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Clinical Trial of the Potassium Channel Activator Diazoxide for Major Depressive Disorder Halted Due to Intolerability

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Abstract

Background—Some glutamatergic modulators have demonstrated rapid and relatively sustained antidepressant properties in patients with major depressive disorder (MDD). Because the potassium channel activator diazoxide increases glutamate uptake via potassium channel activation, we hypothesized that it might exert antidepressant effects by increasing the removal of glutamate from the synaptic cleft, thereby reducing excessive glutamate transmission.

Methods—This randomized, double-blind, placebo-controlled, crossover, single-site inpatient clinical study was conducted at the National Institute of Mental Health (NIMH) to assess the efficacy and safety of a three-week course of diazoxide (200–400 mg daily BID) versus a three-week course of placebo in six participants with treatment-refractory MDD. The primary clinical outcome measure was change in Montgomery-Asberg Depression Rating Scale (MADRS) score from baseline to post-treatment. Quantitative insulin sensitivity check index (QUICKI), as well as concomitant imaging measures (electroencephalography (EEG), proton magnetic resonance spectroscopy (¹H-MRS), magnetoencephalography (MEG)) were used as potential surrogate markers of target (K_{ATP} channel) engagement.

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Disclosures

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Results—The study was halted due to severe side effects. Given the small sample size, statistical evaluation of the effect of diazoxide on MADRS scores or the imaging measures was not pursued. Visual inspection of the QUICKI test revealed no evidence of target engagement.

Conclusions—Though the results are negative, they are an important addition to the literature in this rapidly changing field.

Keywords

glutamate; potassium channel activator; diazoxide; depression

Introduction

At least one third of individuals with major depressive disorder (MDD) remain treatment-refractory after receiving currently available antidepressants¹, underscoring the urgent need for new antidepressant therapies^{2,3}. Of the novel pharmacotherapeutic strategies seeking to rapidly alleviate depressive symptoms, glutamatergic modulators have emerged as promising potential targets.

In clinical studies, glutamatergic modulators such as ketamine have demonstrated rapid and relatively sustained antidepressant properties in patients with MDD⁴ as well as in those with bipolar depression^{5,6}. In addition, a large body of preclinical evidence suggests that chronic administration of existing antidepressants has significant, albeit complex, dampening effects on the glutamatergic system⁷. In this context, the exquisite balance of glutamate transporters is critically important to maintaining homeostatic glutamate uptake from the extracellular space and plays a central role in modulating extracellular glutamate concentrations; these concentrations, in turn, are essential for preventing excitotoxicity in the brain^{8,9}. Astrocytic glutamate transporter dysfunction leads to excessive extracellular glutamate concentrations, which has been hypothesized to result in depressive-like behaviors in rodents, and is possibly related to the pathophysiology of depression in humans¹⁰.

The present study sought to examine the potassium (K_{ATP}) channel activator diazoxide as a possible treatment for MDD. Diazoxide is FDA-approved for the treatment of sulfonyleurea-induced hypoglycemia, hypoglycemia due to hyperinsulinemia¹¹, and hypertension (https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/017453s014lbl.pdf). It is available in an oral formulation, crosses the blood-brain barrier fairly rapidly, and regulates endogenous glucose production that appears to be attributable to extrapancreatic (i.e., CNS) effects via the hypothalamus, where there is increased expression of K_{ATP} channels¹². Diazoxide also has beneficial effects on glucose metabolism. It has been shown to suppress insulin—primarily by inhibiting insulin release from the pancreas—and to lower blood pressure and, as a result, has been studied in obese individuals^{13,14}.

Dosage information available from the manufacturer notes that initial diazoxide doses in adults begin at 3 mg/kg/day (administered orally in a divided dose), with usual doses of 3–8 mg/day and a maximum dose of 15 mg/kg/day (Micromedex®). In one study, obese hyperinsulinemic men received up to 900 mg/day (300 mg TID) for six months; hyperglycemia and edema were dose-limiting events, but only at doses higher than 300

mg/day¹³. A study by Kishore and colleagues found that equipotent diazoxide doses of 4mg/kg/day, or 200–400mg/day across species, rapidly activated the K_{ATP} channel within 135 minutes¹², with corresponding maximally significant decreases in endogenous glucose production by 315 minutes. The same study found that oral administration of diazoxide substantially decreased endogenous glucose production in Sprague Dawley rats as well as nondiabetic humans, without inducing significant changes in blood pressure¹². In rats, the effects of comparable doses of oral diazoxide were abolished by intracerebroventricular administration of the K_{ATP} channel blocker glibenclamide, thus confirming its central specificity.

