

The Use of the 5-HT₃-Receptor Antagonist Ondansetron for the Treatment of Postcardiotomy Delirium

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Objective: To evaluate the effect of the 5-HT₃-receptor antagonist ondansetron in patients with postcardiotomy delirium.

Design: Prospective study.

Setting: University hospital.

Participants: Thirty-five patients who had undergone coronary artery bypass graft surgery.

Interventions: Thirty-five patients, 23 men and 12 women, who developed delirium in the intensive care unit after coronary artery bypass graft surgery were included. Mean patient age was 51.3 years (range, 36 to 79 years). A mental status scoring scale was developed, and patients were scored 0 to 4 according to their delirium status after confirming that there were no correctable metabolic abnormalities as an underlying cause for delirium. Normal behavior was scored as 0, and severe verbal and physical agitation was scored as 4. Patients received a single dose of ondansetron, 8 mg, intravenously and were reevaluated 10 minutes later.

AN ACUTE CHANGE of behavior or mental status in the intensive care unit (ICU) patient requires rapid recognition and treatment. The confused patient is often restless and disorganized. The illusions, hallucinations, and paranoid ideation that accompany confusion can precipitate intense agitation and combativeness.¹⁻³ Agitation can be potentially harmful for a post-cardiac surgery patient. Traditionally, the term *ICU psychosis* has been used to designate florid abnormalities of mood and behavior in ICU patients. The term *psychosis*, however, does not adequately describe the status of confused ICU patients; whereas the term *delirium* more appropriately describes the mental status abnormalities that commonly occur in postcardiotomy patients in the ICU.⁴

Delirium is a reversible organic mental syndrome whose hallmarks are an acute onset of alterations in mental, motor, and autonomic function. Intellectual impairment, particularly of recent memory and orientation, is significant. Behavior may be apathetic and withdrawn, but more commonly the patient is hyperactive and agitated. The symptoms fluctuate markedly and tend to be most severe at night. Abnormal consciousness distinguishes delirium from dementia.^{1,4} There is usually a lucid period of 1 to 3 days after surgery. The patient then may experience perceptual distortion of visual, tactile, proprioceptive, and auditory stimuli, which is associated with anxiety, restlessness, inability to concentrate, and mild confusion. These

Measurements and Main Results: Before the treatment, 7 patients had a score of 2 (20%); 10 patients (28.6%), 3; and 18 patients (51.4%), 4. After the treatment, 28 patients (80%) dropped their score to 0; 6 patients (17.1%) dropped to a score of 1, and 1 patient (2.9%) remained at a score of 4. The mean score dropped from 3.20 + 1.01 to 0.29 + 0.75 after treatment. Wilcoxon signed ranks test was used for statistical evaluation, and the fall in delirium score after ondansetron treatment was found to be statistically significant ($p < 0.001$).

Conclusions: The use of ondansetron was effective and safe and without important side effects. This positive effect of the 5-HT₃-receptor antagonist ondansetron led to speculation that impaired serotonin metabolism may play a role in postcardiotomy delirium.

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KEY WORDS: postcardiotomy delirium, 5-HT₃-receptor antagonism, ondansetron, serotonin

symptoms may progress to paranoid delusions, gross disorientation, illusions, and frank hallucinations, usually of the visual type.^{1,5,6}

The conventional treatment for delirium includes butyrophenones, phenothiazines, benzodiazepines, and other sedatives. All these drugs, however, are accompanied by side effects.^{3,4,7} The serotonergic system, in addition to its effect on depressive syndromes, is implicated in the development of anxiety disorders. Some studies have suggested that the serotonergic system and 5-HT₃ receptors may play an important role in acute delirium.⁸ An increase in cerebral serotonin may also influence dopamine and the psychosis associated with long-term L-dopa therapy in advanced Parkinson's disease.⁹ The serotonergic system, along with many other systems, is affected by cardiopulmonary bypass (CPB). Impaired serotonin activity resulting from CPB may be one of the possible mechanisms that can explain the high incidence of delirium seen in postcardiotomy patients in comparison with other surgeries. A *serotonin syndrome*, which is manifested by an acute change in mental status and behavior, has been previously defined.¹⁰

The purpose of the present study was to determine whether ondansetron hydrochloride, a 5-HT₃-receptor antagonist, could be effective in treating postcardiotomy delirium. Several studies have suggested that ondansetron might have an anxiolytic effect.^{11,12} The positive effect of 5-HT₃-receptor antagonists in the treatment of phobic disorders^{13,14} and an antipsychotic effect associated with long-term L-dopa therapy in advanced Parkinson's disease⁹ also encouraged the authors to undertake this prospective study in postcardiotomy patients.

