Open-Label Uridine for Treatment of Depressed Adolescents with Bipolar Disorder

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Abstract

This report is an open-label case series of seven depressed adolescents with bipolar disorder treated with uridine for 6 weeks. Treatment response was measured with the Children's Depression Rating Scale-Revised and the Clinical Global Impressions scale. Uridine was associated with decreased depressive symptoms, and was well tolerated by study participants. Further systematic studies of uridine are warranted.

Introduction

PEDIATRIC BIPOLAR DISORDER is a poorly understood illness for which new treatments are urgently needed. The small number of approved treatments, and concerns regarding adherence and adverse events present current challenges in management (Frazier et al. 2009). Practice parameters and published algorithms have established mood stabilizers and atypical antipsychotics as first-line agents for pediatric mania (Pavuluri et al. 2004; Kowatch et al. 2005; McClellan et al. 2007). In contrast, there is little evidence or expert consensus regarding treatment for depressed youth with bipolar disorder. For these patients, there is an unmet need for safe and effective pharmacologic interventions.

Converging lines of evidence implicate changes in mitochondrial energy metabolism in the neurobiology of bipolar disorder (Dager et al. 2004; Stork and Renshaw 2005; Kato 2006; Regenold et al. 2009). Experts in neuropsychopharmacology have suggested that modification of glutamatergic system function serves as a rational treatment strategy in the development of interventions for bipolar disorder (Sanacora et al. 2008). One class of molecules with the potential to impact both energy metabolism and excitatory glutamatergic transmission in the brain is the pyrimidine nucleosides. These include uridine, triacetyluridine (a uridine prodrug), and cytidine.

Pyrimidines have beneficial effects on cerebral phospholipid metabolism (Cansev 2006), catecholamine synthesis (Martinet et al. 1978, 1979), and mitochondrial function (Lehninger et al. 2008)—each of which has been linked to the pathophysiology of bipolar disorder (Yoon et al. 2009). The pyrimidines that have been studied as treatments for adults with bipolar depression include cytidine (Yoon et al. 2009) and triacetyluridine (Jensen et al. 2008).

Uridine is a constituent of human mother's milk (Sugawara et al. 1995; Thorell et al. 1996), and is an ingredient in most infant formulas (Wurtman 2008). As a natural substance present in human cells, uridine has few known side effects when administered orally. Oral uridine has been studied as an intervention for depressed adults with bipolar disorder (Repligen 2006, 2008). However, data are lacking in the treatment of youth. As an initial step in the evaluation of uridine as an intervention for pediatric bipolar depression, we treated seven depressed adolescents with bipolar disorder with open-label uridine.

Methods

Approval for the study was obtained from the University of Utah Institutional Review Board (IRB). Informed consent consisted of written parental permission as well as written assent from participants. Parents and participants were informed that five medications (lithium, risperidone, quetiapine, olanzapine, and aripiprazole) are approved by the U.S. Food and Drug Administration (FDA) to treat bipolar disorder in adolescents, and referral for clinical care was offered as an alternative to study participation during the informed consent process. The study was conducted under FDA Investigational New Drug Application No. 74,122. An external Data Safety and Monitoring Board with authority to halt the study was established, and the study was conducted in accordance of the principles of Good Clinical Practice.

Participants were recruited through clinician referrals and IRB-approved advertising. Consecutive patients who met inclusion criteria were enrolled. Inclusion criteria included a primary diagnosis of bipolar disorder I, II, or not otherwise specified and a current depressive episode of >2 weeks duration with a Children's

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TABLE 1. SUMMARY OF OPEN-LABEL URIDINE STUDY RESULTS

No.	Age/sex	Diagnoses	CDRS-R- baseline	CDRS-R (week)	CGI-S- baseline	CGI-I (week)	Adverse events	C-SSRS-baseline	C-SSRS during treatment (week)	C-SSRS-final	Concomitant medications
1	14/F	Bipolar II ADHD	71	20 (6)	5	2 (6)	None	Wish to be dead Many times daily Unable to control	None	None	None
2	15/F	ODD Bipolar I ADHD	71	24 (6)	5	2 (6)	Suicidal ideation ^a	Wish to be dead 2-5 times weekly Unable to control	Wish to be dead (4) 2-5 times weekly Unable to control	None	None
3	17/F	Bipolar NOS ADHD	73	46 (1)	5	3 (1)	Insomnia ^a	Wish to be dead Daily or almost daily Control with difficulty	None	None (week 1)	Aripiprazole 5 mg
4	16/F	phobia Bipolar I ADHD	57	37 (6)	4	2 (6)	Vivid dreams ^b Abdominal cramp ^b Insomnia ^a	Wish to be dead Many times daily Unable to control	None	None	Aripiprazole 2 mg
5	15/M	GAD Bipolar II ADHD	61	28 (6)	4	2 (6)	Insomnia ^a Fatigue ^a Sinusitis ^a	None	None	None	None
6	13/M	Social phobia Bipolar II ADHD	61	27 (6)	4	2 (6)	Hordeolum ^a Abdominal cramp ^b Nausea ^b	None	None	None	None
7	17/F	Bipolar NOS	65	28 (2)	5	3 (2)	Diarrhea ^b Bronchitis ^a Dyspepsia ^b Back pain ^a	None	None	None (week 2)	Norethindrone acetate/ethinyl estradiol 1 mg/20 mcg Ranitidine 100 mg Calcium 1,000 mg

^aAdverse event unrelated to study drug.^bAdverse event possibly or probably related to study drug.