Diazoxide is also known to increase glutamate uptake from the synaptic cleft by activating the K_{ATP} channel to chronically increase expression of the excitatory amino acid transporter (EAAT)-2 system in glial cells. The activation of hypothalamic K_{ATP} channels is key to regulating endogenous glucose production by inhibiting gluconeogenesis and negating the effect of central and systemic insulin. These measures of serial peripheral glucose and/or insulin could be used as a surrogate of target engagement of diazoxide at activating K_{ATP} channels¹². The EAAT-2 transporter—which is predominantly expressed on astroglial cells and is responsible for 90% of total glutamate uptake in the synaptic cleft—is one of the major glutamate transporter systems¹⁵. Studies suggest that astrocytic glutamate reuptake systems may be key to the pathophysiology and treatment of depression¹⁶, and that agents that directly increase astrocytic glutamate uptake may represent a novel class of antidepressants¹⁷.

The present study (NCT02049385) sought to investigate whether diazoxide might exert antidepressant effects by increasing the removal of glutamate from the synaptic cleft, thereby reducing excessive glutamate transmission. This randomized, double-blind, placebo-controlled, crossover, single-site, inpatient clinical study was conducted to assess the efficacy and safety of a three-week course of diazoxide (twice-a-day dosing, 200–400 mg total daily dose) versus a three-week course of placebo. The proposed duration of the trial was 10–12 weeks.

Materials and Methods

Male and female participants were eligible for study participation (clinical trials identifier: NCT02049385) if they were between 18 and 65 years old, met Diagnostic and Statistical Manual (DSM-IV) diagnostic criteria for MDD without psychotic features (confirmed by the Structured Clinical Interview for DSM-IV), and were currently experiencing a major depressive episode lasting at least four weeks. All participants were studied at the Clinical Center of the National Institute of Mental Health, National Institutes of Health (NIMH-NIH) in Bethesda, Maryland, USA. Participant demographics are listed in Table 1. All participants had an initial Montgomery-Asberg Depression Rating Scale (MADRS) score of at least 20 at screening and at baseline prior to being randomized into the study.

Participants were randomized to order of treatment, and each course was separated by a two-week washout period (Day –14 to Day 0) prior to the administration of either diazoxide or placebo. The starting dose of 300 mg/day BID was the treatment target for all participants

unless tolerability issues ensued. The dose of diazoxide/placebo could be increased to 400 mg/day BID in subjects who did not meet response criteria by Day 14; response criteria were defined as having a 50% decrease in MADRS score. If no response after two weeks on diazoxide/placebo was observed, a dose of 400 mg/day BID could be given the last week in each phase for non-responders.

The original experimental design of the study was as follows. To test surrogate neurobiological markers of antidepressant therapeutic response and/or target engagement in the brain (ie, K_{ATP} channel activation, which is implicated in glutamate uptake), participants received an oral glucose tolerance test (OGTT) after an overnight fast using standard oral 75g glucose loading on Days 0 and 36. OGTT glucose/insulin levels were calculated via the quantitative insulin sensitivity check index (QUICKI) as a surrogate measure of decreased endogenous glucose production or K_{ATP} channel activation; simultaneous electroencephalography (EEG) recording was used to measure pharmacokinetic and pharmacodynamic CNS effect (particularly gamma power in frontal regions)¹⁸. In addition, prefrontal glutamate levels were measured using proton magnetic resonance spectroscopy (¹H-MRS), and affective and cognitive function was measured with quantitative magnetoencephalography (MEG) at baseline and at the end of each treatment phase¹⁹. These measures were correlated with peripheral blood biomarkers obtained at baseline and during each study phase.

Participants received diazoxide or placebo one hour before the OGTT. Blood was sampled for glucose, insulin, and diazoxide levels at -30, 0, 10, 20, 30, 45, 60, 90, 120, 150, 180, 210, and 240 minutes after glucose ingestion using a venous catheter. The primary clinical outcome measure was change in MADRS score from baseline to post-treatment. Side effects were monitored routinely.

From July 2014 to Oct 2015, 12 participants with treatment-refractory MDD were recruited into the study. Six withdrew from the study before randomization, during the initial medication tapering phase. Reasons for withdrawal included: improvement of symptoms (n=1), worsening of symptoms during drug free period (n=2), unrelated medical events (n=1), and patient decision to withdraw for unknown reasons (n=2). Among the six participants who progressed into the randomization phase, only one was able to complete the entire study; the five other participants withdrew from the study due to intolerable side effects (Table 1).

