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Systemic lithium reabsorption from lithium-chloride-coated heat and moisture exchangers

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Abstract *Objective:* To evaluate possible reabsorption and systemic effects of lithium released by lithium-chloride-coated heat and moisture exchangers (HMEs) during prolonged mechanical ventilation.
Design: Prospective study, including all patients mechanically ventilated for 5–30 days.
Setting: A 7 bed general-traumatological ICU in a University Hospital.
Patients: 27 consecutive ICU patients, admitted following trauma, neurosurgery and respiratory insufficiency, mechanically ventilated for at least 5 days, with a lithium coated hygroscopic HME in the circuit.
Measurements and results: Serum lithium levels were measured daily, with a standard laboratory spectrophotometric method, from admission to discharge from the ICU, and showed a reabsorption of lithium in all the patients; in the adults, levels were 5 to 15 times lower than therapeutic range, while in a child therapeutic and even toxic levels were reached.
Conclusions: LiCl coat enhances HMEs' performance greatly, but reabsorption and systemic action must be considered. In adults, serum lithium levels were lower than the therapeutic range, but lithium is effective at low concentrations and it has a narrow therapeutic range; moreover, toxicity can be observed within this range too. In children, the risk of toxicity is much greater. When lithium coated HMEs are used, the risk/benefit ratio between good performance and systemic reabsorption must be evaluated carefully.

Key words Nebulizers and Humidifiers · Heat and moisture exchangers (HMEs) · Inhalation of drugs · Lithium administration and dosage · Lithium Chloride · Lithium Toxicity

Introduction

Mechanical ventilation with dry, cool gases leads to dehydration and dysfunction of epithelial cells in the proximal airways, destruction of mucous glands and cilia [1–5], and the result of these changes is impaired function of the mucociliary elevator [4–6], subsequent sputum retention and atelectasis, reduced FRC, hypoxia [7], increased likelihood of pneumonia, and heat loss [4, 5]. Therefore medical gases, that have virtually negligible water content at room temperature [1–3], must be warmed and humidified adequately, because the tracheal cannula bypasses the nose and the throath, natural heat and moisture conditioners of inspired tidal volume.

In many ICUs, heated water humidifiers have been used widely to overcome these problems quite effectively, because they can supply the patient with gases warmed up to 29–33 °C and with a relative humidity of 95–100%. Some disadvantages have been outlined: (1) the potential

to deliver excessive vapour with the consequent problem of water intoxication [6], possibly with dilution of pulmonary surfactant [8]; (2) excessive heating and potential thermal injury [9]; (3) likelihood of acting like reservoir for bacterial growth, resulting in increased incidence of nosocomial infections [10, 11–13]; (4) electrical hazards; for these reasons, careful management, continuous monitoring, and servocontrol mechanisms are required to check proper functioning of the equipment.

Heat and moisture exchangers (HMEs) might be a simple solution to the problems of conditioning respiratory gases and, eventually, of reducing the contamination of apparatus. These devices are unexpensive, convenient and easy to use, they pose no electrical hazards [2], but they increase slightly the resistance of the circuit, and the superimposed ventilatory dead space might not be negligible in case of small tidal volumes, both during mechanical and spontaneous ventilation.

There are three main types of HMEs: all conserve heat and moisture during expiration ("loading phase") and return them to the gas of the following inspiration ("unloading phase"), but their mechanisms of action differ [2]: (1) the condenser humidifier operates by condensation of water vapour in expired gas and evaporation on inspiration; (2) the hydrophobic HME relies on the low thermal conductivity of its elements to allow a temperature gradient to develop within the humidifier as the latent heat of vaporisation is taken from the fresh gas, and the amount of water loss during the "loading phase" depends upon the magnitude of the temperature gradient produced; (3) the hygroscopic HME chemically adsorbs a portion of the expired water vapour on the humidifier elements, that is collected by dry inspiratory gases.

Performance in hygroscopic HMEs is enhanced by compounds such as LiCl, $CaCl_2$, $MgCl_2$, improving water retention capacity [14], but reabsorption of these substances via the bronchopulmonary tract and a resulting systemic action cannot be excluded [15]. Recently, concern has been raised on the risk of lithium absorption from lithium-containing HMEs, especially during prolonged anaesthesia and long term ventilation in the Intensive Care Unit (ICU) [15].

Lithium is an element which is not usually represented in the human organism, but it can interfere with many metabolic reactions and its compounds are used widely both for the treatment and the prophylaxis of manic depressive illness [16]. It has a very narrow therapeutic range (0.7–1.25 μmol/l) and toxic symptoms (nausea, vomiting, somnolence, neurological signs, diabetes insipidus, arrhythmias) may appear even with concentrations within therapeutic limits; furthermore, lithium may interact with many drugs used in the intensive care setting, particularly with diuretics and muscle relaxants, which could be potentiated, and it could be difficult to distinguish between their own pharmacological action and the enhancement due to lithium. Moreover, it seems that lithium salts determine a poliuric syndrome sometimes associated with renal insufficiency, possibly following the association with neuroleptic drugs [17, 18].

