Clonidine Use in the Intensive Care Unit of a Tertiary Care Hospital: Retrospective Analysis

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ABSTRACT

Background: The α_2-adrenergic agonist clonidine may have beneficial effects in terms of analgesia and sedation for patients in the intensive care unit.

Objective: To examine clonidine prescribing practices in the intensive care unit of a tertiary care hospital and to determine the effect of this drug on requirements for analgesia and sedation.

Methods: This study was an observational chart review of all patients admitted to the medical–surgical intensive care unit at the Ottawa Hospital — General Campus who received a prescription of clonidine from July 1, 1999, to December 31, 2000. The primary analysis evaluated prescribing practices for clonidine. Patients who received clonidine solely for pain or sedation (or both) were included in the secondary analysis, which evaluated any response to the drug in terms of requirements for other medications for analgesia and sedation.

Results: The charts for 160 patients were reviewed for this study, of whom 155 were eligible for inclusion in the analysis of clonidine prescribing practices. Critically ill, ventilator-dependent patients with extended stays in the intensive care unit constituted the majority of the patients who received clonidine. The mean maximum daily dose was 0.26 mg. Thirteen patients were eligible for the secondary analysis, which examined decreases in requirements for pain medication or sedation (or both). A trend toward decreased opioid and benzodiazepine needs was observed, but the change was not statistically significant. For 6 patients (with a mean clonidine dose of 0.34 mg/day), opioid requirements decreased after clonidine was started, and for 3 patients (with a mean clonidine dose of 0.17 mg/day), opioid requirements increased.

Conclusions: The ability of clonidine to provide analgesia and sedation has yet to be quantified experimentally in the intensive care environment. This study provides insight into the use of clonidine to decrease pain and sedation requirements in an intensive care unit setting and suggests that doses higher than those routinely used may be required to achieve the desired effect.

Key words: clonidine, pain, sedation, intensive care unit

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RÉSUMÉ

Historique : La clonidine, agoniste des récepteurs α_2-adrénergiques, pourrait exercer des effets bénéfiques au plan de l'analgésie et de la sédation chez les patients en soins intensifs.

Objectif : Analyser les habitudes de prescription de la clonidine dans une unité de soins intensifs (USI) d'un hôpital de soins tertiaires et déterminer l'effet de ce médicament sur les besoins en analgésie et en sédation.

Méthodes : Cette étude observationnelle a examiné les dossiers médicaux de tous les patients admis à l'USI médico-chirurgicale de l'Hôpital d'Ottawa — Campus Général, qui ont reçu une ordonnance de clonidine entre le 1er juillet 1999 et le 31 décembre 2000. L'analyse primaire évaluait les habitudes de prescription de la clonidine. Les patients qui ont reçu de la clonidine spécifiquement à une fin analgésique ou sédative (ou les deux) ont été inclus dans l'analyse secondaire, qui évaluait les réponses des patients à ce médicament selon leurs besoins d'autres analgésiques ou sédatifs.

Résultats : Des 160 dossiers de patients examinés, 155 étaient admissibles à l'analyse des habitudes de prescription de la clonidine. Les patients en phase critique, sous respirateur, dont le séjour à l'USI était prolongé, constituaient la majeure partie des patients qui ont reçu de la clonidine. La dose maximale quotidienne moyenne était de 0,26 mg. Treize patients étaient admissibles à l'analyse secondaire qui examinait leurs besoins en analgésie ou en sédation (ou des deux). On a observé une tendance à la baisse des besoins en opioïdes et en benzodiazépines, qui n'était toutefois pas statistiquement significative. Chez six patients (recevant une dose moyenne de clonidine de 0,34 mg/j), les besoins en opioïdes ont diminué après qu'ils eurent commencé à recevoir de la clonidine, mais ils ont augmenté chez trois patients (recevant une dose moyenne de clonidine de 0,17 mg/j).

Conclusions : La capacité de la clonidine à exercer des effets analgésiques et sédatifs n'a toujours pas fait l'objet d'évaluations quantitatives dans un environnement de soins intensifs. Cette étude ouvre de nouvelles perspectives sur l'utilisation de la clonidine pour réduire les besoins en analgésiques et sédatifs dans ce contexte, et laisse croire que des doses supérieures à celles utilisées habituellement pourraient être nécessaires afin d'obtenir l'effet souhaité.