ADHD = attention-deficit/hyperactivity disorder; CDRS-R = Children's Depression Rating Scale-Revised Raw Score; CGI-I = Clinical Global Impressions-Improvement Score; CGI-S = Clinical Global Impressions-Severity Score; C-SSRS = Columbia-Suicide Severity Rating Scale; ODD = oppositional defiant disorder; GAD = generalized anxiety disorder; NOS = not otherwise specified.

FIG. 1. CDRS-R scores during 6 weeks of treatment with uridine. CDRS-R = Children's Depression Rating Scale-Revised.

Depression Rating Scale-Revised (CDRS-R) (Poznanski and Mokros 1996) raw score >40 . Consistent with the preliminary nature of the study, few exclusion criteria were applied. For example, no restrictions were placed on concomitant medications or psychosocial interventions. The study's exclusion criteria were psychotic symptoms, suicidal ideation with high risk for suicidal behavior, primary Axis I diagnosis other than bipolar disorder, Young Mania Rating Scale (YMRS) score >10 (Young et al. 1978), positive pregnancy test, known or suspected mental retardation, positive urine drug screen, or unstable medical condition.

Diagnoses were established with the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL) (Kaufman et al. 1997). Before receiving study drug, a complete blood count, metabolic panel, lipid profile, thyroid-stimulating hormone, and urinalysis were obtained to establish that participants were in generally good health, and to rule out the presence of undiagnosed medical conditions. The laboratory studies were repeated at the conclusion of study drug administration, to prospectively identify any abnormalities associated with uridine administration.

Participants received fixed-dose uridine 500 mg twice daily for 6 weeks. At each treatment visit, the following rating scales were administered: The CDRS-R, YMRS, and the Columbia-Suicide Severity Rating Scale (C-SSRS) (Posner 2010). Adverse events were recorded at every study visit. Change in CDRS-R raw score was the primary outcome measure, with C-SSRS results and treatment-emergent adverse events serving as secondary outcomes.

Results

Summary results for each study participant are presented in Table 1. All participants were Caucasian. None of the participants initiated or terminated psychosocial treatment during the study. Five of the seven participants completed 6 weeks of treatment with uridine. Two participants withdrew consent before receiving a full course of investigational drug. In both cases, the participant and parent reported that the decision was not based on efficacy or adverse events. The demographic data of the two withdrawn adolescents were similar to other remaining participants. One participant withdrew after 2 weeks of treatment due to a scheduling conflict; the other withdrew after 1 week for reasons unrelated to study participation. Both early terminators experienced a reduction in

their CDRS-R raw score. The individual participants' CDRS-R raw scores over time are depicted graphically in Figure 1.

The mean CDRS-R score at study entry was 65.6. The mean CDRS-R score for participants completing 6 weeks of treatment with uridine was 27.2. If the two early terminators are included in a Last Observation Carried Forward analysis, the mean final CDRS-R raw score for all participants was 30—an average score, which, notably, would not meet the study's inclusion criterion of >40 . The mean reduction in CDRS-R raw score using Last Observation Carried Forward data was 54%, and no participant failed to achieve the a priori definition of treatment response: A 30% reduction in CDRS-R raw score.

At the fixed dose of 500 mg twice daily, uridine was well tolerated by participants. Adverse events, which are summarized in Table 1, were self-limited: No participant experienced an unresolved treatment-emergent adverse event, and neither of the two participants who withdrew from the protocol based their decision on adverse events. No participant attempted suicide, engaged in self-harm, required psychiatric hospitalization, or experienced a manic switch during the study. There were no serious adverse events (United States Food and Drug Administration 1996). Administration of the C-SSRS-Baseline revealed that four of seven participants had a history of suicidal ideation, although none reported a prior attempt. The C-SSRS-Since Last Visit was administered at every encounter. One participant endorsed a "Wish to be Dead" during treatment week 4. This was not considered drug-related, as the C-SSRS-Baseline documented that intermittent suicidal ideation was present before study entry. The detail embedded in the C-SSRS allowed the investigators to compare the frequency and controllability of the thoughts; we were reassured when the week 4 ideation was not more severe than the suicidal ideation previously experienced. In fact, the participant and her mother were impressed at how rapidly the suicidal ideation resolved. Overall, the study's drug-related adverse events were consistent with studies of uridine studies for medical disorders, in which gastrointestinal symptoms (e.g., nausea and abdominal cramps) are most frequently reported.

