

The Effect of Clonidine on Gastrointestinal Side Effects Associated with Ultra-Rapid Opioid Detoxification

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Given the frequent failure rates and occurrence of early relapses with conventional opioid detoxification programs, the technique of ultra-rapid opioid detoxification (UROD) has become increasingly popular (1). This technique allows for rapid opioid withdrawal using a combination of oral (PO) and IV administered opioid antagonists (e.g., naloxone, nalmefene, and/or naltrexone). In an effort to reduce the systematic side effects associated with opioid withdrawal, the UROD procedure is normally performed under general anesthesia (2,3). However, acute short-lasting opioid withdrawal symptoms (e.g., hypertension, tachycardia, sweating, shivering, abdominal cramping, muscle pain, anxiety, nausea, vomiting, and diarrhea) can be even more debilitating than those associated with conventional opioid withdrawal programs (4).

Clonidine, an α_2 -adrenergic agonist, has been shown to suppress the opioid withdrawal symptoms in rats (5). In addition, clonidine has been found to possess antidiarrheal activity in humans with chronic diarrhea (6–9), and in animals after morphine withdrawal (5,10,11). Therefore, we performed a retrospective chart evaluation involving UROD procedures performed at two major medical centers in Los Angeles to evaluate whether the dose of clonidine administered during a UROD procedure influenced patient outcome with respect to gastrointestinal (GI) side effects.

Methods

A retrospective evaluation of the medical charts of 138 UROD patients at Cedars-Sinai Medical Center ($n =$

54) and Centinela Hospital Medical Center ($n = 84$) in Los Angeles was conducted. The UROD protocols were approved by both medical centers and the chart review was considered to be exempt from IRB approval because the patient charts were reviewed anonymously. All of the study patients were addicted to either heroin, methadone, codeine, hydromorphone, oxycodone, or hydrocodone.

Upon arrival in the UROD treatment room, standard anesthetic monitors were applied, as well as a bispectral index (BIS[®]) monitor (Aspect Medical Systems, Inc. Natick, MA). Patients were premedicated with IV midazolam or diazepam (Tables 1 and 2). Anesthesia was induced with propofol, 1.5–2.0 mg/kg IV, and succinylcholine, 40–100 mg IV, was administered to facilitate tracheal intubation. Anesthesia was maintained using a propofol infusion (50–200 μ g/kg/min) to maintain a BIS value in the range of 55–60. Glycopyrrolate, 0.2 mg IV, was given at both the start and the end of the procedure as an antisialagogue, and a combination of ondansetron (4–8 mg IV) and droperidol (0.625–1.25 mg IV) was administered for antiemetic prophylaxis. Sandostatin (0.2–0.4 mg IV) was the standard therapy for diarrhea at both medical centers.

At Cedars-Sinai Medical Center, clonidine, 0.1 mg PO, was given to patients for premedication before the UROD procedure. Clonidine was subsequently administered in doses of 0.1–1.5 mg via the nasogastric (NG) tube. Acute opioid withdrawal was initiated using naltrexone, 37.5–400 mg, via the NG tube. At Centinela Hospital Medical Center, clonidine was administered incrementally in 0.1-mg IV doses during the UROD procedure. Naltrexone, 300–350 mg via the NG tube, and/or naloxone, 5–15 mg IV, was then administered over 20–30 min to initiate the opioid withdrawal process, followed by either nalmefene (4–12 mg IV), or a combination of nalmefene (4 mg IV) and naloxone (25 mg IV) which was infused over an 8-h period.

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Table 1. Demographic Characteristics, Anesthetic Medications, Withdrawal Symptoms, and Discharge Times After UROD Procedures Performed at Cedars-Sinai Medical Center