Mots clés : clonidine, douleur, sédation, unité de soins intensifs

INTRODUCTION

Clonidine is an α_2-adrenergic agonist that has traditionally been used to treat hypertension.[1] The adverse effects of clonidine, such as hypotension, rebound hypertension, bradycardia, dry mouth, and sedation, as well as the introduction of newer, better-tolerated agents, have resulted in a decrease in the use of clonidine as an antihypertensive agent.[2] However, its use for other indications is the subject of continuing research.[2] For example, clonidine may be useful in migraine prophylaxis; in the treatment of a variety of conditions, such as menopausal flushing, opioid, nicotine, or alcohol withdrawal, Gilles de la Tourette syndrome, congestive heart failure, and anxiety; for augmentation of general and local anesthesia; for sedation; and for acute and chronic pain management.[2,3] Recently, investigators have focused on the efficacy of clonidine in management of surgical and cancer pain.

α_2-Adrenoreceptor agonists have modest antinociceptive activity, as demonstrated in animal studies, in which co-administration with opioids enhanced analgesia relative to that induced by opioids alone.[4] In humans, data on the interactions between α_2-adrenergic agonists and opioids are conflicting, and such interactions often depend on the type of surgery and the route of administration of both α_2-adrenergic agonists and the opioid. α_2-Adrenoreceptor agonists decrease the amount of opioid analgesia required in certain patient populations.[1,4]

Opioids are considered first-line therapy in acute pain management for critically ill patients; however, their side effects are considerable, including respiratory depression, sedation, nausea, vomiting, pruritis, constipation, and physiologic dependence.[5] Some of these effects may be useful in certain situations and may provide benefit for the patient in an intensive care unit (ICU) setting (e.g., sedation). Studies have shown that clonidine may provide adjunctive analgesia when combined with opioids.[1,4]

The analgesic action of clonidine appears to be due to stimulation of central postsynaptic α_2-adrenoreceptors, predominantly located on the primary afferent terminals of neurons in the superficial laminae of the spinal cord and within several brain stem nuclei.[2,6] Clonidine is thought to exert its sedative and hypnotic effects via the locus ceruleus, a small nucleus in the brain stem.[2] This specific nucleus has been associated with a wide variety of physiologic regulatory processes, including regulation of sleep and wakefulness.[6] α_2-Adrenergic agonists inhibit the locus ceruleus through a G-protein mechanism involving the inhibition of adenylate cyclase.[6]

Several studies involving surgery patients have focused on the preoperative use of clonidine to provide sedation and anxiolysis, to decrease requirements for anesthesia, to reduce intraocular pressure, and as an anti-sialogogue.[2] Clonidine has shown postoperative benefit in potentiating analgesia induced by opioids and local anesthetics.[2] To date, no published studies have evaluated clonidine as an analgesic in ICU patients, although a reduction in postsurgical analgesic requirements by up to 50% has been reported.[1,4,7-11] In one study comparing clonidine and placebo administered before colonic resection, fentanyl requirements after the surgery were lower among patients treated with clonidine.[11] Similarly, a study of patients who had undergone abdominal hysterectomy found that those who received clonidine required approximately 45% less morphine by patient-controlled analgesia (PCA) than those who received placebo.[4] In a placebo-controlled trial of patients undergoing knee surgery, Park and others[1] found that cumulative PCA morphine requirements were 37% lower in those who received oral clonidine. Marinangeli and others[12] examined the effects of clonidine on propofol and thiopental requirements and sedation levels under general anesthesia during elective surgery. They found statistically significant reductions in thiopental and propofol requirements (30% and 23%, respectively), and a reduction in mean sedation scores of 50%.[12] However, Benhamou and others,[7] in a placebo-controlled trial of oral clonidine, found no significant decrease in the cumulative dose of PCA morphine required by patients undergoing major abdominal surgery. It has been well documented that clonidine can cause sedation, yet this effect has been difficult to quantify. Sedation requirements are more difficult to define and measure than requirements for analgesia, and no studies evaluating the influence of clonidine on sedation requirements have been conducted in the ICU setting.

