RAP

Original article

Lithium in the era of prolonged-release formulations: a position paper

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Abstract

In the treatment of bipolar disorder, lithium still represents the golden standard, as it is used as a first-line therapy in both the prophylaxis and treatment of acute mania, and as an augmentation treatment to increase the efficacy of antidepressants in unresponsive patients. It is also effective in reducing the risk of suicide in patients with and without bipolar disorder, and it exerts immunomodulatory and neuroprotective actions. Despite these facts, lithium has been greatly underutilized in mood disorders for a number of reasons that include a narrow therapeutic window, the existence of various ranges within which it is necessary to keep its values, and a series of collateral effects that need to be cautiously handled. According to scientific literature, we hypothesize that prolonged-release (PR) lithium formulations may provide a number of potential advantages over immediate-release (IR) formulations, including: 1. more stable lithium serum concentrations while reaching the effective interval and on the long term; 2. a reduced risk of some adverse events, specifically with regards to renal functions, determining an improving in adherence, and 3. a more convenient dosing regimen, that may also improve adherence to therapy. Future trials comparing compliance rates, efficacy and adverse events associated with the PR and IR lithium formulations are required to confirm potential advantages that could further widen the clinical use of lithium.

KEY WORDS: lithium, bipolar depression, mania, prolonged release, suicide.

Introduction

The efficacy of lithium in a variety of conditions represents a well-known and established fact that goes far beyond the psychiatric area, as reported by a meta-analysis showing that lithium can be considered as the third most efficacious drug in comparison to other common medical drugs used in different diseases in terms of effect range (1).
Lithium has been shown to reduce the risk of manic relapse by 38% and depressive relapse by 28%, with a better profile in terms of prophylactic effect when compared to Valproate (2). Lithium is also the only mood-stabilizing agent that has been shown to reduce the rate of hospitalization in unipolar depression (3), and the only drug for bipolar disorder (BD) that has been demonstrated to have an anti-suicidal effect, with a reduction of suicide risk up to 50% (2). The drug can also be useful in the treatment of acute episodes, as the main augmenting strategy for antidepressants in treatment-resistant depression (4).
In addition to its mood-stabilizing and anti-suicidal properties, lithium exerts distinctive biological effects, with immunomodulatory and neuroprotective actions which may further substantiate its clinical usefulness (5).

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Regardless of these facts, lithium has been greatly underutilized in the treatment of mood disorders. In fact, this molecule presents contrasting clinical experiences compared to other therapeutic strategies for a number of reasons, including: a narrow therapeutic window, the existence of various ranges within which it is necessary to keep its values, and a series of collateral effects that need to be cautiously handled.
Ironically, despite being a molecule with a broad efficacy, lithium is therefore underutilized in comparison to other mood stabilizers. Mood stabilizers can be divided into first-generation (aside from lithium, there are valproates and carbamazepine) and second-generation, such as atypical antipsychotics (clozapine, olanzapine, quetiapine, aripiprazole, risperidone), and anticonvulsant (lamotrigine, oxcarbazepine) (5).
The current global decline in the use of lithium does not have an actual scientific basis; an urgent systematic approach is required to reverse this concerning trend and to improve the overall clinical and functional outcomes for BD patients (6).
This inconsistency could be also explained by the fact that for many years pharmaceutical companies have invested on new drugs, pushing the market towards other directions (other anti-epileptic mood stabilizers, atypical antipsychotics) and convincing both old and new generations of psychiatrists. Occasionally, lithium is considered an elite drug, given that it is mostly prescribed to patients pertaining to large specialized centres and in private care.
Lithium is not widely prescribed because clinicians advocate its prescription only to an “ideal” patient, with a very clear diagnosis, or to patients whose cognitive aspects are more functional, often associated with a higher adherence to the treatment.
The arrival on the market of new prolonged-release (PR) lithium formulations, potentially more manageable with regards to collateral effects, is contributing to change this scenery, pushing clinicians towards re-evaluating their position and facilitating the use of this molecule.
Despite having a similar profile of efficacy, some differences between PR and IR formulations have emerged in regard to pharmacokinetics, repercussions on lithium plasma concentrations, administration of doses, dosages, and short- and long-term collateral effects. The purpose of this paper is to provide the clinical point of view of several young psychiatrists, members of the Italian Psychiatric Society (SIP Giovani) (youth division), regarding the main differences between immediate-release lithium carbonate (Li IR) and prolonged-release lithium sulphate (Li PR).

