BRIEF COMMUNICATIONS

ONDANSETRON HYDROCHLORIDE FOR THE TREATMENT OF DELIRIUM AFTER CORONARY ARTERY SURGERY

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Delirium remains the most common psychiatric disorder seen early after cardiac operations, with an incidence of 13% to 70%. It is characterized by reduced levels of consciousness, perceptual disturbances (eg, hallucinations), a disturbance in the sleep-wake cycle, and disturbed psychomotor activity.[1,2] The serotonergic system, which has been implicated in the development of anxiety disorders, is affected by cardiopulmonary bypass (CPB) along with many other systems and may be one of the contributing factors causing delirium. The purpose of this study was to determine whether ondansetron, a 5HT3 receptor antagonist, could be effective in treating this disorder.

Methods. After the approval of the ethical commission and institutional review board, informed consent was obtained from family members of 35 patients in whom delirium developed in the intensive care unit after coronary artery surgery. Patients with previous psychiatric disorders were excluded. Every effort was made to correct any metabolic abnormality, such as hypoxia, low cardiac output, and electrolyte disturbance before evaluation, that could cause this disorder. Before the operation, patients were premedicated with midazolam (0.07-0.1 mg/kg administered intramuscularly). Anesthesia was induced with fentanyl and midazolam, and all patients received standard doses of morphine and midazolam perfusion for basal sedation and analgesia in the early postoperative period. Patient characteristics are shown in Table I. After going through previous anxiety and agitation scores, a scoring system was developed with the collaboration of the departments of neurology, psychiatry, and anesthesiology, and pretreatment scoring was done. Afterward, all patients received a single dose of ondansetron (Zofran; Glaxo Wellcome, Greenford, Middlesex, United Kingdom; 8 mg administered by means of an intravenous bolus). Two intensivists who were trained for 2 weeks by the team preparing the scoring system evaluated and scored each patient without knowing whether they received the drug. Patients were re-evaluated 10 minutes later, and a postdrug score was assigned. Evaluation before and after treatment was not done by the same intensivist to reduce the risk of bias.

Table I. *Patient characteristics*

Age (mean)	51 ± 19
Male	23
Female	12
Onset of delirium after surgery (h)	35 ± 7

The time of onset of delirium symptoms was mostly 1.5 days after surgery in the intensive care unit.

Results. The Wilcoxon signed-rank test was used for statistical evaluation, and the fall in delirium score after ondansetron treatment was found to be statistically significant (P = .001, Table II). One patient who continued to have a score of 4 despite treatment had to be fully sedated.

Discussion. Large numbers of vasoactive substances, including histamine and serotonin, are produced or affected by CPB and cardiac operations.[3] The lungs, brain, and, to a lesser extent, the kidneys have long been considered the primary targets of inflammatory mediators released during CPB. Recent studies indicate that vasoactive compounds, such as histamine and 5HT, are released by platelets during platelet aggregation.[3] The lung plays an important function in the uptake and release of vasoactive substances, and the lung is known to inactivate circulating serotonin and bradykinin and participates in the uptake of norepinephrine. It has been hypothesized that systemic hypertension after CPB is caused by depressed clearance of neurohumoral substances by the damaged lung after CPB. Data suggest that the diminution in the lung's ability to remove substances like norepinephrine and serotonin from the circulation is directly related to the duration of CPB. During CPB, many factors, such as high-dose heparin, the shear effect on thrombocytes causing mast cells to release serotonin, and inactivation of metabolic lung function, can be factors contributing to the much higher incidence of postoperative delirium after cardiac operations in comparison with other operations.[3,4] A phenomenon referred to as the *serotonin syndrome* has been described after the use

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Table II. *Mental status of patients with postcardiotomy delirium* before and after ondansetron*

	State of awareness		*Agitation†*		
			Nonaggressive		
	Normal	*Confusion*	*Verbal§*	*Psychomotor‖*	*Aggressive‡*
	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.
¶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 rank test) ($P < .001$).
#One patient who remained in score 4 despite ondansetron did not respond to neuroleptics and had to be fully sedated.

of serotomimetic agents alone or in combination with monoamine oxidase inhibitors (MAOIs). Main features include change in mental status and behavior (agitation, confusion, disorientation, and restlessness) and some motor system dysfunctions. Several patients given a diagnosis of serotonin syndrome had minor symptoms, including agitation, poor concentration, and restlessness.[5] Many of our patients, especially those with scores of 3 and 4, had symptoms resembling those of a milder form of the serotonin syndrome. Serotonin is implicated in the cause of anxiety panic disorders and social phobia, and preliminary findings from two multicenter studies suggested that patients with panic disorder and social phobia benefit from long-term oral treatment with ondansetron. Ondansetron has been used in schizophrenia for its antipsychotic effect and in the treatment of social phobias for its anxiolitic effects.[6,7] Data emerging from these studies suggest that ondansetron may be helpful in treating anxiety and panic disorders without major side effects. Our findings were similar. The effect of the drug varied from patient to patient, but it lasted between 1 and 3 hours. Although headache and constipation have been described with the long-term use of the drug,[6] this was not our experience. We realize that there is no single best treatment for postcardiotomy delirium, but we do suggest the use of ondansetron because its use was safe, effective, and without side effects.

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