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Lithium treatment in children and adolescents with anorexia nervosa: clinical use, side effects and tolerability

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Summary. Purpose. Current guidelines, due to potential toxicity and lack of clinical evidence, do not recommend the use of lithium in the treatment of Anorexia Nervosa (AN). Scarce evidence is available on the use, side effects, and tolerability of this drug in children and adolescents with AN, a population characterized by specific clinical, metabolic, and hydro-electrolytic balance features. Here we report a case series of children and adolescents hospitalized for AN and treated with lithium. **Methods.** Case series reporting the use of lithium in 7 female young patients with AN. Reasons for introduction, dosages, formulation, plasma levels, adverse drug reactions (ADR) and modifications of electrocardiogram (EKG) and plasma levels of glucose, cholesterol, creatinine, urea, sodium, and thyroid-stimulating hormone (TSH) were assessed. **Results.** Reasons for the introduction of lithium included unstable mood, insufficient compliance with nutritional programs, and psychomotor agitation. In all of the patients an improvement on target symptoms was observed. Lithium was started at 171.4 (+/-56.7) mg/day, up to 600.0 (+/-173.2) mg/day. The most frequent scheme was three times daily. The mean plasmatic concentration was 0.6 (+/-0.3) mmol/L at one month. One patient experienced polyuria, polydipsia and dry mouth, and another showed increased creatinine kinase. No major modifications of EKG, glucose, cholesterol, creatinine, urea, sodium emerged. **Conclusions.** In this sample of children and adolescents hospitalized for AN, lithium was administered to improve psychiatric symptoms impairing compliance. All the patients experienced an improvement on these symptoms after being administered lithium. ADR were reported in 2 cases. These data should be investigated in wider populations and controlled studies.

Key words. Adolescents, anorexia nervosa, children, lithium, mood stabilizers, paediatric.

Trattamento con litio in bambini e adolescenti con anoressia nervosa: uso clinico, effetti collaterali e tollerabilità.

Riassunto. Scopo. Le linee guida attuali, a causa della potenziale tossicità e della mancanza di evidenze cliniche, non raccomandano l'uso del litio nel trattamento dell'anoressia nervosa (AN). Sono, in particolare, disponibili scarse evidenze sull'uso, gli effetti collaterali e la tollerabilità di questo farmaco in bambini e adolescenti con AN. Per documentare l'utilizzo del litio in tale popolazione, caratterizzata da specifiche caratteristiche cliniche, metaboliche e di alterato bilancio idro-elettrolitico, riportiamo una serie di casi di bambine e adolescenti ricoverate per AN e trattate con litio. **Metodi.** Sono state valutate le ragioni dell'introduzione del farmaco, i dosaggi, la formulazione, litiemie plasmatiche seriate, le reazioni avverse ai farmaci (ADR) e le modifiche dell'elettrocardiogramma (ECG) e dei livelli plasmatici di glucosio, colesterolo, creatinina, urea, sodio e tireotropina (TSH). **Risultati.** Le ragioni per l'introduzione del litio includevano tono dell'umore fluttuante o instabile (71,4%), insufficiente compliance verso i programmi nutrizionali (71,4%) e agitazione psicomotoria (14,3%). In tutti i pazienti è stato osservato un miglioramento dei sintomi target. Il litio è stato iniziato a 171,4 (+/-56,7) mg, fino a 600,0 (+/-173,2) mg. Lo schema più frequente è stato tre volte al giorno. La concentrazione plasmatica media era di 0,6 (+/-0,3) a un mese. Una paziente ha manifestato poliuria, polidipsia e secchezza delle fauci, e un'altra ha mostrato un aumento della creatinina chinasi plasmatica (CPK). Non sono emerse rilevanti modifiche di parametri ECG, glucosio, colesterolo, creatinina, urea, sodio. **Conclusioni.** In questo campione di bambine e adolescenti con AN, il litio è stato somministrato per migliorare i sintomi psichiatrici con un impatto sulla compliance. Tutte le pazienti hanno riscontrato un miglioramento dei sintomi target dopo la somministrazione di litio. In 2 casi sono state riportate ADR lievi e controllabili. I risultati qui riportati necessitano di essere studiati in popolazioni più ampie e studi controllati.