Efficacy

The prophylactic effectiveness of lithium in the treatment of bipolar disorder seems to be accepted nowadays beyond any doubts, as it has been widely demonstrated in three meta-analyses (7-9).

In terms of comparison between Li IR and Li PR, the first clinical evaluations of the patients on PR treatment and the early study data indicate a similar profile of efficacy between the two formulations (10). In the study by Durbano et al. (10), subjects switched from traditional IR to PR, showing no worsening of their clinical state and, in some cases, improving their scores in both the Melancholia Scale and Mania Scale. This may be attributed to the fact that Li PR provides more stable Li plasma levels, granting a more uniform pharmacological response.
The Authors of this paper report that some concerns expressed by clinicians could be determined by the initial difficulty in deciding the correct dosage of Li PR in relation to a previous assumption of Li IR. The simple equivalence between 2 tablets of Li PR and 900 mg of Li IR does not always faithfully apply to every singular patient. The absence of blood peaks could be a mechanism able of justifying a better efficacy profile. This observation is, however, just a preliminary speculation that needs clinical confirmations on the long-term.

Compliance

Given the importance of long-term continuous treatment in reducing morbidity and mortality in BD patients, and the rate of non-compliance in this group of subjects, a prolonged-release preparation that simplifies medication regimens and reduces side effects promises an improved patient compliance and, thus, greater long-term benefits in terms of efficacy. The increased compliance and the reduction of the adverse effects might represent an additional element capable of favouring the patient’s positive perception of the drug and, therefore, improving its perceived effectiveness.
The Authors of this paper emphasize the evident compliance improvements, accompanied by a general reduction of daily administrations. This aspect makes the patient more inclined to simply accept the treatment, mostly when it is prescribed with a singular night-time administration. This possibility is described in the literature (11) and can represent a specific and suggested way of administration.
In some cases, nevertheless, a double administration (morning and evening) could be useful in order to guarantee a better 24-hour coverage. Individual variations in terms of pharmacokinetics leave this problem still open to debate, although the majority of clinicians are inclined towards the singular night-time administration.

Adverse effects

The observational study of Durbano (10), in which 47 patients already in treatment with lithium were switched to a once-daily administration of lithium PR, revealed that treatment with PR was be better tolerat-

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ed (9.1 *vs* 18.3% incidence of adverse effects in favour of Li PR) and more manageable than traditional IR treatment with an equivalent clinical efficacy. Patients who had previously been treated with standard IR preferred the PR formulation.

The Authors of this paper emphasize the improvements achieved in terms of the adverse events profile with Li PR, specifically in terms of kidney-related effects. Gastrointestinal effects appear to be comparable, with an even higher frequency, although transient in its nature, in patients taking Li PR. These observations appear to be consistent with scientific literature: some lithium-related adverse events appear to be a function of the rate of increase of serum lithium concentration, which has implications regarding the type of lithium formulation prescribed to a patient (12, 13). A recent study showed that the slower increase in serum lithium concentrations and lower Cmax values with PR *versus* IR formulations of lithium appear to translate into a reduced rate or degree of severity for some lithium-related adverse events, including tremor, upper gastrointestinal cramping, nausea, rash, cognitive dulling, urinary frequency and neuromuscular slowing (14). These data were confirmed in a recent observational study (10) and in a comparative trial showing that long-term treatment with lithium PR produced less impairment of the kidney's ability to concentrate urine than lithium IR (15).

