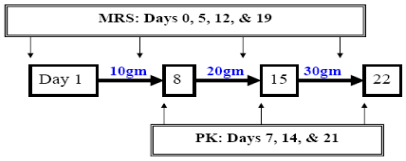
A single-center, phase 1, open label, dosage-escalation study of creatine monohydrate in subject with amyotrophic lateral sclerosis

E-M. Ratai[1,2], N. Atassi[2,3], S. Wallace[2,4], J. Bombardier[1], D. Greenblatt[5], M. Cudkowicz[2,3], and A. Dibernardo[2,3]

[1]Department of Radiology, A. A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Charlestown, MA, United States, [2]Harvard Medical School, Boston, MA, United States, [3]Neurology, Massachusetts General Hospital, Charlestown, MA, United States, [4]Psychiatry, Massachusetts General Hospital, Charlestown, MA, United States, [5]Pharmacology & Experimental Therapeutics, Tufts University School of Medicine, Boston, MA, United States

Introduction:
Amyotrophic lateral sclerosis (ALS) is a rare degenerative disorder of large motor neurons of the cerebral cortex, brain stem and spinal cord that results in progressive wasting and paralysis of voluntary muscles [1]. No treatment prevents, halts or reverses the disease, although a small delay in mortality occurs with the drug riluzole [2], an anti-excitotoxic agent that inhibits the release of glutamate [3]. The cause of selective motor neuron death in ALS is unknown. Many pathogenetic mechanisms have been proposed including mitochondrial dysfunction, glutamate-mediated excitotoxicity, free radical-mediated oxidative cytotoxicity, inflammation, and cytoskeletal abnormalities (reviewed in [4]). Creatine has been shown to stabilize the mitochondrial transition pore, buffer intracellular energy stores, stimulate synaptic glutamate uptake, and scavenge reactive oxygen species. Furthermore, studies in animal models of Huntington's disease (HD) and ALS suggest that creatine's neuroprotective effects are dose-dependent [5]. Creatine is safe and well tolerated but failed to demonstrate efficacy in ALS at 5 and 10 gm/day [6-8]. The purpose of this study was to establish serum pharmacokinetics (PK) of orally administered creatine at several doses of 5gm BID (twice a day), 10gm BID and 15gm BID, to help determine the optimal dose for further clinical testing in ALS and to assess whether oral intake produces increased concentrations of creatine in the brain utilizing *in vivo* MR Spectroscopy.

Methods:
Six ALS patients were enrolled in this open-label pilot study after informed consent was obtained. Patients escalated weekly through 3 different dose levels (5 gm BID, 10 gm BID, 15 gm BID). Creatine blood levels were collected over 5 hours on day 7 of each dose. Pharmacokinetics analysis was performed on the individual plasma concentration-time data, using actual sampling times.



Magnetic resonance spectroscopy (MRS) was performed in the frontal cortex at baseline and 5 days after each dose increase. All MR experiments were performed in a 3 T MRI system (TimTrio, Siemens). MRS was performed using a point resolved spectroscopy sequence (PRESS) using the following parameters: TE = 30 ms, TR = 2000 ms, 128 acquisitions, and a voxel size of 2 x 2 x 2 cm. All spectra were processed offline using LCModel to determine the quantities of the brain metabolites N-acetylaspartate (NAA), choline (Cho), creatine + phosphocreatine (Cr), myo-Inositole (MI), and the sum of glutamine and glutamate (Glx). Metabolite concentrations on MR Spectra were compared between baseline and highest dose (15 gm BID) using a paired-t-test.

Results:
Pharmacokinetics analysis showed dose-related increase in serum concentration of creatine at all doses (10, 20, and 30 gm/day). *In vivo* MR spectroscopy in the frontal cortex over the course of creatine monohydrate treatment reveals an 8% increase in Cr between pre-treatment and 3 weeks post treatment ($p = 0.07$; Figure 1). In addition a 17% decrease in Glx is observed between pre-treatment and 3 weeks post treatment ($p = 0.035$; Figure 2). The Glx resonance consists predominantly of glutamate, an excitatory neurotransmitter which is thought to be increased in neurodegenerative diseases. Excess of glutamate surrounding neural cells can be toxic and can eventually result in neuronal death. None of the other metabolites such as NAA, MI, and Cho revealed any significant changes during creatine treatment. Figure 3 displays the percent changes in NAA/Cho. NAA is predominantly (>95%) located in neurons, thus NAA serves a marker for neuronal health. Elevations in Cho have also been documented in a variety of neuroinflammatory and neurodegenerative diseases and likely reflect increased membrane turnover and may be observed in glial activation and inflammation. However the minimal increase in NAA/Cho of 6% is statistically not significant. Figure 4 summarizes the metabolite concentration changes comparing baseline to 15 BID.

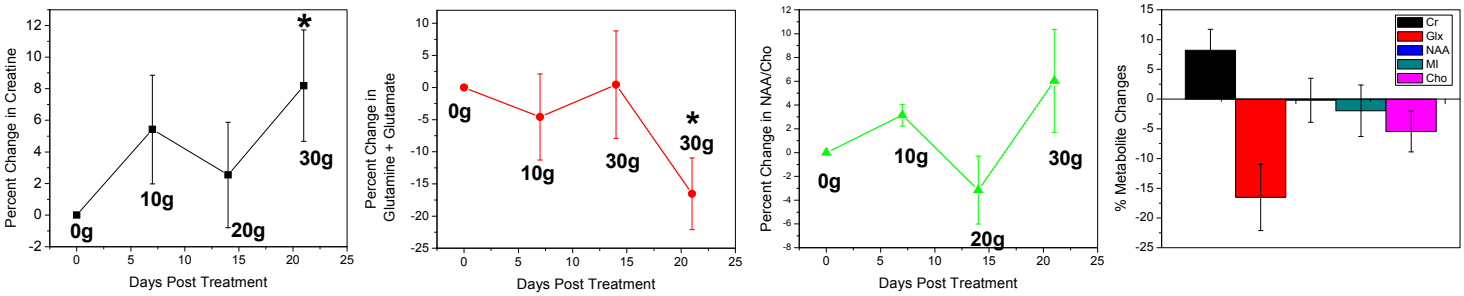


Figure 1-3: Metabolite concentration changes during treatment escalation**. Figure 4:** Metabolite concentration changes comparing baseline to 15 BID.

Conclusions:
Creatine serum levels increased with daily use of 5, 10, 15 gm BID. MR Spectroscopy results are suggestive that creatine crosses the blood brain barrier when given at a high dose of 15 gm BID. Furthermore, glutamine and glutamate levels decreased post treatment.

References:
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