Parole chiave. Adolescenti, anoressia nervosa, bambini, litio, pediatria, stabilizzatori dell'umore.

Introduction

Anorexia nervosa (AN) is characterized by restriction of energy intake, intense fear of gaining weight and disturbed body image, with emotional, behavioral and social impairment[1,2]. International guidelines identify psycho-behavioral therapies as the main treatment for AN; pharmacological therapy may be

considered either for the management of comorbid psychiatric conditions or for behavioral agitation[1,2]. Specifically, previous reports suggest that valproate may be helpful to improve psychiatric symptoms impairing compliance with treatments in AN[3,4]. Less is known about potential benefits of lithium in managing eating disorders (ED). In the pediatric population, it represents an effective treatment for acute manic episodes or aggressiveness in many psychiatric conditions[5,6]. Regardless, inadequate data exist about the full variety of benefits and tolerability of lithium treatment in pediatric patients, due to its narrow therapeutic window and potentials for toxicity[6]. Side effects may involve the central nervous system, kidneys, cardiovascular system, skin or metabolism[5].

The role of lithium in AN was first studied in adult patients, whose weight gain was described as possibly linked to the treatment[7,8]. Scarce evidence is available regarding the possible side effects and tolerability profile of lithium in children and adolescents with AN. Given the relevant modifications in metabolism, patients with AN may be exposed to a series of potential harms due to the administration of this ion. Given the lack of evidence in this field, the aim of the present report is to describe the effects of treatment with lithium carbonate in a case series of 7 pediatric inpatients with AN in our Center for Feeding and Eating Disorders.

Methods

Patients

This study is a retrospective chart review of 7 patients hospitalized between 01/01/2013 and 31/12/2019 in the Regional Centre for Feeding and Eating Disorders in children and adolescents in Bologna, Italy. Inclusion criteria were: a) a diagnosis of Anorexia Nervosa according to the Diagnostic and Statistical Manual of Mental Disorders - fifth edition (DSM-5) criteria[9]; b) a treatment with lithium during hospitalization; c) acquisition of informed consent. Patients without complete clinical documentation were excluded from the study. Demographic and clinical data were obtained. Diagnoses of subtypes of AN (anorexia nervosa, binge/purging subtype - ANBP; anorexia nervosa, restrictive subtype - ANR) were performed by clinicians trained in the field of ED. The Eating-Disorders Inventory-3 (EDI-3) was administered to all patients[10]. The patients received at admission a complete psychiatric evaluation and were administered the Self Administrated Psychiatric Scales for Children and Adolescents (SAFA) to assess psychiatric comorbidity[11]. Concerning the treatment with lithium, we recorded: length of treatment, dosage at introduction, maximum dosage, frequency of dosing (once daily - OD; twice daily - BDS; three times per day - TDS), and formulation (carbonate, normal release, slow release). Reasons for the administration and for the interruption of the treatment, if necessary, were documented as well. Clinical evidence of adverse-effect reactions (ADR) was also recorded. Plasma levels of glucose, total cholesterol, creatinine, urea, sodium, and thyroid-stimulating hormone (TSH) were recorded before and after the start of lithium. The results of electrocardiograms (EKG) before and after treatment introduction were reported as well. Finally, clinical documentation was screened for the presence of tremors or paresthesia before and after lithium. Blood levels of lithium were assessed, considering the first three available lithium concentrations. All the concurrent psychopharmacological treatments were noted, as well as the use of Naso-Gastric Tube feeding (NGT) when necessary. The body mass index (BMI) of the patients at hospital admission and discharge was recorded.

Results

Demographic and clinical variables

Seven female patients (mean age 16.0 (+/-1.6) years) with a diagnosis of AN and receiving treatment with lithium were enrolled. The main characteristics of the patients are reported in table 1. One patient (case 2) presented clinical features of AN, despite later receiving a diagnosis of BN. The mean duration of hospitalization was 143.0 (+/-83.6) days. Mean BMI was 15.7 (+/-3.1) at admission and 16.4 (+/-2.3) at discharge. The mean difference between admission and discharge was +0.7 (+/-1.7). Five patients (71.4%) were treated with NGT during the hospitalization.