Results

Given that only one participant completed both treatment arms, no formal analysis of the primary outcome measure (MADRS) was possible. No short-term effect of diazoxide was apparent; at Day 7, the median change in MADRS score was 0% in the six participants in the diazoxide condition and +10% for the three participants in the placebo condition (Table 1).

Six participants completed the OGTT during the diazoxide phase, and three during the placebo phase. Given the small sample size, statistical comparison between conditions was

not pursued. Visual inspection revealed no evidence of target engagement (Figure 1). Because only one patient completed the study, analyses of other measures were not pursued; these included EEG, ¹H-MRS, MEG, and the peripheral samples.

The most common side effects in those participants receiving diazoxide were: headache (4/6), hypotension (3/6), edema (3/6), muscle/bone/joint pain (3/6), nausea (3/6), elevated liver enzymes (2/6), weakness (2/6), stomach/abdominal discomfort (2/6), tachycardia (2/6), weight gain (2/6), and dizziness/faintness (2/6). These side effects were significant enough that almost all patients withdrew from the study.

Discussion

Due to the significant rate of participant drop out during the medication tapering and medication administration phases, this trial was terminated prior to achieving the target enrollment of 20 subjects. Concomitantly, the FDA issued a warning for the occurrence of pulmonary hypertension in infants and newborns treated with diazoxide (<https://www.fda.gov/Drugs/DrugSafety/DrugSafetyPodcasts/ucm455659.htm>).

The largest literature review of diazoxide conducted to date, which included 644 cases²⁰, found that this agent is implicated in a wide range of side effects. These include electrolyte imbalances that result in the expansion of extracellular fluid volume (hypotension, fluid retention, and edema), likely due to potent renal sodium and chloride retention but not affecting potassium excretion. Cases of pulmonary hypertension, cardiotoxicity, and/or heart failure have also been reported, likely due to the nonselective activation of the K_{ATP}-channel, as its malfunction has been implicated in the progression of heart disease^{20,21}. In addition, rare cases of renal failure, anaphylaxis, and bone marrow suppression have been also reported²⁰.

In sum, the occurrence of intolerable side effects related to diazoxide use may preclude its investigation and use as an antidepressant agent. If future studies of diazoxide are undertaken, investigators should consider using lower doses of diazoxide (less than 200 mg), which may minimize adverse events and consequent withdrawals, though it may also limit the potential antidepressant effect of this agent. It should be noted that the increased need for novel antidepressants may warrant future studies targeting the EAAT2 promoter as a screening paradigm for identifying novel compounds capable of regulating perturbed glutamate transport at the synapse¹⁵.

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Figure 1.

Results of the oral glucose tolerance test (OGGT) and serial glucose levels (mg/dl) for participants receiving diazoxide (n=6) or placebo (n=3) after an overnight fast and 75g glucose challenge are shown in panel A. Glucose levels were within the normal range: 60 minutes, <180 mg/dL; 120 minutes, <155 mg/dL; 180 minutes, <140 mg/dL. Results of the OGGT and serial insulin levels (mIU/L) are shown in Panel B. Insulin levels were within the normal range: 30 minutes, 30–230 mIU/L; 60 minutes, 18–276 mIU/L; 120 minutes, 16–166 mIU/L; 180 minutes, <25 mIU/L. Panel C displays results from the quantitative insulin sensitivity check index (QUICKI) derived from this formula:

$$1/(\log(\text{fasting insulin } \mu\text{U/mL}) + \log(\text{fasting glucose mg/dL})).$$

Table 1
Demographics, side effects, and MADRS score related to diazoxide treatment in participants with MDD

Subject No.	Sex	Age (Year)	Dose (mg/day)	Time in study (Days)	Change in MADRS Score* at Day 7, Diazoxide	Change in MADRS Score at Day 7, Placebo	Major side effects
1	M	65	200	10	-3%	n/a	Elevated liver function test, headache, edema, muscle/bone/joint pain
2	F	40	200	46	+10%	+7%	Hypotension, muscle/bone/joint pain, nausea, weakness, stomach/abdominal discomfort, tachycardia
3	M	48	400	57 [#]	+3%	+12%	Headache, hypotension, weight gain, dizziness/faintness
4	F	37	200	10	-3%	n/a	Headache, edema
5	M	33	400	49	-9%	+10%	Muscle/bone/joint pain, weakness
6	F	56	200	8	+12%	n/a	Elevated liver function test, headache, hypotension, edema, nausea, stomach/abdominal discomfort, tachycardia, weight gain, dizziness/faintness

MDD: Major depressive disorder; MADRS= Montgomery Asberg Depression Rating Scale;

* change: a negative value denotes improvement

[#] patient completed the study