	PO clonidine dose (mg)		
	≤0.5	0.5–1.0	>1.0
No.	7	16	31
Age (yr)	39 ± 9	40 ± 8	37 ± 9
Sex, M/F (<i>n</i>)	5/2	8/8	25/6
Weight (kg)	74 ± 16	76 ± 19	74 ± 15
Height (cm)	178 ± 7	171 ± 11	176 ± 9
Opioid abuse, <i>n</i> (%)			
PO	3 (43)	3 (19)	7 (23)
IV	4 (57)	13 (81)	24 (77)
Hypnotics used during detoxification			
Diazepam (mg, IV)	26.3 ± 16.0	22.1 ± 8.5	23.1 ± 11.5
Midazolam (mg, IV)	6.0 ± 2.8	6.0 ± 2.5	5.5 ± 2.9
Propofol (mg, IV)	2875 ± 903	2410 ± 790	2458 ± 844
Opioid antagonists			
Naltrexone (mg, PO)	228 ± 56	245 ± 89	250 ± 78
Naloxone (mg, IV)	1.9 ± 1.3	3.3 ± 2.1	2.9 ± 1.9
Procedure time (min)	396 ± 100	366 ± 149	380 ± 112
Withdrawal symptoms, <i>n</i> (%)			
During the UROD procedure			
Vomiting	1 (14)	2 (13)	3 (10)
Diarrhea	2 (29)	2 (13)	3 (10)
Muscle spasms	4 (57)	7 (44)	17 (55)
After the UROD procedure			
Nausea	1 (14)	5 (31)	15 (48)
Vomiting	1 (14)	4 (24)	14 (45)
Diarrhea	5 (71)	6 (38)	8 (26)*
Discharge time (h)	21 ± 3.8	21 ± 3.8	20 ± 5.5

Values are mean ± SD, *n*, or percentages.

UROD = ultra-rapid opioid detoxification, PO = oral.

* *P* < 0.05 versus clonidine ≤0.5-mg subgroup.

Approximately 4 h after the initial withdrawal symptoms ended, patients were administered an additional dose of naloxone, 2–4 mg IV, and then carefully observed for further clinical signs of acute opioid withdrawal. If no withdrawal symptoms were observed, the propofol infusion was discontinued and patients were allowed to awaken from anesthesia. Patients were then transferred to the intensive care unit for continuous electrocardiogram monitoring. Naltrexone, 25 mg PO, was given before discharge and all patients were subsequently administered naltrexone daily for 6 mo.

The occurrence of acute withdrawal symptoms (e.g., hemodynamic changes, nausea, vomiting, and diarrhea) requiring a therapeutic intervention were recorded before discharge from the hospital. These data were analyzed according to the total dose of clonidine administered either PO (at Cedars) or IV (at Centinela). The overall incidences of GI side effects were compared at these two institutions.

Statistical analyses were performed using one-way analysis of variance or Student's *t*-test for continuous variables, and when significant differences were determined, a *post hoc* intergroup comparison was performed using a Newman-Keuls multiple-comparison

test. Categorical data were analyzed using χ^2 or Fisher's exact test as appropriate. All tests were two-sided and *P* values < 0.05 were considered statistically significant.

Results

The clonidine subgroups were comparable with respect to demographic characteristics, dosages of sedative-hypnotics, and opioid antagonist medications administered during the UROD procedure at both medical centers (Tables 1 and 2). However, at Centinela Hospital, the clonidine subgroup receiving the larger total dose of clonidine (>1.0 mg IV) required a smaller dose of propofol than the subgroup receiving the smaller dosage of clonidine (≤1.0 mg IV). The incidences of withdrawal symptoms (e.g., vomiting, diarrhea, and muscle spasms) were not significantly different among the clonidine subgroups at either medical center during the UROD procedure. However, the incidence of diarrhea after the UROD procedure was significantly decreased in patients who received larger dosages of clonidine (>1.0 mg IV or PO) compared with the smaller dosage subgroups at both centers (Tables 1 and 2).

Table 2. Demographic Characteristics, Anesthetic Medications, Withdrawal Symptoms, and Discharge Times After UROD Procedures Performed at Centinela Hospital Medical Center

	IV clonidine dose (mg)	
	≤1.0	>1.0
No.	20	64
Age (yr)	36 ± 7	35 ± 8
Sex, M/F (<i>n</i>)	14/6	48/16
Weight (kg)	72 ± 11	73 ± 12
Height (cm)	176 ± 13	177 ± 12
Opioid abuse, <i>n</i> (%)		
PO	5 (25)	19 (30)
IV	15 (75)	45 (70)
Sedative hypnotics drugs		
Diazepam (mg, IV)	10.9 ± 3.6	11.3 ± 4.2
Propofol (mg, IV)	3384 ± 1026	2612 ± 851*
Opioid antagonists		
Naltrexone (mg, PO)	270 ± 73	276 ± 72
Nalmefene (mg, IV)	10.2 ± 1.3	9.2 ± 1.8
Naloxone (mg, IV)	4.6 ± 6.5	5.1 ± 7.1
Procedure time (min)	279 ± 74	277 ± 70
Withdrawal symptoms, <i>n</i> (%)		
During the UROD procedure		
Vomiting	1 (5)	2 (3)
Diarrhea	1 (5)	0 (0)
Muscle spasms	17 (85)	46 (72)
After the UROD procedure		
Nausea	7 (35)	19 (30)
Vomiting	5 (25)	17 (27)
Diarrhea	5 (25)	4 (7)*
Discharge time (h)	23 ± 1.1	23 ± 1.2

Values are mean ± SD, *n*, or percentages.