In the ICU, sedatives are most often used to keep patients comfortable, to reduce anxiety, and to provide some amnesia of the ICU experience, whereas opioids are often used for analgesia. Achieving all of these objectives may also be necessary for effective mechanical ventilation. However, achieving these goals may be difficult because of side effects, specifically confusion, oversedation, and delirium. Reducing the doses of opioids and sedatives while maintaining desirable levels of sedation and pain control may lead to improvements in medical care.

Clonidine is prescribed relatively frequently in the ICU at the Ottawa Hospital, for a variety of indications. Unfortunately, there is little published literature on the use of this drug in the ICU setting. This study was designed to describe prescribing practices for oral clonidine in this ICU and, more specifically, to determine the effect of this drug, if any, on requirements for analgesia and sedation.

METHODS

This chart review included all patients in the ICU at the Ottawa Hospital — General Campus for whom clonidine was prescribed from July 1, 1999, to December 31, 2000. This ICU is a 24-bed medical–surgical unit in a university-affiliated tertiary care hospital. The Ottawa Hospital Research Ethics Board approved the study.

The study consisted of 2 separate analyses. The first was designed to investigate prescribing practices for clonidine (including dose, duration, patient population, indications, and adverse effects). Physician orders and progress notes were used to determine the indication for clonidine use in each case. Patient information was collected to define the characteristics of the patient population typically receiving clonidine and the prescribing parameters under which this medication was used. Patients who had received clonidine before admission to the ICU were excluded from this analysis.

The second analysis identified and defined the sub-population who received clonidine solely for pain and sedation, to assess whether use of this drug altered patients' requirements for other medications. Patients were excluded from the second analysis for the following reasons: clonidine had been prescribed for some indication in addition to pain relief or sedation, the patient had been in the ICU less than 24 h before initiation of clonidine, or a new co-analgesic or sedative had been prescribed any time during the 24-h period before clonidine was initiated or any time during the 24-h period after the maximum dose of clonidine was reached (i.e., patients were included if doses of analgesics and sedatives had been adjusted or the drugs had been discontinued, but not if new agents had been added). Total doses of analgesics (opioids, acetaminophen, or nonsteroidal anti-inflammatory drugs), sedatives (benzodiazepines or propofol), and antipsychotics (haloperidol) in the "pre-clonidine" and "post-clonidine" periods were compared. The pre-clonidine period was defined as the 24 h immediately before initiation of clonidine; the post-clonidine period was the 24 h after the maximum dose of clonidine was achieved or the 24-h period starting 48 h after the first dose, whichever came first. The maximum dose of clonidine was defined as the highest daily dose of clonidine. The doses of all opioids were converted to the morphine equivalent, and the doses of all benzodiazepines were converted to the lorazepam equivalent. Doses of fentanyl were converted to morphine equivalent on the assumption that 10 µg of fentanyl was equivalent to 1 mg of morphine.[13] Doses of midazolam, oxazepam, and alprazolam were converted to lorazepam equivalents on the assumption that 1.4 mg of midazolam, 15 mg of oxazepam, and 0.5 mg of alprazolam were equivalent to 1 mg of lorazepam.[14] Visual pain scale (scored from 0 to 5), heart rate, and median systolic and diastolic blood pressure, which are normally recorded in the patient chart, were used to assess pain; the Ramsay scale (scored from 1 to 6, with 1 representing agitation) was used to assess sedation and agitation.[15] These parameters were also compared for the pre-clonidine and post-clonidine periods. All data were analyzed with descriptive and inferential statistical methods. Distribution of characteristics is represented as mean values. Sedation and analgesia requirements before and after clonidine use were compared with a 2-tailed Student's *t*-test.

