EXPERT OPINION

Myo-inositol in a new pharmaceutical form: a step forward to a broader clinical use

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Objective: Dose-dependent side effects related to myo-inositol (MI) oral administration represent a significant shortcoming for its clinical use. Aiming to search for a pharmaceutical form able to be better absorbed, the pharmacokinetic (PK) profile of the new manufactured MI soft gelatin capsule form was evaluated and compared with the commercially available MI powder.
Research design and methods: A single-dose relative trial, consisting of four phases, was performed on 20 healthy volunteers who received different doses of MI powder and MI soft gelatin capsules. PK profiles related to the two pharmaceutical forms were obtained by analysis of MI plasma concentration, and the respective MI bioavailability was compared.
Results: The administration of MI powder and MI soft gelatin capsules resulted in a different bioavailability. MI soft gelatin capsule form showed similar PK parameters compared with three times higher doses of MI in powder form.
Conclusions: MI soft gelatin capsules displayed an improved bioavailability, allowing to substantially reduce the administered dose and to minimize the dose-dependent side effects. Considering the number of conditions in which MI supplementation is recommended, this evidence could support a broader use of MI in clinical practice.

Keywords: bioavailability, myo-inositol, PCOS, pharmacokinetics, PMDD, psychiatric disorders, soft gelatin capsules

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1. Introduction

Myo-inositol (MI) is a precursor for many inositol-containing compounds that play critical and diverse roles in signal transduction, membrane biogenesis, vesicle trafficking and chromatin remodeling [1].

Indeed, many studies support the notion that MI is one of the precursors for the synthesis of phosphatidylinositol polyphosphates (PIPs) that are a source of several second messengers including diacylglycerol, which regulates some members of the protein kinase C family, inositol-1,4,5-triphosphate, which modifies intracellular calcium levels, and phosphatidylinositol-3,4,5-phosphate, involved in the signal transduction [1-3].

MI is a component of cell membranes and plays an important role in cell morphogenesis and cytogenesis, lipid synthesis, structure of cell membranes and cell growth. Related to all of these signaling pathways, MI regulates a variety of cellular processes including gametogenesis, fertilization, cell proliferation, cell development, secretion, contraction and neural activity [4,5].

Several trials highlighted that the administration of MI at high dose could result in mild gastrointestinal side effects such as diarrhea and nausea, which led to reduced patients' compliance [6]. Dose-dependent side effects are a strong shortcoming for MI clinical use, and in literature an incidence of about 5% gastrointestinal side effects

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Table 1. Pharmacokinetic parameters after oral administration of 0.6 g or 1.2 myo-inositol (MI) in soft gels and 2 g or 4 g of MI in powder.

Parameter	Mean (SD)					
	MI soft gels 0.6 g	MI powder 2 g	p-Value	MI soft gels 1.2 g	MI powder 4 g	p-Value
C_{max} (μmol/l)	31.5 (3.2)	36.3 (3.2)	NS	41.5 (3.5)	45 (3.5)	NS
T_{max} (min)	180 (6)	183(10)	NS	120 (7)	122 (12)	NS
$AUC_{(0\text{-}1440)}$	34809.5 (5509.3)	37452.2 (5219.9)	NS	40702.4 (6089.2)	44325.6 (6529.9)	NS

Data are tabled as mean ± SD.

$AUC_{(0\ -\ 1440)}$: (μmol·min/l) area under the plasma concentration–time curve to the last measured concentration; C_{max}: (μmol/l) maximum observed plasma concentration during the 0 – 1440 min dosing interval; SD: Standard deviation; T_{max}: Time to peak concentration.

is reported for doses higher than 12 g. Therefore, the development of different MI pharmaceutical forms that are able to improve the absorption rate and reduce side effects represents one of the main challenges in the clinical practice.

It is well known that oral absorption can be influenced by a variety of factors such as the physiochemical properties, formulation and dose of the compound, as well as the physiology and pathology of the gastrointestinal tract (GIT).

Nowadays, common approaches used to enhance oral absorption are based on the chemical modification of the molecule (salt, amorphous form and prodrug) and/or on the use of a vehicle in which the compound is soluble and remains soluble upon contact with the GIT environment.

More recently, the development of soft gelatin (soft gel) capsule form offered several advantages such as improving swallowability, masking odors and unpleasant taste and protecting the encapsulated compound against oxygen and light.

A soft gel is a single unit dosage form, consisting of a liquid or a semi-solid fill enveloped by a hermetically sealed shell. Its use is ideal to deliver compounds with sufficient solubility in a pharmaceutically acceptable non-aqueous vehicle, thereby removing any dissolution-rate-limiting steps and yielding to a faster, uniform and enhanced absorption [7].

Indeed, several studies were reported that highlight the advantages of this pharmaceutical form in terms of bioavailability and compliance above all.