The aim of this study was to monitor serum lithium concentrations in 27 consecutive patients (26 adults and 1 child), admitted to our ICU, and mechanically ventilated with hygroscopic, lithium coated HME in the circuit, and to ascertain whether they could reach therapeutic or toxic levels during long-term ventilation.

Methods, materials and patients

According to our ventilatory equipment management protocol, two hydrophobic antibacterial and antiviral filters are mounted on the inspiratory and expiratory ports of the ventilator (Servoventilator 900C, Siemens Elema, Sweden) to preserve the patient and the equipment from contamination (these filters are changed every 72 h); immediately distal to the Y connector of the disposable circuit (discarded when the patient is discharged from the ICU or every week), a hygroscopic HME (Icor Mediflux model 1 for the adults, model 2 for children, Dahlhausen, Sweden) conditions inspiratory gases and is connected to the tracheal tube (or cannula) through a standard disposable mountpiece. The mountpiece and the HME are changed every 24 hours and whenever they are grossly soiled by bronchial secretions.

According to the artificial airway management protocol of the Unit, sterile suction of bronchial secretions without routine instillation of normal saline in the bronchial tree is performed when required.

From September 1st 1993, all mechanically ventilated patients admitted to our general ICU following neurosurgery, head trauma, and respiratory insufficiency were eligible for the study. Daily, blood samples for serum lithium concentration were drawn until discharge from the ICU, following clinical improvement or death. Initially, preexisting or actual therapy with lithium salts was the only criteria for exclusion; but in one case, preadmission lithium therapy was known only 6 days following admission, when a good history was obtained and the first samples were already in the laboratory; data from this patient are discussed separately.

Serum lithium concentration was measured with a flame spectrophotometer (Eppendorf 700), according to the standard laboratory method, its lower detection limit is traced, conventionally identified with 0.01 mmol/l, while 0.05 mmol/l is a true "reading". Accuracy and sensitivity, both of the method and of the instrument, were checked with control sera at medium (level 2) and high (level 3) levels (Beckman, lots H111172 and H111173), and the results are shown in Table 1.

For internal reasons in the laboratory, each morning, sera were stocked and the analysis was performed once a week.

For the purpose of this study, only 27 patients who were mechanically ventilated for 5–30 days (mean 13±6, median 13 days),

Table 1 Measured lithium concentration in the two standard sera (level 2 and level 3)

	Standard value		Measured values			
	Mean	Limits	1	2	3	4
Level 2	1.0	0.7–1.3	1.0	1.0	1.0	1.0
Level 3	1.8	1.5–2.1	1.75	1.75	1.75	1.75

were considered, and their demographic characteristics were: 14 males and 13 females, aged 7–81 years (mean 50±21, median 60 years), weighing 16–80 kg; they were all admitted to the ICU following general or neurological surgery and/or trauma.

Results

Twenty-two patients survived, were weaned from mechanical ventilation and discharged from the ICU. Five died in the ICU and data from these patients about the time required for serum lithium levels to return to zero are missing.

At the time of the first measurement, lithium was absent from the sera of all the patients but one, as expected. Typically, traces of the element (0.01 to 0.05 mmol/l) appeared in the blood from the first to the fourth day (mean 2.2±1.4, median 2 days) of mechanical ventilation with the lithium-HME. In the following days, it remained at this level or it might increase to 0.1 mmol/l. Serum lithium levels oscillated during all the period of mechanical ventilation between 0.01 mmol/l and 0.1 mmol/l, without any detectable reason or correlation with the renal function or with other clinical variables. Following ventilatory weaning, serum lithium levels went back to normal within two or three days (mean 2±1, median 2 days) (Fig. 1).

The described pattern is typical for the adults. In the pediatric case, a 7 year-old girl with a brain tumor, admitted to the ICU following surgery, on the sixth and seventh days of mechanical ventilation, serum lithium concentration rose to 1.2 and 1 mmol/l, respectively; in the following days, without any appreciable reason, it came back to 0.1 mmol/l, on the 16th day of mechanical ventilation, it rose to 3.9 mmol/l, then returned to the usual low range (0.1–0.05 mmol/l) and finally disappeared following weaning and extubation, according to the kinetics of the drug.

