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Salsalate as an adjunctive treatment for psychopathology and cognition in patients with schizophrenia: a pilot study

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Abstract

Objective—This pilot study examined the effect of adjunctive salsalate on psychopathology and cognition in patients with schizophrenia.

Methods—This was a 12-week, open label trial of salsalate (1.5g, twice per day) in patients with schizophrenia. Psychopathology, cognition and daily function were assessed at baseline and week 12 using various rating scales. Blood levels of inflammatory markers including white blood cell count (WBC), high sensitivity C reactive protein (hsCRP) and interleukin-6 (IL-6) were also measured.

Results—Eight subjects completed the study. There was no significant change in any of the rating scales at week 12. However, there was a trend decrease in the Positive and Negative Syndrome Scale (PANSS) total score, and a trend improvement in the Brief University of California San Diego Performance-based Skills Assessment (UPSA-B) total score (58.3 ± 11.4 versus 53.5 ± 11.9 , $p = 0.072$; 69.7 ± 18.2 versus 79.1 ± 15.9 , $p = 0.084$ respectively). There was a trend improvement in quality of life as measured by the Quality of Life Scale (QLS) total score (74.0 ± 20.8 versus 76.9 ± 22.7 , $p = 0.080$). There was a significant decrease in WBC count (6.8 ± 1.3 versus 6.0 ± 1.2 th/mm³, $p = 0.022$). There was no change in levels of hsCRP or IL-6 over 12 weeks (p 's > 0.1).

Conclusion—Salsalate may have positive therapeutic effect in patients with schizophrenia. Future studies to examine potential benefits of salsalate as an adjunctive treatment to improve clinical symptoms and daily function in patients with schizophrenia are warranted.

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Conflict of interest

Other authors report no competing interests.

Keywords

salsalate; schizophrenia; psychopathology; cognition; inflammation

Introduction

Patients with schizophrenia tend to have abnormal immune activation resulting in elevated pro-inflammatory cytokine levels, ultimately leading to functional brain impairments and psychotic symptoms (Mitra et al 2017). Cognitive deficits are also considered a core feature of schizophrenia. Increasing evidence suggests that cognitive impairment is associated with inflammatory processes in patients with schizophrenia (Cabrera et al 2016, Misiak et al 2017).

Recent clinical trials suggest that anti-inflammatory agents may have therapeutic effect in schizophrenia treatment. Cyclooxygenase-2 (COX-2) inhibitors such as celecoxib reduce the production of pro-inflammatory cytokines. It was reported that celecoxib had significant benefit in improving schizophrenia symptoms as measured by the PANSS total score (Muller et al 2002). Another study in patients with chronic schizophrenia reported that celecoxib significantly reduced the PANSS total score and the positive symptoms subscale score (Akhondzadeh et al 2007). In a 6-week trial of celecoxib augmentation to amisulpride treatment in patients with early stage schizophrenia, the authors reported a significant reduction in the PANSS total score and the negative symptoms subscale score (Muller et al 2010). None of these three studies examined the effect of celecoxib on cognitive function. Another commonly used anti-inflammatory agent, aspirin, was also studied in the schizophrenia population. It was reported that aspirin (1000mg/day) as an adjunctive treatment for 3 months significantly reduced schizophrenia symptoms as measured by the PANSS total score and the positive symptoms subscale score; however, there was no significant improvement in cognitive function (Laan et al 2010).

The cardiovascular safety of celecoxib and other COX-2 inhibitors remains uncertain (Nissen et al 2016, Solomon et al 2005); cardiovascular disease is a serious comorbid medical condition in patients with schizophrenia. The cardio-protective non-selective COX inhibitor aspirin is arguably preferable. However, it is well established that aspirin, especially used in a relatively high dose, is associated with a significant risk of GI bleeding (Lanas & Ferrandez 2002). Despite the promise of potential benefit of celecoxib and aspirin in schizophrenia treatment, the adverse safety concerns related to these two drugs limit their potential clinical utility in this patient population.

Anti-inflammatory salicylates exist as two different forms: nonacetylated (e.g., sodium salicylate, salsalate, and trilisate) and acetylated (e.g., aspirin). Lacking an acetyl group, nonacetylated salicylates like salsalate do not modify COX enzymes or inhibit platelets, which is likely the difference that minimizes the risk of cardiovascular disease related to celecoxib or the risk of bleeding related to aspirin (Manrique et al 2008). Salsalate has been marketed since 1972 as an oral analgesic, antipyretic and anti-rheumatic drug. Salsalate has proven to be safe and well tolerated in the general population (Hauser et al 2016).

