European Review for Medical and Pharmacological Sciences 2011; 15: 931-936

Inositol safety: clinical evidences

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Abstract. – Myo-inositol is a six carbon cyclitol that contains five equatorial and one axial hydroxyl groups. Myo-inositol has been classified as an insulin sensitizing agent and it is commonly used in the treatment of the Polycystic Ovary Syndrome (PCOS). However, despite its wide clinical use, there is still scarce information on the myo-inositol safety and/or side effects. The aim of the present review was to summarize and discuss available data on the myo-inositol safety both in non-clinical and clinical settings.

The main outcome was that only the highest dose of myo-inositol (12 g/day) induced mild gastrointestinal side effects such as nausea, flatus and diarrhea. The severity of side effects did not increase with the dosage.

Key Words:

Myo-inositol, PCOS, Side effects, Dosage, NTDs.

Introduction

Myo-inositol (also known as inositol, hexahydroxycyclohexane, or cis-1,2,3,5-trans-4,6-cyclohexanehexol) is a six carbon cyclitol that contains five equatorial hydroxyl groups and one in axial position. The main source of myo-inositol is the diet, indeed it is found in a wide variety of foods such as whole grains, seeds, and fruits. Myo-inositol can also be synthesized from glucose, the immediate precursor being fructose 6-phosphate, which is converted to myo-inositol by a cyclase. Myo-inositol is a precursor in the phosphatidylinositol cycle. It is a source of several second messengers including diacylgycerol, 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-biphosphate, which is involved in the signal transduction. It is a component of cell membranes and is an essential nutrient required by the human cells for the growth and survival in the culture. In humans and other species, Myo-inositol can be converted to either L- or D-chiro-inositol by epimerases. Early studies showed that inositol urinary clearance was altered in type 2 diabetes patients, the next step was to link impaired inositol clearance with insulin resistance (for a review see[1]). Because of these properties, inositol have been classified as "*insulin sensitizing agent*"[2].

In the recent years, inositol has found more and more space in the reproductive clinical practice[3-6]. Indeed, since the main therapy for Polycystic Ovary Syndrome (PCOS) is the use of insulin sensitizing agent inositol is mainly use as a chronic treatment for this disease[2,5,7,8]. Furthermore, recently it was proposed as a preventing agent for folate-resistant neural tube defects (NTDs)[9,10].

The toxicity of Myo-inositol has not been directly investigated. However, a number of studies have been conducted to investigate the efficacy of myo-inositol in preventing the pathological changes associated with experimental diabetes[11,12] (and other pathology models) and as a cancer chemoprevention agent[13-16]. The data of these studies provide useful data for evaluating the toxicity of myo-inositol. The relevant studies will be described and discussed hereafter.

With the present review we aim to summarize some data that are availed in the literature in both non clinical and clinical settings.

Non Clinical Studies

Pugliese et al[11] investigated the potential effect of myo-inositol on diabetes-induced vascular functional changes. Myo-inositol was administered to diabetic rats as supplement in the diet, ranging from 0.5, 1, or 2% (w/w). Vascular functional changes were evaluated by examining: (1) ^{131}I-labeled bovine serum albumin (BSA) permeation of vessels in multiple tissues, (2) glomerular filtration rate (GFR), estimated as renal plasma clearance of ^{57}Co-labeled EDTA, (3) regional

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blood flows, measured with 15-microns 85_{Sr}-labeled microspheres, and 4) endogenous albumin and IgG urinary excretion rates, quantified by radial immunodiffusion assay. After 1 month of induced-diabetes, ^{131}I-BSA tissue clearance increased significantly (2- to 4-fold) in the anterior uvea, choroid-sclera, retina, sciatic nerve, aorta, new granulation tissue, diaphragm, and kidney but was unchanged in skin, forelimb muscle, and heart. Myo-inositol-supplemented diets reduced diabetes-induced increases in ^{131}I-BSA clearance (in a dose-dependent manner) in all tissues. However, only in new granulation tissue and diaphragm did the 2% myo-inositol diet completely normalize vascular albumin permeation. Diabetes-induced increases in GFR and in urinary albumin and IgG excretion were also substantially reduced or normalized by dietary myo-inositol supplements. Increased blood flow in anterior uvea, choroid-sclera, kidney, new granulation tissue, and skeletal muscle in streptozotocin-D (STZ-D) rats also was substantially reduced or normalized by the 2% myo-inositol diet. Notably, the Authors noted that myo-inositol had minimal if any effects on the above parameters in control rats.