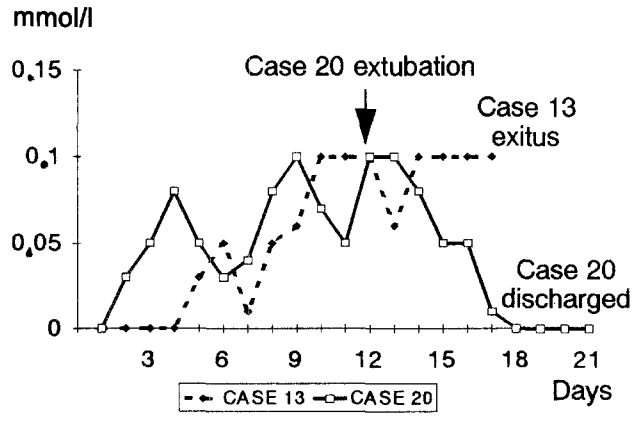

Fig. 1 Pattern of serum lithium level in two typical cases. In both cases a slow rise in the first days of mechanical ventilation can be observed, followed by a steady state. Case 13 died on day 18, when he was still ventilated. Case 20 was weaned and discharged from the ICU; in this case, lithemia returns to undetectable levels few days following weaning and extubation

In the case of the patient on lithium carbonate therapy at home, a 81 year-old man, with a cervical spine lesion and partial medullary lesion, basal lithium level was 0.1 mmol/l (clearly the therapy at home was insufficient) and remained constant at the same level even if the lithium carbonate was not administered. Following successful weaning, serum lithium levels returned to zero within three days.

In all the cases, significative reductions of creatinine clearance and signs or renal insufficiency were not observed.

Discussion

Mean measured lithium chloride content in the routinely used Icor mod. 1 HME is 140 mg (range 81–251 mg), and up to 80% of this amount (i.e. 64–200 mg, mean 110 mg) can be released into the inspiratory gases [15] because of the high water solubility of the salt. The trachea and the bronchopulmonary tract are a well known and effective route of drug administration, used widely during cardiac arrest when veins are difficult to cannulate [19], and this accounts for the systemic absorption of lithium. Moreover, daily substitution of the HME that has released its lithium salt, with a fully lithium-loaded new one, can be considered equivalent to the administration of a quotidian "dose" of the drug, grossly evaluable to 100 mg/day of LiCl (80% of the HME lithium content).

In the adult patient, this amount is one tenth approximately of the recommended oral dose of lithium carbonate (1200–1400 mg/day) [16] and a serum level 5–15 times lower than the usual therapeutic range is obtained usually. An equilibration between daily "administration" through the HME and elimination is reached rapidly and maintained as long as the HME is used. This amount of lithium can be sufficient to maintain a pre-existing low lithemia, in case of chronic therapy, as is shown by the data from the patient treated with lithium carbonate before the admission to the ICU.

Observed oscillations in the serum lithium concentration between 0.05 and 0.1 mmol/l in the adult can be explained by random differences in the release and the absorption of the salt, as well by unidentified modifications in the metabolic patterns of the patient, or by intrinsic biases in the accuracy of the laboratory method.

In the child, it seems much easier to reach unwanted "therapeutic" or even toxic levels. To our knowledge, lithium salts are not a pediatric drug, then it is impossible to compare a standard daily dose with the amount contained and absorbed through the filter, in any case this is sufficient to obtain a higher "steady state" serum concen-

tration. In this case too, it has been impossible to identify the reasons of the high, possibly toxic peak exactly, also because the very high serum level (3.9 mmol/l and 2 mmol/l on the following day) were known some days later, when the results from the laboratory arrived and the serum level had already returned to the low, usual range. In any case, most of the weaning had been performed already and it was planned to stop the mechanical ventilation in the same day.

Measured serum levels can be lower than possible peaks, because the amount of LiCl can differ between different lots of HMEs, and within the same lot too [15]; moreover, the kinetic of lithium salt release and absorption may differ greatly, according to the minute volume and the temperature gradient between the patient and the room. Furthermore, it is reasonable to think that the maximum release occurs in the first hours of exposition, when the HME is fully loaded [15], then lithium measurements in the morning, when the HME has released most of the salt, might be lower than peaks, that can be suspected because peak serum concentrations occur two to four hours following an oral dose [16].

In ICU patients, toxicity signs (if eventually present) can be confused with manifestations of the principal illness and can be missed, and this probably happened when 3.9 mmol/l were reached in the case of the young girl. Beside the direct toxicity, pharmacological interferences with many drugs used in the intensive care setting might be possible, if higher concentrations were reached for any reason.

Lithium absorption has an erratic, unpredictable pattern, that explains toxic levels observed in the child, but the possibility of toxicity in the adults too cannot be excluded because our group of patients is too small.

In conclusion, the adjunct of LiCl to a hygroscopic HME enhances its performance [14], but other salts can enhance the performance of HMEs satisfactorily too, and are not toxic, therefore the reabsorption of LiCl, its possible systemic effects or pharmacological interferences and toxicity suggest not to use lithium-coated HMEs any more.

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