RESULTS

A total of 1868 patients were admitted to the ICU during the study period, of whom 160 (9%) received clonidine. Five patients were receiving clonidine before admission to the ICU and were therefore excluded from the first analysis, which left 155 patients for evaluation (Table 1). The average age was 59.0 years (range 19 to 88 years), and 63% of the patients were men. The diagnosis on admission varied, the most common being respiratory disease, multiple trauma, and septic shock. One hundred and twenty-one (78%) of the patients were dependent on a ventilator when clonidine was initiated. The average duration of clonidine use was 9.0 days (range 1 to 34 days). Clonidine was tapered before discontinuation in 52 patients (34%). Clonidine was prescribed for a variety of indications, and some patients received the drug for more than one indication (Table 2). The average maximum daily dose was 0.26 mg (range 0.05 mg to 0.8 mg) (Figure 1). No documented significant adverse effects were directly attributable to the use of clonidine. Patients had been in the ICU for 7.9 days, on average, before initiation of clonidine and were not discharged for another 9.2 days, for a total average stay of 17 days in the ICU. In contrast, the average stay for all patients in this ICU during the study

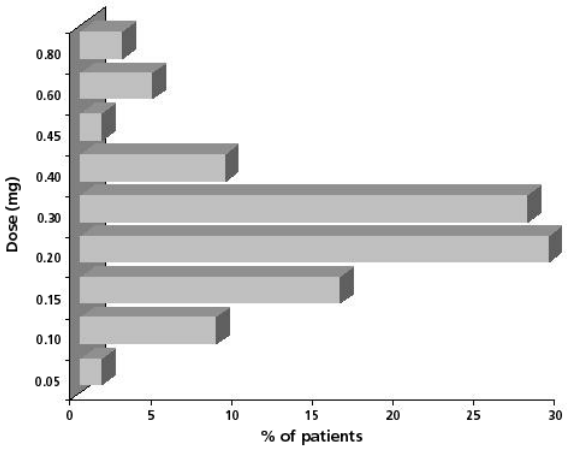

Figure 1. Maximum daily dose of clonidine among 155 patients in the intensive care unit. Doses not indicated on *y* axis (e.g., 0.25, 0.35) were not observed.

period was 5.7 days. One hundred and twenty-one (78%) patients survived and were transferred from the ICU.

For 66 of the 155 patients, pain or sedation (or both) was the primary or secondary indication for clonidine use. This subgroup was similar to the entire population in terms of patient demographic characteristics and clonidine use (Table 1).

Thirteen patients met the criteria for inclusion in the secondary analysis. Patients were excluded from the secondary analysis because clonidine had been prescribed for a stated indication in addition to or exclusive of pain or sedation (98 patients), because of changes in their sedative agent (25 patients) or changes in their analgesic agent (14 patients), or because the length of stay in the ICU was less than 24 h (11 patients). For some patients there was more than one reason for exclusion from the secondary analysis.

The prescribing pattern for clonidine in the 13 patients in the secondary analysis was not consistent. The most common starting dose was 0.05 mg, and no reliable method could be discerned for dose escalation. Typically, doses were increased on a daily or every-other-day basis as patient hemodynamics permitted.

Four of the 13 patients were not taking opioids during clonidine use. For the 9 patients who were taking opioids, the average daily dose in morphine equivalents was 44.7 mg (95% confidence interval [CI] 12.5 to 76.9 mg) before clonidine initiation and 28.2 mg (95% CI –0.9 to 57.3) in the post-clonidine period (p = 0.1) (Table 3). For 6 of these 9 patients, the amount of opioid required (per 24-h period) decreased, but for the other 3 patients, the requirement increased. Two patients were not taking

Table 1. Patient Characteristics

Variable	Mean (and Range) or No. (and %) of Patients: All Patients (n = 155)		Pain and Sedation Patients* (n = 66)	
Age				
Mean (and range)	59.0	(19–88)	57.7	(24–83)
Sex				
Female	57	(37)	29	(44)
Male	98	(63)	37	(56)
APACHE II score				
Mean (and range)	21.0	(3–39)	21.1	(7–36)
Days in ICU				
Before clonidine initiation	7.9	(1–44)	8.8	(1–26)
After clonidine initiation	9.2	(1–43)	9.2	(1–36)
Ventilator dependent†				
Yes	142	(92)	61	(92)
No	13	(8)	5	(8)
Clonidine started while receiving ventilation				
Yes	120	(77)	58	(88)
No	22	(14)	3	(5)
Not ventilated	13	(8)	5	(8)
Duration of clonidine use (days)				
Mean (and range)	9.0	(1–34)	8.6	(1–30)
Clonidine tapered				
Yes	52	(34)	27	(41)
No	103	(66)	39	(59)
Outcome				
Survival	121	(78)	49	(74)
Death	34	(22)	17	(26)
Maximum daily clonidine dose (mg)				
Mean (and range)	0.26	(0.05–0.80)	0.26	(0.05–0.80)