Coppey et al[12] studied whether administration of myo-inositol could prevent the detrimental changes of motor nerve conduction velocity, endoneurial blood flow and endothelium-dependent vascular relaxation of arterioles induced by experimental diabetes animal model. Diabetic male rats of 8-9 weeks old were fed with 1% by weight of myo-inositol as a dietary supplement for a period of about 8 weeks. Administration of myo-inositol completely reversed the decrease in intracellular myo-inositol content caused by experimental diabetes. Treating diabetic rats with myo-inositol improved the reduction of endoneural blood flow and motor nerve conduction velocity and prevented the metabolic derangements associated with either activation of the polyol pathway or increased non-enzymatic glycation. Myo-inositol treatment did not prevent the gross signs of diabetes-associated toxicity, such as decrease in body weight change, increase in blood glucose or serum free fatty acids (FFA) and triglycerides (TG). In the myo-inositol group, the values of these parameters were the same as the in the diabetic untreated group. This clearly shows that myo-inositol did cause no further functional impairment in diabetic rats.

Solomonia et al[17] investigated whether treatment with myo-inositol could influence the biochemical changes triggered by kainate-induced status epilepticus (SE) in rats. The effects of myo-inositol were investigated after both acute (1 day) and sub-acute (28 days) administration.

For the acute administration the study was performed on three different groups, (1) male Wistar rats received intraperitoneal injection of kainic acid (10 mg/kg). Six hours following the treatment, rats received myo-inositol 30 mg/kg, by injection; (2) rats received only 30 mg/kg myo-inositol (by injection); (3) rats treated with only saline as controls.

For the sub-acute study also three different groups were analysed (1) rats were treated on day 1 with kainate received twice a day myo-inositol for 28 days; (2) rats were not treated with kainate on day 1 and received myo-inositol for 28 days; (3) rats were not treated with kainate and received saline instead of myo-inositol as controls. Changes in proteins expression in the hippocampus and neocortex, were evaluated. Proteins studied were: GLUR1, subunit of glutamate receptors, calcium/calmodulin-dependent protein kinase II (CaMKII); and heat shock protein 90. No changes were found in the acute experiments. However, on 28th day of experiment the amounts of GLUR1 and CaMKII were strongly reduced in the hippocampus of KA treated animals but MI significantly halted this reduction. Notably, in the group that received myo-inositol alone didn't show change in the amounts of studies proteins.

Chronic Studies and Carcinogenesis

Liao et al[18] studied the effects of myo-inositol and hexaphosphate inositol (HI) on the carcinogenesis associated to ulcerative colitis (UC) in a newly developed mouse model. Female C57BL/6 mice were subjected to long-term, cyclic dextran sulphate sodium (DSS) treatment and fed a 2-fold iron-enriched diet. In this long-term study of chronic UC and associated colorectal carcinogenesis, mice were randomized into six groups. Group 1, Group 2 and Group 3 were administered water, 1% inositol and 1% HI, respectively, in the drinking water throughout the experiment as negative controls (n = 5 mice per group). Group 4, Group 5 and Group 6 mice were subjected to cyclic DSS treatment. Group 4 received no further treatment (positive control), whereas groups 5 and 6 mice were administered 1% myo-inositol or 1% HI, respectively in the drinking fluid. The study lasted 255 days. Myo-inositol and HI did not induce any change in body weight

or food consumption, both in DSS-treated and untreated mice. In mice not treated with DSS, myo-inositol or HI did not induce any change in body weight, food consumption or mortality, as compared to negative controls receiving water. No colorectal tumors were found in mice receiving Myo-inositol of HI. The colons of these mice were morphologically normal. Myo-inositol 1% caused a significant reduction of tumour frequency, tumour multiplicity and tumour volume. The Authors' conclusion is that inositol compounds may act as preventive agents for chronic inflammation-carcinogenesis. The inhibition of UC-associated carcinogenesis by inositol compounds might relate to their function on the modulation of macrophage mediated inflammation, nitro-oxidative stress and cell proliferation in UC-associated carcinogenesis.

Kassie et al[14-16] have examined the inhibitory capacity of myo-inositol (56 μmoles/g diet, i.e., 10 mg/g or 1% diet), in combination with N-acetyl-S-(N-2-phenethylthiocarbamoyl)-l-cysteine (PEITC-NAC) on tobacco carcinogen-induced lung adenocarcinoma in mice. They found that none of the chemopreventive agents, alone or in combination, significantly reduced body weight gain of the mice. The absolute and relative weights of liver and kidney of mice from the treatment groups were similar to those of the control group. In addition, histopathologic examination of the studied organs reveal no abnormalities except a dose-dependent increase in the frequency of eosinophilic bodies within the cytoplasm of urinary bladder epithelial cells.