Discussion

The authors report results of what we believe to be the first study of uridine as a treatment for depressed adolescents with bipolar

disorder. Open-label uridine 500 mg twice daily for 6 weeks was associated with a mean decrease in CDRS-R raw score of 35.6, representing a reduction of 54% compared with baseline scores at study entry.

The benefit associated with uridine was not associated with switches to mania, treatment-emergent suicidal behavior, or serious adverse events. No clinically significant laboratory abnormalities were associated with uridine in our study. Although not measured systematically, improvement in psychosocial domains such as school performance, peer relations, and family function appeared to be associated with uridine treatment as well. Feedback from participants and parents suggests that uridine would score well on measures of patient acceptability and patient satisfaction.

Although uridine is a novel treatment for pediatric bipolar disorder, the history of uridine's use in medicine suggests that it may have few of the medically significant adverse events associated with mood stabilizers and second-generation antipsychotics. Reports of uridine treatment for the metabolic disorder Hereditary Orotic Aciduria began to appear in the 1960s (Becroft et al. 1969). Some patients with this disease have been treated for over 20 years with oral uridine at doses up to 300 mg/kg per day, including two women who between them had six successful pregnancies, and one man who fathered a child. Six of the seven infants were normal; the seventh was born with congenital anomalies caused by a genetic mutation identified in the infant's mother and several maternal family members (Webster 1995). Patients with Hereditary Orotic Aciduria report abdominal cramps and diarrhea as the only adverse events that appear to be related to uridine.

The collective evidence for mitochondrial dysfunction in bipolar disorder suggests a potential role for uridine in the treatment armamentarium. This evidence includes the co-morbidity of mood disorders with mitochondrial disorders (Kato 2006), molecular genetic studies (Konradi et al. 2004), neuroimaging (Stork and Renshaw 2005), postmortem research (Andreazza et al. 2010), and critical reviews (Quiroz et al. 2008). Rational development of new treatments for bipolar disorder would include compounds designed to normalize the bioenergetic abnormalities associated with mitochondrial dysfunction (Kato 2007). Other potential mechanisms of uridine in treating bipolar depression include change in phospholipid metabolism (Cansev 2006; Wurtman et al. 2000), catecholamine synthesis (Wang et al. 2005), or synaptogenesis (Wurtman et al. 2009).

Preclinical studies suggest that pyrimidines have antidepressant properties (Carlezon et al. 2002, 2005). Studies of pyrimidines in adults with bipolar disorder have been promising as monotherapy (Repligen 2006, 2008; Jensen et al. 2008) and as an adjunct to valproate (Yoon et al. 2009). Notably, participants treated with cytidine + valproate in the latter study experienced a rapid improvement in depressive symptoms in weeks 1–4, when compared with placebo + valproate patients. This phenomenon was echoed in our study, in which participants reported a decline in depressive symptoms within the first 2 weeks of treatment.

Given the lack of an exclusion criterion for current psychotropic medications, one notable aspect of the study sample is that just two of seven participants were on concomitant medications. Possible reasons for this include inadequate access to care, patient and family preference, and treatment adherence. The latter has been found to be poor in naturalistic studies of adolescent bipolar disorder (Coletti et al. 2005; DelBello et al. 2007) and in research settings (Drotar et al. 2007). One study found that after hospital discharge on an atypical antipsychotic, 43% of adolescents had stopped the medication at the behest of a parent or physician (Pogge

et al. 2005). This underscores the need for treatments with improved patient, parent, and physician acceptability. As a substance known to be present in human mother's milk and commercial infant formula, if proven effective, uridine may be more acceptable than current drugs to the parents and physicians of adolescents with bipolar disorder.

The limitations of this pilot case series include its small sample size, the absence of a blinded placebo control group, and the heterogeneity of the population under study. Future work will be designed to address these limitations.

Conclusions

In this pilot case series, uridine was efficacious and well tolerated by study participants. Rapid onset of action may be a distinguishing feature of uridine. Open-label studies are an initial step in testing a novel intervention, and these findings should be considered preliminary. Uridine should not enter clinical practice as a primary treatment for depressed adolescents with bipolar disorder until randomized placebo-controlled trials have been performed to confirm its efficacy.

Disclosures

Dr. Kondo, Dr. Sung, Ms. Hellem, Ms. Delmastro, Dr. Jeong, Dr. Kim, and Dr. Shi. have no pharmaceutical company consultancies, honoraria, stock ownership, stock options, gifts, vacations, equity interests, patent arrangements, or other vested financial interests to declare. Dr. Renshaw serves as a consultant to Kyowa Hakko, Novartis, and Roche. He has received research support from GlaxoSmithKline and Roche. He is an inventor on a patent application that describes the use of uridine as a treatment for bipolar disorder. This patent application has been assigned to McLean Hospital and is licensed to Repligen Corporation. The University of Utah manages conflicts of interest related to intellectual property. As part of this management, Dr. Renshaw did not evaluate any of the study participants at any point in time.

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