Treatments with lithium

The mean dosage at the start of the lithium treatment was 171.4 (+/-56.7) mg/day, with a minimum of 100 and a maximum of 400 mg. The mean maximum reached dosage was 600.0 (+/-173.2) mg (range 300-900 mg). The most frequent treatment scheme at maximum dosages was three times daily (3 patients), followed by once daily in the morning (2 patients), and once daily (2 patients). All the patients received lithium carbonate, normal release, and in 2 patients a lactose and gluten-free version was administered. The mean duration of inpatient treatment with lithium was 103.6 (+/-77.9) days (range 19-239 days). All of the patients had concurrent psychopharmacological drug treatments when lithium was introduced (table 1). Lack of compliance with the nutritional program, unstable mood and insufficient compliance represented a general clinical reason for lithium introduction. No patient interrupted treatment with lithium due to the lack of clinical efficacy; all patients were discharged with the indication to continue treatment with lithium

Table 1. Demographic and clinical characteristics of the patients.

	Diagnosis	Comorbidity	Age at admission (years)	Admission BMI	Discharge BMI	Concurrent treatments	Lithium at start (mg)	Lithium max (mg)	Frequency	Reason for introduction	ADR
Patient 1	ANR	None	12.7	11.4	15.7	Sertraline (concurrent), olanzapine	150	600	BDS	Compliance	
Patient 2	ANBP	None	17.3	20.0	20.1	Fluoxetine and quetiapine (concurrent)	150	300	OD	Unstable mood	Polyuria, polydipsia, dry mouth
Patient 3	ANR	None	16.8	12.9	13.8	Quetiapine (concurrent)	150	600	BDS	Compliance, unstable mood, agitation	
Patient 4	ANR	DMDD	16.1	13.9	14.2	Olanzapine and promazine	150	600	TDS	Compliance, unstable mood	
Patient 5	ANR	Bipolar disorder, type 1	15.9	16.3	16.1	Olanzapine and valproate	150	600	OD	Unstable mood	Increased CK
Patient 6	ANBP	None	16	18.1	18.6	Fluoxetine and quetiapine	300	900	TDS	Compliance, unstable mood	
Patient 7	ANR	None	17.3	17.3	16.2	Quetiapine	150	600	TDS	Compliance	

Legend: ANBP= anorexia nervosa, binge/purging; ANR= anorexia nervosa, restrictive; ADR= adverse drug reactions; BDS= two times daily; BMI= body-mass Index; CK= creatinine kinase; DMDD= disruptive mood dysregulation disorder; OD= once daily; TDS= three times daily.

on account of its positive effect on the target symptoms. Plasma lithium levels were assessed in all the patients. We considered the first 3 lithium levels, corresponding at nearly two weeks (mean 13.0+/-9.1), one-month (29.4+/-7.7) and two months (53.8+/-16.3) days after the introduction of lithium. The mean plasma levels of lithium were 0.3 (+/-0.2) mmol/L (reference value 0.6-1.2) at the first blood sample, 0.6 (+/-0.3) at the second sample, and 0.6 (+/-0.4) at the third sample.

Adverse drug reactions (ADR)

One patient reported polydipsia, polyuria, and dry mouth. These symptoms spontaneously resolved and did not reappear when lithium was increased from 150 to 300. The main variations of blood glucose, total cholesterol, creatinine, urea, sodium, TSH are reported in table 2. Inverted T-waves or signs of cardiac arrhythmia were not observed during treatment. QTc difference after the introduction of lithium was -3.3 (+/-21.6) msec (min. -30, max. 30).

Discussion

While lithium is a first line treatment for bipolar disorder, and has a role in the management of a series of mental health conditions[5,12], its role in the treatment of AN and EDs in children and adolescents is limited according to the current literature; moreover, the majority of papers describe the effects on the adult population[8]. This paper aims to document effects, side effects and tolerability of lithium as an adjunctive treatment in AN. In our sample all patients were hospitalized because of weight loss and critical physical conditions. Recurrence of complex psychiatric symptoms justified the choice of lithium treatment. When it was added to the therapy, all of our patients were already receiving a pharmacological treatment (olanzapine, quetiapine and sertraline); so, lithium was mostly administered as an augmentation of compliance as a part of a multidisciplinary assistance, since a subtler management of mood and behavioral instability was required.