In a recent published paper, the authors compared the clinical effectiveness of MI in premenstrual dysphoric disorder; in particular, they compared in a double blind randomized placebo controlled trial two different MI pharmaceutical forms: 12 g of MI in powder and 3.6 g of MI in soft gel capsules. After a placebo wash-out phase, the authors reported no difference in the effectiveness of these two pharmaceutical forms concerning GI side effects: indeed, no GI events were reported in the soft gel-treated group while one event was described in the powder-treated group [8].

Based on this evidence, aiming to minimize the dose-dependent side effects occurred after MI administration, we tested a new MI soft gelatin capsule formulation and we compared its bioavailability with the commercially available powder form. A single-dose relative bioavailability trial was conducted and the absorption parameters were evaluated.

2. Materials and methods

2.1 Patients and methods

The study involved 20 volunteers, 8 men and 12 women, enrolled at the AGUNCO Obstetrics and Gynecology Center (Rome, Italy). Subjects were evaluated on the basis of medical history, physical examination and laboratory screenings, and subjects who were found in poor general health were excluded. Volunteers were aged between 18 and 35 years, with a body mass index (BMI) ranging between 21 and 25 kg/m^2; additional demographic data were weight in the range of 55 – 86 kg and height 165 – 187 cm.

Before entering the trial a written informed consent was obtained from the volunteers, and the study was approved by the ethical committee.

Based on previously reported clinical studies, subjects received different doses of MI in two different pharmaceutical forms: soft gel capsule (patent pending) or powder. Pharmacokinetic (PK) parameters were evaluated based on the analysis of the MI plasma concentration. Blood samples were collected by venous puncture at pre-dose (0), and at 30, 60, 90, 120, 180, 300, 420, 540 and 1440 min post administration.

The study consisted of four different phases:

Phase I: 0.6 g of MI soft gel capsules was administrated

Phase II: 2 g of MI powder was administrated

Phase III: 1.2 g of MI soft gel capsules was administrated

Phase IV: 4 g of MI powder was administrated

Each phase was separated by a washout period of 15 days.

MI quantification was performed by Chelab Pharma Division using gas chromatography-mass spectrometry (GC-MS) analysis after extraction with organic solvents and derivatization.

Injection (1.0 μl) was performed in a split-less mode at 270°C and a capillary column Agilent 122-5532 DB-5 ms (0.25 mm × 30 m × 0.25 μm) was used. Total run-time was 15 min : oven at 70°C from 0 to 1 min; 20°C/min to 150°C; 10°C/min to 240°C; 4 min at 320°C post run. The

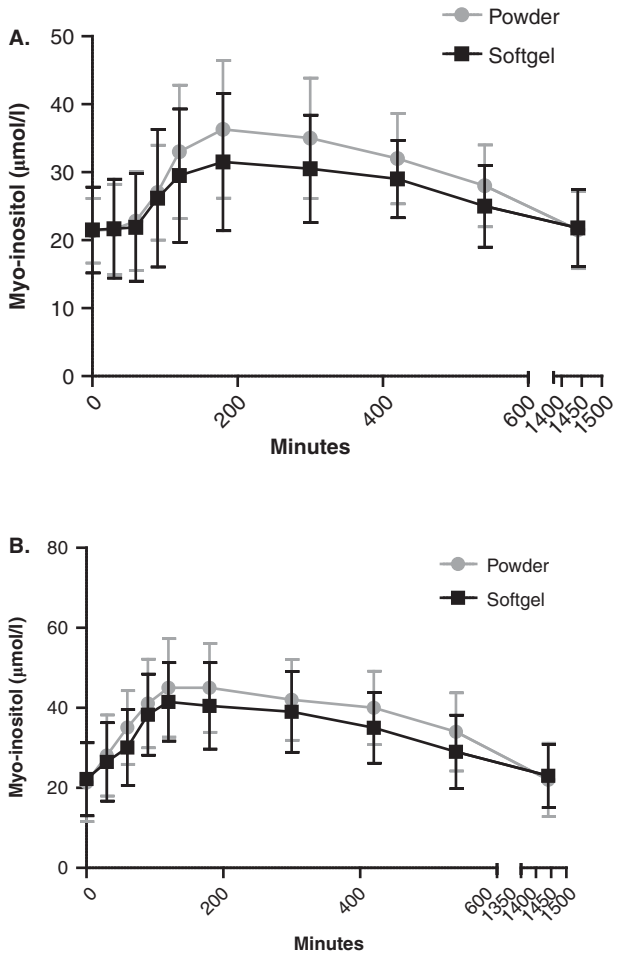

Figure 1. A. Comparison of the plasma concentration–time data profile for Phase I and Phase II (myo-inositol (MI) soft gel capsules 0.6 g and MI powder 2 g). **B.** Comparison of the plasma concentration–time data profile for Phase III and Phase IV (MI soft gel capsules 1.2 g and MI powder 4 g).

flow rate was fixed to 1.2 ml/min and results were analyzed by an MS 5973 Network Series detector in sim mode.

2.2 PK parameters

C_{max} and T_{max} were obtained directly from the plasma concentration, while area under the curve ($AUC_{(0\text{-}1440)}$) was calculated by trapezoidal method between 0 and 1440 min (see **Table 1**).