We conducted a 12-week, open label pilot trial of salsalate (1.5g, twice per day) as an adjunctive therapy in patients with schizophrenia to examine salsalate's effects on psychopathology, cognition and daily function.

Methods

Subjects

The study was approved by the local institutional review board. Adult outpatients with schizophrenia or schizoaffective disorder were recruited from community based mental health clinics. Psychiatric diagnosis was determined using the Structure Clinical Interview for DSM-IV (SCID) (Spitzer et al 1992). Other inclusion criteria included: 1) age 18–65 years; 2) stable dose of the current antipsychotic drug for at least one month; 3) able to complete the cognitive assessment battery (must be English speaking); 4) for female patients, non-childbearing potential or child-bearing potential but willing to practice appropriate birth control methods during the study. Exclusion criteria included: 1) inability to provide informed consent; 2) current substance abuse; 3) psychiatrically unstable per treating clinician's judgment; 4) significant medical illnesses including uncontrolled hypertension, diabetes, seizure disorder, severe cardiovascular, cerebrovascular, pulmonary, or thyroid diseases; 5) currently on immunosuppressant medication including oral steroids; 6) use of anti-coagulants; 7) history of chronic infection (including, HIV and hepatitis), malignancy, organ transplantation, blood dyscrasia, central nervous system demyelinating disorder, and any other known autoimmune or inflammatory condition; 8) pregnancy or breastfeeding; 9) pre-existing chronic tinnitus; 10) known hypersensitivity or allergic reaction to salsalate.

Procedure

Potential subjects underwent a diagnostic evaluation at the clinic. Psychiatric diagnosis was determined using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) (Spitzer et al 1992). Fasting blood samples for inflammatory biomarkers including white blood cell counts (WBC), interleukin 6 (IL-6) and high sensitivity C-reactive protein (hs-CRP) were obtained.

On a separate day, eligible subjects came to the clinic for baseline visit. Subjects completed the clinical assessment battery including the Positive and Negative Syndrome Scale (PANSS) (Kay et al 1987), the Calgary Depression Rating Scale (CDSS) (Addington et al 1993), the Quality of Life Scale (QOL) (Heinrichs et al 1984), the Brief University of California San Diego Performance-based Skills Assessment (UPSA-B, including communication and finance subtests) (Mausbach et al 2007), and the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) cognitive battery (Nuechterlein et al 2008). Side effects/safety assessment included vital signs and the Side Effect Questionnaire (SEQ). At the end of this visit, the study medication salsalate was dispensed to the subject (500mg pills, 3 pills each time, twice per day, which is the FDA recommended dose for osteoarthritis or rheumatoid arthritis treatment). A dose-reduction plan was specified a priori with stepped reductions of 500mg for side effects related to salicylate use, such as tinnitus or headache.

Subjects had follow-up visits at weeks 2, 4, 6, 8, and 10. Each visit consisted of side effects/safety assessment. At the end of each visit, the study medication was dispensed to the subject. At week 12, subjects had the last study visit. The visit consisted of side effects/safety assessment, and the rating scale assessment. Fasting blood samples for inflammatory biomarkers were obtained.

Laboratory assays

Blood samples were obtained after a 10-hour fast. WBC with differential was analyzed using a COULTER LH 750 Hematology Analyzer (Beckman Coulter, Inc., Brea, CA). hsCRP and IL-6 levels were measured using enzyme-linked immunosorbent assays (ELISA).

Statistical analysis

Statistical analysis was performed using SPSS (version 24, Armonk, NY). Descriptive statistics were performed to summarize demographic and clinical characteristics of the study sample. Repeated-measures comparisons (baseline versus week 12) for outcome measures were performed using paired-samples t test. For all analyses, a p value less than 0.05 (2-tailed) was used for statistical significance.

Results

Seventeen subjects were screened. Among them, 13 were enrolled and 8 completed the study. The results were based on completers only. For the 8 completers, 6 were male and 2 female; 6 were Caucasians and 2 African Americans; 6 were on an atypical antipsychotic agent, 1 on a typical antipsychotic agent, and 1 on both typical and atypical agents; 4 were on an anti-depressive agent and 1 on a mood stabilizer. The study sample's age, age of illness onset, disease duration, and years of formal education were 42.8 ± 9.8 years, 23.3 ± 7.7 years, 19.6 ± 9.9 years, 12.3 ± 2.1 years (mean $\pm$ SD) respectively.