Tilton et al[19] focused in studying the effects of dietary myo-inositol supplementation on diabetes-induced vascular structural lesions in retina and kidney. The study lasted for a period of 9 months during which diabetic-induced male Sprague-Dawley rats were assigned in three different groups: 1) rats were fed with 2% myo-inositol diet for 9 months; 2) rats were left untreated for 5 months then treated with myo-inositol for the 4 months; 3) rats were left untreated for 9 months. Controls included untreated and myo-inositol-treated groups. As expected, weight gain was impaired and plasma glucose, glycosylated hemoglobin, food consumption, urine volume, and albuminuria were increased significantly in diabetic versus age-matched control rats. Plasma myo-inositol levels were increased approximately five-fold in controls and approximately six- to eightfold in diabetic rats treated with myo-inositol. In general, myo-inositol did not affect any of the above parameters in control or diabetic rats. However, retinal capillary basement membrane width (CBMW) was increased significantly (approximately 50% versus controls) after 9 months of diabetes and in the control group myo-inositol increased CBMW to the level of untreated diabetic rats (myo-inositol had no effect on CBMW in each diabetic group). The number of retinal capillaries containing pericyte nuclei and pericyte capillary coverage were increased in untreated as well as myo-inositol-treated diabetic rats and in the myo-inositol-treated control group. Glomerular CBMW was increased after 5 and 9 months of diabetes versus age-matched controls, and was increased even more by myo-inositol. Mesangial fractional volume of the glomerulus was increased 36% by diabetes and was decreased slightly but significantly by myo-inositol. These results indicate that diets supplemented with 2% myo-inositol cause capillary basement membrane thickening and pericyte changes in retinal capillaries of normal rats. Myo-inositol supplementation cause further thickening of glomerular CBM in diabetic rats and is ineffective in preventing or reversing diabetes-induced retinal CBM thickening.

Safety data in Humans from Clinical Trials

Besides animal model studies, several clinical trials have been carried out in order to evaluate the effects of myo-inositol in pathologic conditions, mainly neuropsychiatric disease (depression, Alzheimer disease, panic disorder) and polycystic ovary syndrome (PCOS)[20,21]. The duration of myo-inositol exposure in these trials ranged from 1 to 12 months. The doses ranged from 4 to 30 g/day.

The safety data of the trials report mild side effects such as, nausea and one of flatus and mild insomnia only at 12 g/day or higher. Results are shown in Table I.

Summary

Non Clinical Data

Data from *sub-acute studies* indicate that a diet containing up to 2% w/w causes no toxic effects in rats.

Pugliese et al: the Authors noted that myo-inositol had minimal if any effects on the above parameters in control rats.

Table I. Safety data from Clinical trials.

Study	Pathology	Patients (inositol group)	Placebo-controlled trials			Adverse events
			Dose	Duration	Dropouts	
Papaleo et al, 2008	PCOS	30	4 g/day	12 months	None	
Gerli et al, 2007	PCOs	45	4 g/day	14 weeks		None
Agostini et al, 2006	Erectile dysfunction in type II diabetes men	88	4 g/day	1 month	None	Two patients complained of mild insomnia and one of flatus
Barak Y et al, 1996	Alzheimer's disease	12	6 g/day	1 month		
Allan SJ et al, 2004	Psoriasis, bipolar disorders	15 inositol + lithium 8 inositol	6 g/day	1 month		None
Levine J et al, 1997	Depression	13	12 g/day	1 month	11 4 placebo 7 inositol	1 nausea and 1 flatus 2 mild increases in glycemia after 4 week 1 transient, although the patient continued (at her request) to receive inositol. The other patient showed the same mild increase several weeks after discontinuation of inositol.
Benjamin J et al, 1995	Panic disorder with or without agoraphobia	21	12 g/day	1 month		Two patients complained of sleepiness while taking Inositol
Palatnik A et al, 2001	Depression panic	25	18 g/day	1 month	4 had no panic attacks	3 subjects nausea, tiredness, headache, and dizziness
Gelber D et al, 2001	Bulimia nervosa and binge eating	24	18 g/day	6 weeks		_
Fux M et al, 1996	Obsessive-compulsive disorder	13	18 g/day	6 weeks		_
Levine J et al, 1996.	Antidepressant	18+36	18 g/day	1 month		_
Stephen Lam et al, 2006	Safety tolerability	16	From 12 to 30 g/day	1 month		The most frequently reported symptoms were flatulence, loose stool, or diarrhea
	MTD	10	18 g/day	3 months		Mild gastrointestinal symptoms were experienced for the first month only

Coppey et al: Authors clearly show that myo-inositol did not cause any further functional impairment in diabetic rats.

Solomonia et al: Rats not treated with kainate, administration of myo-inositol did not produce any change in the amounts of GLUR1 and CaMKII.

Human (Clinical) Data

In the reported studies more than 250 subjects have been exposed to myo-inositol for varying periods.

Clinical trial data indicate that adverse events related to myo-inositol treatment are:

Gastrointestinal symptoms (nausea, flatus, loose stools, diarrhoea) at dose of 12 g/day or higher. Furthermore the severity of adverse events stays the same also at 30 g/day.

Notably the dosage of 4 g/day of inositol commonly used in clinics is completely free of side effects.

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