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Delirium and Circadian Rhythm of Melatonin During Weaning From Mechanical Ventilation

An Ancillary Study of a Weaning Trial

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BACKGROUND: Delirium is frequent in patients in the ICU, but its association with the outcome of weaning from mechanical ventilation has not been assessed. Circadian rhythm alteration may favor delirium. In the current study, we assessed the impact of delirium during weaning and associated alterations in the circadian rhythm of melatonin excretion.

METHODS: This was a substudy of 70 participants of the B-type Natriuretic Peptide for the Fluid Management of Weaning trial, comparing two fluid management strategies during weaning. Patients with or without delirium (as assessed using the Confusion Assessment Method for the ICU) were compared in terms of baseline characteristics and outcomes and the circadian rhythm of melatonin excretion using the 24-h excretion of its urinary metabolite 6-sulfatoxymelatonin (aMT6s).

RESULTS: Among the 70 patients included, 43 (61.4%) experienced delirium at the initiation of weaning. Delirium at the initiation of weaning was associated with more alcohol consumption, a greater severity of illness, and medication use before weaning (including neuromuscular blockade, antibiotics, sedatives, and narcotics). Delirium at the initiation of weaning was associated with more respiratory and neurologic complications and a reduced probability of successful extubation (Cox multivariate model hazard ratio of successful extubation = 0.54; 95% CI, 0.30-0.95; $P = .03$). Delirium was also associated with a significant reduction in peak, mean, amplitude, and total values of aMT6s urinary excretion during the first 24 h of weaning (general linear model F statistic = 5.81, $P = .019$).

CONCLUSIONS: Delirium is frequent at the initiation of ventilator weaning. It is associated with a prolongation of weaning and an alteration in the circadian rhythm of melatonin excretion.

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ABBREVIATIONS: aMT6s = 6-sulfatoxymelatonin; BMW = B-type Natriuretic Peptide for the Fluid Management of Weaning; BNP = B-type natriuretic peptide; CAM-ICU = Confusion Assessment Method for the ICU; HR = hazard ratio; RASS = Richmond Agitation-Sedation Scale

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Delirium is a common form of organ dysfunction in the ICU, with some studies showing that > 80% of noncomatose patients develop delirium at some point during the ICU stay.[1] Patients who develop delirium have higher mortality and fewer days free of the ventilator than do those who never develop delirium.[1] Delirium may prolong mechanical ventilation by interfering with weaning.[2] Indeed, weaning contributes at least 40% of the total duration of mechanical ventilation, and successful weaning requires the preservation of brain function.[3] However, delirium has received little attention during weaning from mechanical ventilation.

Delirium may be associated with an alteration of sleep and circadian rhythm in patients in the ICU.[4] Numerous risk factors for delirium, including sensory impairment, severe illness, sepsis, metabolic disorders, CNS injury, substance abuse and withdrawal, and oversedation, affect the sleep-wake cycle.[5] Sleep deprivation, which is known to lead to many of the clinical and physiologic manifestations also found in delirium, is frequent in patients in the ICU[6] and may be associated with delirium.[4]

To assess the circadian rhythm, melatonin metabolites can be measured. Melatonin is a major secretory product of the pineal gland, which plays an important physiologic role in sleep and circadian rhythm regulation.[7] After metabolism and degradation of melatonin in the liver, the excretion of melatonin takes place in the kidneys as 6-sulfatoxymelatonin (aMT6s), which can be measured directly.[7] Urine concentrations of aMT6s have been shown to correlate well with simultaneously sampled plasma levels of melatonin in healthy individuals.[8]

We performed the current study to examine the relationship between delirium and difficulties in weaning from mechanical ventilation. We also compared the circadian rhythm of melatonin excretion between patients with and without delirium.