MATERIAL AND METHOD

Thirty-five patients who developed delirium in the ICU after coronary artery surgery were included in the study. There were 23 men and 12 women. Mean age was 51.3 years (range, 36 to 79 years). All patients were extubated at the time that the evaluation was made (Table 1). Patients who were under any psychiatric treatment or described

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Table 1. Patient Data

Age mean (yr)	51.3 ± 18.7
Male (n)	23
Female (n)	12
Onset of delirium after surgery (hr)	35 ± 6.5*

*The time of onset of delirium was about 1.5 days after surgery, in the intensive care unit.

panic or anxiety disorders were not included in the study. Patients who showed signs of depression or fluctuated between depression and a manic state preoperatively were excluded.

Before the operation, all patients were premedicated with midazolam, 0.07 to 0.1 mg/kg intramuscularly. Anesthesia was induced with fentanyl, 25 µg/kg, and midazolam, 0.15 to 0.35 mg/kg. All patients received standard doses of morphine, 10 to 20 µg/kg/hr, and midazolam, 8 to 15 µg/kg/hr, infusions for basal sedation and analgesia in the early postoperative period.

A mental status scoring scale for cases of postcardiotomy delirium was developed with the collaboration of the neuropsychiatry and anesthesiology departments to evaluate the status of each patient correctly. Mental status scoring of delirium in the patients mainly included parameters of consciousness, state of awareness, and agitation. Consciousness was found to be normal (score 0) or confused (ie, disturbance of orientation as to time, place, or person) (score 1). Agitation was evaluated as nonaggressive or aggressive. Nonaggressive agitation was evaluated as verbal (with disturbance in structure of association in speech) and scored as 2 or nonverbal (mainly with psychomotor symptoms) and scored as 3. Aggressive agitation was scored as 4 (Table 2).

While evaluating these patients, every effort was made to correct any metabolic abnormalities, such as hypoxia, low cardiac output, or alcohol withdrawal. After this evaluation, all patients received a single dose of ondansetron, 8 mg, as an intravenous bolus. None of the patients

was aware of the treatment. Patients were reevaluated 10 minutes later, and a second scoring was performed.

RESULTS

Before the treatment, 7 patients had a score of 2 (20%); 10 patients (28.6%), a score of 3; and 18 patients (51.4%), a score of 4. Mean score was 3.20 ± 1.01 (n = 35). After the treatment, 28 patients (80%) dropped to a score of 0, 6 patients (17.1%) dropped to a score of 1, and 1 patient (2.9%) remained at a score of 4. Mean score was 0.29 ± 0.75 (n = 35) (Fig 1). The patient who remained with a score of 4 did not respond to neuroleptics and had to be fully sedated. The mean delirium score dropped from 3.20 ± 1.01 to 0.29 ± 0.75 after treatment (Fig 2). The Wilcoxon signed ranks test was used for statistical evaluation, and the fall in delirium score after ondansetron treatment was found to be statistically significant (p < 0.001).

DISCUSSION

Delirium is common after cardiac surgery; this confusional state is present in 30% to 35% of patients undergoing otherwise uncomplicated procedures.¹⁵ In the Newcastle study, the neurologic and neuropsychologic complications of a cohort of 312 patients undergoing coronary artery bypass graft surgery were compared with those found in a group of 50 patients undergoing major surgery for peripheral vascular disease. Frequency and severity of central nervous system complications were significantly higher in the coronary artery bypass graft surgery group, likely reflecting cerebral changes resulting from CPB.¹⁶

Overall the weight of evidence supports the argument that CPB increases the risk of postoperative neurologic dysfunction. Exposure to CPB leads to an increased short-term risk of

Table 2. Mental Status of Postcardiotomy Delirium* Patients Before and After Ondansetron

	State of Awareness		Agitation†		
	Normal	Confusion	Nonaggressive		Aggressive‡
			Verbal§	Psychomotor	
Patients (n = 35)	Good cooperation, slightly disoriented	Good cooperation, mild-moderate disorientation, restlessness	Cooperation possible but disoriented, difficulty in remembering and an expression of fear, noncompliant	Uncooperative disoriented, difficulty in remembering, physical movements in bed that can cause self-damage, fear and anxiety¶	Uncooperative disoriented, verbal and physical abuse, shouting, self-destructive and can harm others, obnoxious, visual hallucinations, paranoid delusions
Mental status scores	0	1	2	3	4
No. of patients before ondansetron			7 (20%)	10 (28.6%)	18 (51.4%)
No. of patients after ondansetron**	28 (80%)	6 (17.1%)			1†† (2.9%)

*Delirium—bewildered, restless, confused disoriented reaction associated with fear and hallucination.