APACHE = Acute Physiology and Chronic Health Evaluation, ICU = intensive care unit.
*Patients who received clonidine for pain or sedation (or both) as the primary or secondary indication.
†At any time during ICU stay.

Table 2. Reasons for Initiation of Clonidine (n = 155 Patients)

Indication	No. (and %) of Patients*	
Sedation	65	(42)
Pain control	54	(35)
Agitation	53	(34)
Hypertension	48	(31)
Withdrawal	35	(23)
After myocardial infarction	3	(2)
Congestive heart failure	1	(1)
Other	4	(3)

*For some patients, more than one indication was documented.

Table 3. Mean Daily Doses of Other Drugs

Drug*	*n*	Mean Daily Dose (and 95% CI) (mg)		*p* Value
Opioids (morphine equivalent)	9			0.1
Before clonidine		44.7	(12.5 to 76.9)	
After clonidine		28.2	(–0.9 to 57.3)	
Benzodiazepines (lorazepam equivalent)	11			> 0.1
Before clonidine		14.6	(–5.0 to 34.2)	
After clonidine		3.9	(1.5 to 6.3)	
Haloperidol	4			> 0.1
Before clonidine		7.8	(–5.1 to 20.7)	
After clonidine		4.6	(0.3 to 8.9)	
Propofol	7			> 0.1
Before clonidine		373.2	(–21.5 to 767.7)	
After clonidine		213.4	(–154.3 to 581.1)	
Metoprolol	4			> 0.1
Before clonidine		86.9	(41.2 to 132.6)	
After clonidine		103.3	(38.2 to 168.4)	
Acetaminophen	5			> 0.1
Before clonidine		520.0	(–499.2 to 1539.2)	
After clonidine		1430.0	(687.1 to 2172.9)	

**n* values represent the number of patients taking the specified drug (not all patients were receiving all medications). "Before clonidine" means at 24 h before initiation of clonidine. "After clonidine" means at 24 h after the time when the maximum dose of clonidine was achieved or after the 24-h period starting 48 h after the first dose.

benzodiazepines either before or after clonidine initiation. For the 11 patients who were taking benzodiazepines, the average daily dose, in lorazepam equivalents, was 14.6 mg (95% CI –5.0 to 34.2) and 3.9 mg (95% CI 1.5 to 6.3) in the pre-clonidine and post-clonidine periods, respectively ($p > 0.1$) (Table 3). For 6 of these 11 patients, the amount of benzodiazepine required decreased, whereas for the other 5 the requirement increased. Among the 7 patients using propofol, the requirement for this drug decreased for 6 patients and increased for 1 patient. Haloperidol, ß-blockers, and acetaminophen were used in combination with benzodiazepines and opioids in some patients, but no significant change in requirements for these drugs was observed.

The patients with a decrease in opioid requirements had a mean clonidine dose of 0.34 mg/24 h, whereas those with an increase had a mean dose of 0.17 mg/24 h. The patients with a decrease in benzodiazepine requirements had a mean clonidine dose of 0.28 mg/24 h, whereas those with an increase had a mean clonidine dose of 0.30 mg/24 h.

For all 13 patients, at least 2 scores on the visual pain scale were recorded during clonidine treatment. Five of the 13 patients had a decrease in their pain scale measurement, no patients had an increase, and 8 patients showed no change. Median heart rate, systolic blood pressure, and diastolic blood pressure did not change significantly after initiation of clonidine (Figure 2).

DISCUSSION

Among the ICU patients in this retrospective study, clonidine was prescribed primarily for pain control, sedation, or agitation. The data suggest that clonidine was prescribed for patients in whom weaning from the ventilator was difficult and for those with a prolonged ICU stay. The doses used in this ICU appear to be at the low end of the traditional hypertension dosing range, likely because of a cautionary approach (i.e., to avoid affecting the patients' hemodynamic characteristics).