Besides, it should be taken into account that the overall reduction in adverse events with lithium PR *versus* lithium IR formulations may lead to a reduced rate of drug discontinuation with PR formulations, although this has not been evaluated in a controlled clinical trial.

Although lithium PR appears to be superior than the IR formulations in terms of adverse effects, the Authors of this paper emphasize that the management of this drug always needs to be closely monitored, as recently reported by Gitlin and colleagues (16).

Lithium plasma concentrations

Toxicity and lithium adverse effects are directly correlated with its plasmatic concentrations. Because of this, a close therapeutical management represents a central topic in lithium therapy.

A recent study showed a slower increase in lithium serum concentrations and lower Cmax values with PR *versus* IR formulations (17). It is therefore possible to take into account higher serum lithium concentrations, given the absence of potentially harmful blood peaks. Authors agree on how, with the Li PR, the current existent lithium serum ranges referred to Li IR will probably change, as a consequence of a different kinetics. It is hence suggested to establish more flexible lithium serum concentration ranges and to not consider as an absolute reference for the switch the mathematical conversion in mg/mmol. Finally, it needs to be considered that lithium serum concentration responds to the patient's individual absorption and must be evaluated in each case. Authors suggest that the early data on the switch between formulations indicate that the equivalence between two tablets of Li PR and 900 mg of Li IR does not necessarily lead to the development of equal lithium serum concentrations. Therefore, the patient's individual response needs to be monitored. Additionally, the Authors report that on the first weeks of treatment with lithium PR a slower absorption compared to the experience with lithium IR, is sometimes observed. Afterwards the absorption would tend to be more consistent, with higher levels of lithium serum concentration compared to the first weeks, despite using similar dosages. It is therefore suggested to conduct the weekly measurements of lithium serum concentrations for 2 months and a half in patients that use Li PR. Authors claim they tend to prescribe a night-time use of up to 2 tablets and that they have not detected any changes on the serum concentration when passing from a singular night-time administration to a dual (morning and evening) administration.

Withdrawal effects

The suspension of carbolithium is almost always a complex event, not risk-free, even in terms of suicidal risk. This eventuality, however, becomes necessary in all those cases in which significant problems of renal and thyroid nature arise. The advantages of a prolonged-release administration would certainly be represented by the possibility of inducing less serious adverse effects and, consequently, the need to suspend the drug only on rare occasions. Furthermore, the prolonged-release administration seems to guarantee a less drastic transition where lithium levels elapse even slower. Some studies, in fact, speculate that the difference in activity between the PR Lithium and the IR Lithium is due to a difference in action at a molecular level on the lithium effectors (17). Additionally, the re-integration of lithium with the Lithium PR, after the suspension of Lithium IR, allows to faster achieve levels of efficacy than the re-integration of Lithium IR.

Conclusions

In the treatment of bipolar disorder, lithium still represents the golden standard, despite the increasing number of other mood stabilisers and antipsychotic treatments frequently proposed as alternatives. Nevertheless, treatment with lithium must be always monitored to avoid the adverse events associated with the therapy. According to the literature (17), we hypothesize that lithium PR formulations provide a number of potential advantages over IR formulations, including: 1) More stable lithium serum concentrations during the adjustment interval and on the long term, potentially able to determine higher profiles of efficacy; 2)

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A reduced risk of some adverse events, specifically at a renal level, determining an improving in adherence; 3) A more convenient dosage regimen that may also improve adherence to therapy. Thus, lithium PR formulations may be used over the IR formulations to reduce the treatment-associated adverse events and improve the overall efficacy of lithium in the management of BD. Given the relevance of long-term continuous treatment in reducing morbidity and mortality in bipolar disorder and the rate of non-compliance in subjects with this disorder, a prolonged-release preparation that simplifies the medication regimens and reduces the side effects promises improved patient compliance and, thus, a greater long-term efficacy. Future trials comparing compliance rates, efficacy and adverse events associated with the PR and IR lithium formulations are required to confirm these qualitative clinical but still anecdotal considerations.

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