†Agitation—anxiety associated with severe motor restlessness, which was evaluated as verbal (score 2) or psychomotor (score 3).

‡Aggressive—forceful, goal-directed action that may be verbal or psychomotor and is the motor counterpart of rage, anger, or hostility.

§Verbal—disturbance in structure of association in speech (irrelevant answer, word salad, neologism).

||Psychomotor—restlessness, hyperactivity with some mental symptoms.

¶Anxiety—feelings of apprehension because of unconscious conflict with motor tension and autonomic hyperactivity.

**The fall in mental state score from a preoperative mean score of 3.20 ± 1.01 (n = 35) to a mean score of 0.29 ± 0.75 (n = 35) after ondansetron treatment was found to be statistically significant (Wilcoxon signed ranks test) (p < 0.001).

††One patient who remained in score 4 despite ondansetron did not respond to neuroleptics and had to be fully sedated.

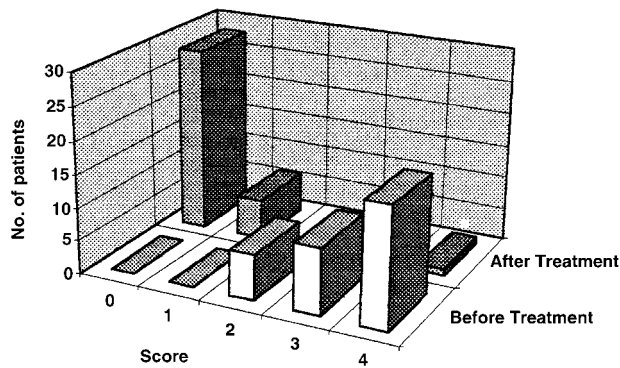


Fig 1. 97.1% of patients dropped to scores of 0 and 1 after ondansetron treatment ($p < 0.001$, Wilcoxon signed ranks test).

neuropsychologic dysfunction, which is usually multifactorial in origin.¹⁷ CPB elicits a generalized inflammatory response. Many vasoactive substances, including histamine and serotonin, are produced or affected by CPB and cardiac surgery.¹⁸ The lungs, the brain, and, to a lesser extent, the kidneys have long been considered the primary targets of inflammatory mediators released during CPB.¹⁹ The lungs also play an important role in the uptake and release of vasoactive substances, and serotonin is normally effectively removed in the pulmonary circulation, probably through endothelial cells.²⁰ Decreased pulmonary extraction of serotonin because of altered endothelial cell function after CPB may play a role in impaired levels of serotonin.²¹

Klimenko and Tatarko²² have shown in animal models that mast cells may have a stimulating effect on reparative processes during inflammatory responses, and this effect involves histamine, serotonin, and heparin. Ketanserin was shown to inhibit serotonin-induced vasoconstriction in hypertensive postcardiotomy patients.²³

Studies indicate that vasoactive compounds, such as 5-HT, are released by platelets during platelet aggregation.²⁴ Golino et al²⁵ have shown that after angioplasty in humans, high concentrations of 5-HT are present in coronary sinus blood samples. Pakala et al²⁶ have shown that in a rabbit model of angioplasty involving the femoral artery, there was ongoing platelet deposition at the site of vascular injury, with progressive accumulation of 5-HT. The concentration of 5-HT measured at the local injury site in the animal model or in coronary sinus was excessively high.

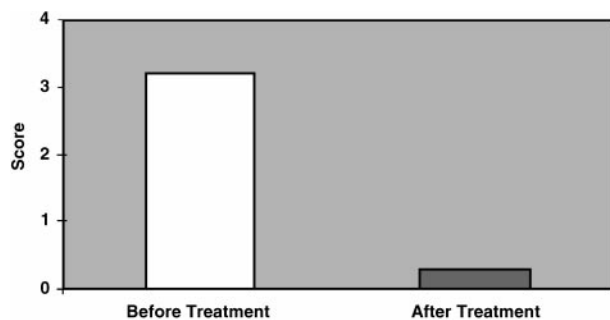


Fig 2. The mean delirium score dropped significantly after ondansetron treatment ($p < 0.001$).