As with all chart reviews, there were limitations to this analysis. One significant drawback is that only 13 patients were evaluated in the secondary analysis. This analysis included patients for whom the only indications for clonidine use were pain control or sedation, but excluded those who received clonidine solely for agitation. This exclusion criterion was probably overly strict, since sedation is commonly used to control agitation. Patients for whom new analgesics or sedatives were prescribed 24 h before or after initiation of clonidine were also excluded, to eliminate the confounding effect of new medications (i.e., clonidine versus the new analgesic or sedative). This

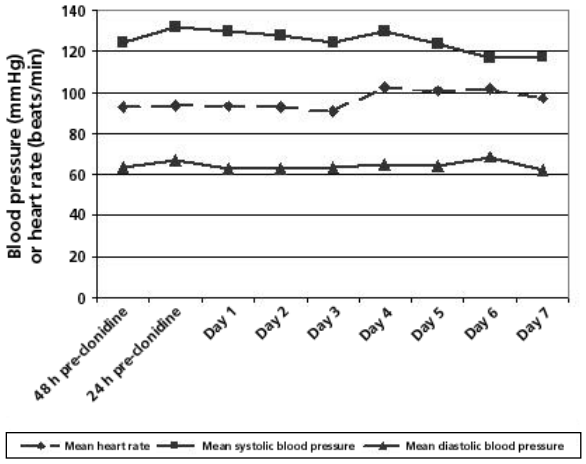

Figure 2. Median blood pressure and heart rate for 155 patients receiving clonidine in the intensive care unit.

criterion resulted in the exclusion of approximately 25% of the original patient population. Ramsey scores for sedation and visual analogue scores for pain were not useful in this retrospective analysis, as they had been inconsistently documented on the flow sheet. Ultimately, an underlying assumption of the analysis was that the Ramsay score and the visual analogue score remained the same before and after clonidine initiation, but that the dose of benzodiazepine or opioid required to achieve those same scores would be less.

It is well documented that if clonidine is used as an antihypertensive, rebound hypertension can occur if the drug is withdrawn abruptly. The withdrawal syndrome typically associated with clonidine is more common in patients with severe hypertension who have received high doses of the drug (0.9 to 2 mg/day).[16] The duration of treatment associated with the withdrawal syndrome is unknown. In this analysis, 52 (34%) of the patients had their clonidine dose tapered before discontinuation. Given the short duration of clonidine therapy in the ICU (relative to the duration of therapy when this drug is used as an antihypertensive), it is unclear whether tapering is required in this patient population.

In the secondary analysis, 6 of 9 patients had a decrease in opioid requirements, 6 of 11 had a decrease in benzodiazepine requirements, and 6 of 7 had a decrease in propofol requirements. These data represent a decrease in more than 50% of the patients in each group. Even though statistical significance was not achieved for any of the medication groups, a strong trend toward decreasing opioid requirements was evident. With such a small sample size, it is difficult to evaluate whether the effect was due to clonidine. These patients all had extended ICU stays, and the data might simply indicate that patients were improving over time.

The dose of clonidine may play a role in its efficacy in pain control. The dose of clonidine was greater among patients whose opioid requirement decreased. This suggests that to achieve a decrease in opioid requirements, patients might benefit from doses of clonidine higher than the mean dose used in this ICU during the analyzed period. This effect was not demonstrated for sedation requirements. Since individual patient hemodynamics did not appear to be affected by clonidine at the doses used, a daily dose of clonidine greater than 0.26 mg might be attainable to achieve the desired effects on pain.

In summary, the ability of clonidine to provide analgesia and sedation in the ICU setting has yet to be quantified experimentally. This study documented the prescribing practices of clonidine in the ICU in the authors' institution. It provides some insight into the efficacy of clonidine for pain control and sedation and suggests that higher doses may be required to achieve the desired effect. However, it remains unclear whether clonidine has an important effect on analgesic or sedative requirements or leads to improvement in patient outcomes. Additional study with a randomized controlled trial is warranted to further evaluate clonidine's role and effects in the ICU setting.

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