UROD = ultra-rapid opioid detoxification, PO = oral.

* *P* < 0.05 versus clonidine ≤1.0-mg subgroup.

A comparison of the overall incidences of GI side effects at the two medical centers revealed less frequent incidences of vomiting (4% versus 11%, *P* > 0.05), and diarrhea (1% versus 13%, *P* < 0.05) during the UROD procedures at Centinela (versus Cedars-Sinai). However, muscle spasms were less frequent during the UROD procedures at Cedars-Sinai compared with Centinela (52% versus 75%, *P* < 0.05). After the UROD procedure, the incidences of nausea (39% versus 31%, *P* > 0.05) and vomiting (35% versus 26%, *P* > 0.05) were similar at the two medical centers. However, the incidence of diarrhea was significantly reduced after the UROD procedure at Centinela compared with Cedars-Sinai (11% versus 35%, *P* < 0.05).

Discussion

The acute withdrawal symptoms associated with the UROD procedure can lead to dehydration and electrolyte disturbances, as well as patient discomfort. Clonidine, an α₂-adrenergic agonist, has been reported to be effective in suppressing symptoms of opioid withdrawal (12-16). There are no clinical studies evaluating the antidiarrheal activity of clonidine during

and after UROD procedures. In animal studies, clonidine has been reported to prevent naloxone-precipitated morphine withdrawal symptoms in a dose-dependent manner (5,10,11). In a rat study (10), diarrhea occurred in all animals undergoing morphine withdrawal without clonidine. However, clonidine, 0.1 mg/kg IV, decreased the incidence of diarrhea by 50%, and a 0.3-mg/kg IV dose effectively prevented diarrhea in this animal model. In our retrospective clinical assessment, the incidence of diarrhea seemed to be decreased with increasing dosages of clonidine when given either PO or IV to patients undergoing UROD procedures. A comparison of the overall antidiarrheal efficacy of clonidine suggested that the IV route of administration was more effective than giving the drug PO.

Clonidine has been used to treat patients with intractable diarrhea secondary to diabetes, cholera, or small bowel transplantation (6-8). Previous animal and human studies have suggested that the antidiarrheal properties of clonidine are largely attributed to effects on fluid absorption in the small bowel and intestinal motility (9,17-20). Although the site of action of clonidine in preventing diarrhea associated

with opiate withdrawal is unclear (5), some authors have suggested that withdrawal-induced diarrhea may be mediated through α_2 -adrenoceptors located on intestinal smooth muscle (10,11).

During the UROD procedure, clonidine was administered primarily to attenuate the systemic effects associated with opiate withdrawal (21). Most of the published studies used clonidine, 5–6 $\mu\text{g}/\text{kg}$ PO, to control opiate withdrawal symptoms (11,12). However, larger doses of clonidine (e.g., >10 $\mu\text{g}/\text{kg}$) have been used in patients undergoing opiate detoxification without significant side effects (14). In this retrospective study, the dosage of clonidine used during the UROD procedures varied from 2 to 30 $\mu\text{g}/\text{kg}$. Although two patients in our study population experienced transient bradycardia after large doses of clonidine (>1 mg IV), this side effect did not require anticholinergic treatment. The use of larger IV doses of clonidine not only decreased the incidence of diarrhea, but also produced a reduction in the propofol dosage requirement during the UROD procedure.

Our current analysis can be criticized because: 1) this was a retrospective chart review, 2) there was no "placebo" control group receiving no clonidine because of ethical concerns, and 3) the dosages of adjunctive drugs were not standardized (e.g., opioid antagonist). In the future, a prospective, randomized, double-blinded dose-ranging study should be performed to more precisely quantify the antidiarrheal effect of clonidine in patients undergoing UROD procedures.

In conclusion, clonidine seems to be beneficial in reducing diarrhea associated with UROD procedures. In addition, the use of larger doses of IV clonidine can also produce a dose-dependent propofol-sparing effect.

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