The acute response of endothelial cells to CPB results in systemic inflammation, coagulation abnormalities, and vasomotor changes, which may all be critical to perioperative outcome.¹⁸ Postcardiotomy delirium may be caused by impaired serotonergic mechanisms and excessive stimulation of the corticolimbic serotonergic receptors. As a result, during CPB, many factors, such as high-dose heparin, the shear effect on thrombocytes causing mast cells to release serotonin,^{18,19,27} and inactivation of metabolic lung function, can contribute to impaired serotonin activity.²⁰ The higher incidence of postoperative delirium after cardiac surgery in comparison with other surgeries can be attributed to one or more of these factors.¹⁵

The results of the present study suggest that ondansetron may represent a novel, acutely effective, and well-tolerated medication in postcardiotomy delirium patients. The most prominent antipsychotic effect of ondansetron was observed in agitation, aggressive psychomotor behavior with visual hallucinations, and paranoid delusions. The overall effect was to improve general functioning. More sensitive and specific rating scales are necessary to assess postcardiotomy delirium. The drug's antipsychotic effect is specifically mediated by central inhibition of 5-HT₃ receptors and does not block dopaminergic transmissions.^{9,28,29}

Delirium occurring after cardiac surgery seems to result, at least in part, from serotonergic receptor overstimulation. 5-HT₃ receptors are present mainly in the corticolimbic areas of the brain, and it is reasonable to assume that ondansetron exerts its serotonergic antagonistic activity in these regions. Ondansetron was suggested to be used as an antipsychotic agent in psychoactive substance abuse and to treat schizophrenic patients. Because it is not a dopamine D₂ antagonist, it does not have the same side effects.^{28,29} Ondansetron's effect on anxiety resembles that of benzodiazepines; however, this anxiolytic effect is not by way of γ -aminobutyric acid receptors, as in the case of buspirone, which is a partial agonist of 5-HT₁ receptors.

Serotonin (5-HT) is implicated in the cause of many anxiety disorders.^{8,9,13} Some preclinical studies with 5-HT₃-receptor antagonists, including ondansetron, have shown their anxiolytic properties.¹¹ Clinical data also suggest a role for the 5-HT₃ receptors in anxiety. Preliminary findings from two multicenter studies suggested that patients with panic disorder and social phobia benefit from long-term oral treatment with ondansetron.³⁰⁻³² Data emerging from these studies suggest that 5-HT₃-receptor antagonists may be helpful in treating a subset of cognitive functions, mostly anxiety and panic disorders. Ondansetron has been used in schizophrenia for its antipsychotic effect and in the treatment of social phobias for its anxiolytic effects.^{28,30} Broacks et al³³ have shown in animal models that the anxiogenic effect caused by m-chlorophenylpiperazine (5-HT₁ antagonist) was reversed by ondansetron. Nowakowska et al³⁴ have shown that ondansetron had an anxiolytic effect in mice in doses of 0.01 to 0.1 mg/kg. Ondansetron may be a new kind of anxiolytic drug other than benzodiazepines and the nonbenzodiazepine anxiolytic buspirone.

A phenomenon referred as the *serotonin syndrome* has been described after the use of serotonergic agents alone or in combination with monoamine oxidase inhibitors.⁹ Main features include changes in mental status and behavior (eg,

agitation, confusion, disorientation, restlessness) and some motor system changes. In an extensive review of the literature, specific diagnostic criteria have been recommended for the serotonin syndrome. First, symptoms must coincide with the initiation or increase of a known serotonergic agent. Second, the patient must have three of the following signs and symptoms: mental status changes, agitation, incoordination, hyperreflexia, shivering, tremor, and fever. Third, other causative agents should be excluded. Fourth, a neuroleptic agent should not have been initiated. Several patients diagnosed with the serotonin syndrome developed minor symptoms, including agitation, poor concentration, and restlessness. Many of the patients in the present study, especially those with scores of 3 and 4, had symptoms resembling those of a milder form of the serotonin syndrome. It would be worthwhile to test ondansetron in cases of serotonin syndrome.

Most of the patients had a significant improvement in the agitation score 10 minutes after receiving ondansetron, suggesting that the serotonergic system and 5-HT₃ receptors might have a role in some delirium cases seen in the ICU after cardiac surgery. Constipation and headache are the major reported side effects of ondansetron. Extrapyramidal side effects and a rise in liver enzymes have been reported. None of these side effects were observed in this study. This lack of side effects, however,

can be due to continuous basal sedation and analgesia. Because 5-HT₃-receptor blockade may aggravate depression, its use is not suggested in patients with signs of depression or in patients fluctuating between depression and manic disorder.³⁵

This experience in a limited number of cases suggests that the serotonergic system and 5-HT₃ receptors might play a role in the pathogenesis of postcardiotomy delirium. The authors' current policy is to start ondansetron as a continuous infusion (maximum dose of 16 mg/24 hr) after a single bolus dose of 8 mg. A further study is underway at this center comparing the effects of neuroleptics alone versus neuroleptics in conjunction with ondansetron in postcardiotomy delirium patients. The authors realize that there is no single best treatment for delirium, and the selection of a particular agent depends on careful assessment and monitoring of the patient. This study, however, suggests the use of ondansetron in such cases because it is safe, effective, and without apparent side effects.

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