Data set were compared using one-way ANOVA with Bonferroni multi-comparison correction test.

3. Results

All the enrolled subjects completed the trial. The analysis of MI plasma concentration allowed us to obtain interesting results about the PK parameters of the two formulations. Data showed MI plasma concentration related to the four phases of the study.

In particular, in **Figure 1A** MI plasma concentrations after administration of 0.6 g of MI soft gel capsules or 2 g of MI powder were comparable; indeed, both pharmacological forms showed very similar PK parameters (**Table 1**). A similar result was observed after administration of 1.2 g and 4 g of MI soft gelatin capsules or MI powder, respectively (**Figure 1B** and **Table 1**).

In both cases the new MI form (soft gel capsules) was promptly absorbed showing a similar MI plasma concentration curve compared with the higher dose of MI powder.

Furthermore, there was no difference in the PK parameters between genders (data not shown).

Subjects that received MI soft capsules did not report any adverse effects while one subject reported a mild GI discomfort after administration of 4 g of MI powder.

4. Discussion

In this present study we have shown that the administration of MI in soft gelatin capsule form results in similar PK parameters as with a three times higher dose of MI in powder form.

MI is widely used in clinical practice due to its role in different cellular processes including cell proliferation, fertilization and neural activity.

Indeed, several clinical trials have already shown that MI plays a crucial role in treating PCOS symptoms such as hyperandrogenism, hyperinsulinaemia and oligo-anovulation (for review see [9]). Furthermore, a crucial role of MI in preventing the ovary hyperstimulation syndrome, during assisted reproductive technology protocol, has also been proposed [10,11].

A number of clinical trials also have suggested that MI administration provides effective results in the treatment of psychiatric disorders such as panic [12], depression [13] and more recently PMDD [8]. In order for MI to be effective, high doses (12 – 30 g) were administered occurring in mild GI discomforts, which reduced the patient's compliance [8]. The clinical use of several pharmacologically active compounds is tempered by their PK shortcomings and the dissolution in a vehicle of soft gelatin capsules often resulted in an enhanced bioavailability.

It is reported that many compounds encapsulated in soft gels are better absorbed compared with other conventional oral pharmaceutical forms. Among all, diclofenac potassium liquid-filled soft gelatin capsules were demonstrated to be more rapidly and consistently absorbed than the commercially available diclofenac potassium tablets, resulting in a shorter and more consistent time to onset of analgesia [14]. Similarly, ibuprofen in soft gel is absorbed faster than both film-coated tablet and liquid (prepared from effervescent ibuprofen tablet) [15]. In addition, cyclosporine, when administrated in soft gel, reaches therapeutic blood levels that are not achievable from the oral solution form [16]. Another example is the soft gelatin capsule containing levothyroxine dissolved in glycerin, that showed the most consistent dissolution pattern when compared with two different tablet formulations (the

generic levothyroxine sodium by Sandoz, Inc. and Synthroid® by Abbott) [17].

Based on these evidences, MI was recently manufactured in a new soft gel capsule form.

In the present study, the PK profile of two MI pharmaceutical forms (powder and soft gel capsules) was evaluated. The concentration of the investigated molecule was measured in blood, followed by a single-dose administration to 20 healthy volunteers. The study was divided into four phases in which the subjects received different doses of MI soft gel capsules or MI powder: each phase was analyzed and the main PK parameters were calculated and compared.

Results clearly showed that despite the difference in MI dosage in the two forms, the PK of one capsule containing 0.6 g of MI was equivalent to the PK of 2 g of MI in powder. These results were confirmed also when two capsules and a double dose of MI in powder were administrated.

Therefore, the new MI form in soft gel capsule results in an improved GI absorption that allows to substantially reduce by one-third the administered dose compared to the powder form, overcoming the dose-dependent GI side effects previously described and thus improving the patients' compliance.

Nevertheless, study limitations are present. Indeed, the present results need to be confirmed on a larger and homogeneous population and a direct dosage comparison needs to be performed. However, the strength of the present paper is that we provide a possible explanation and a rationale for the clinical evidence that two different doses administered in the two different pharmacological forms have the same clinical effectiveness [8].

5. Conclusions

Development of soft gelatin (soft gel) capsules is of growing interest and several studies report the ability to perform a uniform, faster and enhanced absorption compared to other oral forms [14-17].

Dose-dependent side effects are an effective shortcoming for the oral administration of MI and the use of different pharmaceutical forms to improve the oral absorption represents one of the main challenges in the clinical practice.

Indeed, MI was recently manufactured in a new soft gelatin capsule form and in order to compare its absorption characteristics with the commercially available MI powder, a single-dose relative trial was conducted.

MI soft gelatin capsules showed an improved bioavailability that substantially reduces the administered dose, thereby representing a clinical advantage for the treatment of psychiatric disorders and other conditions in which the MI supplementation is recommended.

Declaration of interest

LOLI Pharma provided the medication for this study. V Unfer is a consultant for LOLI Pharma. All other authors declare no conflict of interest.

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