Materials and Methods

Patients

This study was performed in one of the nine participating centers (Henri Mondor University Hospital, Creteil, France) of the B-type Natriuretic Peptide for the Fluid Management of Weaning (BMW) trial,[9] as an ancillary study (planed a priori). We explored delirium and melatonin excretion in all the 70 consecutive participants enrolled in this study. The BMW study was a randomized controlled trial comparing a biomarker-guided depletive fluid management strategy with usual care during ventilator weaning. A detailed description of the BMW study design has been published previously.[9] Inclusion criteria were those allowing early initiation of ventilator weaning: mechanical ventilation through an endotracheal tube for at least 24 h, oxygen saturation ≥ 90% with F_{IO_2} ≤ 50%, and positive end-expiratory pressure ≤ 8 cm H_2O; hemodynamic stability during the previous 12 h; sedation stopped or decreased over the previous 48 h; stable neurologic status with Ramsay score ≤ 5[10]; and a body temperature between 36.0°C and 39.0°C. Permanent noninclusion criteria were pregnancy or lactation, age < 18 years, known allergy to furosemide or sulfonamides, tracheostomy on inclusion, hepatic encephalopathy, cerebral edema, acute hydrocephalus, myasthenia gravis, acute idiopathic polyradiculoneuropathy, decision to withdraw life support, and prolonged cardiac arrest with a poor neurologic prognosis. Temporary noninclusion criteria were extubation scheduled on the same day, persistent acute right ventricular failure, renal insufficiency (defined as any of the following: need for renal replacement therapy, plasma urea > 25 mmol/L, plasma creatinine > 180 μmol/L or creatinine clearance < 30 mL/min, or > 25% increase in plasma creatinine over the previous 24 h), injection of iodinated contrast agent in the previous 6 h, blood sodium level > 150 mEq/L, blood potassium level < 3.5 mEq/L, or metabolic alkalosis with arterial pH > 7.50. When inclusion was delayed because of a temporary noninclusion criterion, enrollment was performed after correction of the abnormal value. The protocol was approved by our institution's local ethics committee (Comité de Protection des Personnes Ile-de-France IX, approval number 06-035), and informed consent was signed by the patient or a close relative. The main result of the BMW trial was to show that a B-type natriuretic peptide (BNP)-guided depletive fluid management strategy decreased the duration of weaning without increasing adverse events.[9]

Delirium Assessment

In all patients, neurologic status was assessed at the initiation of weaning (inclusion), then daily (up to successful weaning or 3 days after inclusion) and before extubation by an investigator not involved in the patient's care (F. R.-C.). Patient status was defined as normal, delirious, or comatose using the Richmond Agitation-Sedation Scale (RASS)[11] for arousal and the Confusion Assessment Method for the ICU (CAM-ICU) for delirium,[12] as described previously.[1] Briefly, the CAM-ICU assessment was positive if patients demonstrated an acute change or fluctuation in the course of their mental status (as determined by abnormalities or fluctuations in the RASS score), in addition to inattention and either disorganized thinking or an altered level of consciousness. By definition, patients were delirious if they responded to verbal stimulation with eye opening (RASS scores of −3 to +4) and had positive CAM-ICU assessments. Patients were defined as comatose if they responded to physical/painful stimulation with movement only but had no eye opening (RASS score, −4) or if they had no response to verbal or physical stimulation (RASS score, −5). We classified patients into the motoric subtypes based on the criteria used by Peterson et al[13] (hypoactive, hyperactive, and mixed). Patients were defined as normal if they were not delirious or comatose.

Circadian Rhythm of Melatonin Excretion

Urine was collected through the indwelling urine catheter in 3-h intervals during the first 24 h of weaning in all included patients. Samples of 5 mL of urine were obtained from each urine portion by nurses during routine care and were stored at −80°C for later analysis. aMT6s was determined from diluted (1/250) urine samples by a radioimmunologic assay according to the manufacturer's instructions (Stockgrand Ltd). The intra- and interassay coefficients of variation were 6.6% and 9.3%, respectively. The amount of aMT6s excretion was calculated as the product of aMT6s concentration by urine volume for each 3-h interval.

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