Despite most of our patients did not experience a significant BMI improvement at discharge, it is conceivable that lithium's possible effect positively influenced compliance and psychiatric symptoms. For this reason, all of our patients continued lithium treatment even after discharge. Major metabolic parameters and EKG did not exhibit any significant variations during the observation.

None of our patients experienced severe side effects from the administration of lithium, and serum levels of this ion always remained normal. Neurological side effects, such as sedation, tremor and ataxia, were not reported. Interestingly, no patient showed a significant weight gain or reported increased appetite during the treatment, despite these effects are commonly reported[5]. This data may be explained with the occurrence of an eating disorder like AN, which normally interferes with food intake and appetite.

Thyroid disorders (such as increased TSH) are common side effects of lithium treatment. In our sample, we observed no alarming variation of serum TSH levels. However, we must consider that lithium may affect thyroid metabolism even several months after the start of treatment[5]: a long-term effect cannot be ruled out, and it is reasonable to continue monitoring over time. For this reason, a specific thyroid follow-up should be routinely offered to patients treated with lithium.

Renal function may also be influenced by lithium[5,6]. Most of our patients reported no renal impair-

Table 2. Levels of blood glucose, cholesterol, creatinine, urea, sodium and TSH before and after introduction of lithium.

	Before lithium	After lithium	Difference	Min.	Max.	Reference
Glucose (mg/dl)	77.9 (+/-11.6)	68.1 (+/-7.7)	-9.7 (+/-14.4)	-24.0	18.0	60-110
Cholesterol (mg/dl)	159.7 (+/-14.2)	171.3 (+/-24.3)	11.7 (+/-29.7)	-17.0	62.0	< 200
Creatinine (mg/dl)	0.6 (+/-0.1)	0.7 (+/-0.1)	0.1 (+/-0.1)	-0.1	0.2	0.50-1.20
Urea (mg/dl)	24.1 (+/-7.5)	30.4 (+/-7.0)	6.3 (+/-6.9)	-3.0	17.0	17-43
Sodium (mmol/L)	141.7 (+/-2.1)	140.4 (+/-1.7)	-1.3 (+/-2.9)	-4.0	5.0	136-145
TSH (micromole/ml)	1.8 (+/-1.0)	3.1 (+/-1.2)	1.3 (+/-1.6)	-0.6	4.4	0.25-4.50

Legend: TSH= thyroid-stimulating hormone.

ment and showed a comprehensive good tolerance. In one case, polydipsia, polyuria and dry mouth were reported despite the absence of significant laboratory or clinical findings; for this reason, these symptoms did not contraindicate the treatment continuation.

Given the setting of our study, the documented treatment duration was short. The risk of long-term lithium therapy, particularly hypothyroidism, should be weighed against the potential benefits. The dangers of lithium toxicity secondary to decreased intake and possibly purging, makes a possible general recommendation of lithium treatment in AN questionable.

In conclusion, this paper described the use of lithium in a small sample of young inpatients with AN. A positive effect on cases with AN complicated by mood instability or scarce compliance was documented. Two of our patients reported ADR, which should be carefully monitored during inpatient and outpatient follow-up. Due to the small size of our sample, further research in the field might be helpful.

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Availability of data and materials: the datasets used and analyzed are available from the corresponding author on reasonable request.

Ethics approval and consent to participate: the study was approved by the Institutional Review Board of the University of Bologna and was performed in compliance with the Declaration of Helsinki and its later amendments. Parents gave informed consent to the processing of personal data at the time of the clinical evaluation.

Authors contributions: SR, LB reviewed literature data; SR and LB collected and analyzed the data; SR, LB and JP wrote the initial draft; JP and AP wrote the manuscript; and AP revised the manuscript.

Label: lithium is currently not approved for the treatment of anorexia nervosa.

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