:425–30

29. Presslich O, Loimer N, Lenz K, Schmid R: Opiate detoxification under general anesthesia by large doses of naloxone. J Toxicol Clin Toxicol 1989; 27:263–70

30. Loimer N, Schmid R, Lenz K, Presslich O, Grunberger J: Acute blocking of naloxone-precipitated opiate withdrawal symptoms by methohexitone. Br J Psychiatry 1990; 157:748–52

31. Legarda JJ, Gossop M: A 24-h inpatient detoxification treatment for heroin addicts: A preliminary investigation. Drug Alcohol Depend 1994; 35:91–3

32. O'Connor PG, Kosten TR: Rapid and ultrarapid opioid detoxification techniques. JAMA 1998; 279:229–34

33. Gerra G, Fertonani G, Tagliavini P, Zaimovic A, Delsignore R, Maestri D, Avanzini P, Caccavari R, Brambilla F: Serotonin function in detoxified heroin abusers: prolactin and cortisol responses to fenfluramine challenge. Psychiatry Res 1995; 58:153–60

34. Langer G, Karazman R, Neumark J, Saletu B, Schonbeck G, Grunberger J, Dittrich R, Petricek W, Hoffmann P, Linzmayer L, Anderer P, Steinberger K: Isoflurane narcotherapy in depressive patients refractory to conventional antidepressant drug treatment. A double-blind comparison with electroconvulsive treatment. Neuropsychobiology 1995; 31:182–94

35. Kienbaum P, Thurauf N, Michel MC, Scherbaum N, Gastpar M, Peters J: Profound increase in epinephrine concentration in plasma and cardiovascular stimulation after mu-opioid receptor blockade in opioid-addicted patients during barbiturate-induced anesthesia for acute detoxification. ANESTHESIOLOGY 1998; 88:1154–61

36. Hoffman WE, Berkowitz R, McDonald T, Hass F: Ultra-rapid opioid detoxification increases spontaneous ventilation. J Clin Anesth 1998; 10:372–6

37. Miyamoto Y, Takemori AE: Sites of action of naloxone in precipitating withdrawal jumping in morphine-dependent mice: Investigations by the ED50 value and CNS content of naloxone. Drug Alcohol Depend 1993; 32:163–7

38. Shook J, Kazmierski W, Hruby V, Burks T: Precipitation of spinally mediated withdrawal signs by intrathecal administration of naloxone and the mu-receptor antagonist CTP in morphine-dependent mice. NIDA Res Monogr 1988; 81:143–8

39. Vining E, Kosten TR, Kleber HD: Clinical utility of rapid clonidine-naltrexone detoxification for opioid abusers. Br J Addict 1988; 83:567–75

40. O'Connor PG, Waugh ME, Carroll KM, Rounsaville BJ, Diagkogiannis IA, Schottenfeld RS: Primary care-based ambulatory opioid detoxification: The results of a clinical trial. J Gen Intern Med 1995; 10:255–60

41. Physicians Desk Reference, 51st edition. Montvale, NJ, Medical Economics Company, 1997, p 959

42. Stephenson J: Experts debate merits of 1-day opiate detoxification under anesthesia. JAMA 1997; 277:363–4

43. Simon DL: The rationale for naltrexone therapy as an alternative to methadone treatment for opiate addiction. Conn Med 1996; 60:683–5

44. Bradley CJ, French MT, Rachal JV: Financing and cost of standard and enhanced methadone treatment. J Subst Abuse Treat 1994; 11:433–42