Paired-samples t test analysis shows that none of the rating scale measures had significant change at week 12 compared to the baseline value. However, there was a trend decrease in the PANSS total score (58.3 ± 11.4 versus 53.5 ± 11.9 , $p = 0.072$, effect size Cohen's $D = 0.75$). There was also a trend improvement in the UPSA-B total score (69.7 ± 18.2 versus 79.1 ± 15.9 , $p = 0.084$, Cohen's $D = 0.71$), mostly reflecting the improvement in the UPSA-B finance subtest score (36.4 ± 8.4 versus 40.9 ± 8.4 , $p = 0.067$, Cohen's $D = 0.77$). Further, there was a trend improvement in quality of life as measured by the QLS total score (74.0 ± 20.8 versus 76.9 ± 22.7 , $p = 0.080$, Cohen's $D = 0.72$). In addition, there was a significant decrease in WBC levels from baseline to week 12 (6.8 ± 1.3 versus 6.0 ± 1.2 th/mm^3 , $p = 0.022$). There was no significant difference in levels of hsCRP or IL-6 over 12 weeks (p 's > 0.1) (Table 1).

Side effect assessment

There were no serious adverse events during the study. Reported side effects were mild and included abdominal discomfort, nausea/vomiting, lightheadedness and bloody urine, each by 1 subject. Two subjects reported mild headache.

Discussion

We believe that the present pilot study was the first one to examine potential benefits of adjunctive salsalate treatment for clinical symptoms, cognition and function in patients with schizophrenia. Even though none of the major outcome measures showed a significant change over the 12-week treatment period, there was a trend decrease in the PANSS total score, a trend improvement in the UPSA-B total score and the finance subtest score and the QLS total score. Salsalate was well tolerated; tinnitus, an established adverse effect of salicylates use, was not reported in our study.

Our study also found a significant decrease in WBC count but no significant changes in hsCRP or IL-6 after 12-week salsalate treatment. WBC count is a nonspecific inflammatory marker. In a previous study, we reported that elevated levels of WBC were associated with more severe schizophrenia symptoms, especially negative symptoms (Fan et al 2010). The anti-inflammatory effect of salsalate treatment may serve as a mediator for its potential therapeutic benefit for schizophrenia. Due to the small sample size, we were not able to conduct further analysis to examine the possible mediating role of WBC in improving clinical symptoms and function in our study.

Recent studies suggest that salsalate is a potent inhibitor of nuclear factor- κ B (NF- κ B) activity, which controls the expression of genes that regulate a broad range of biological processes in the brain, such as apoptosis, synaptic plasticity, neurogenesis, and differentiation (Camandola & Mattson 2007, Yang et al 2007). Song et al. reported that NF- κ B activation and its mRNA expression in peripheral blood mononuclear cells (PBMC) were excessively increased in drug-naïve, first episode schizophrenia patients compared with healthy controls; the study suggested that NF- κ B activation may play a pivotal role in schizophrenia through interaction with cytokines (Song et al 2009). Even though it was not examined in our study, it is speculated that salsalate may improve schizophrenia symptoms by inhibiting NF- κ B activation in addition to its anti-inflammatory property.

Our study failed to show a significant therapeutic effect of salsalate on various outcome measures. The absence of a placebo control group further increases the uncertainty of our trend level findings. The small sample size and the relatively short treatment time period (12 weeks) could be among the possible reasons. In addition, the chronicity of illness in our study sample (disease duration 19.6 ± 9.9 years) might be another reason. A recent review of six studies that examined celecoxib adjunctive treatment in schizophrenia suggested that celecoxib treatment most likely shows beneficial effects in the early stage, rather than the chronic stage of illness (Marini et al 2016).

Inflammation also plays an important role in the development of obesity, diabetes, hyperlipidemia and metabolic syndrome, which are common comorbid medical problems in the schizophrenia patient population (Fan et al 2007, Song et al 2014). Therefore a possible added benefit of salsalate treatment is to address metabolic problems in patients with schizophrenia. Goldfine et al. reported that salsalate improves markers of glycemic control in patients with type 2 diabetes (Goldfine et al 2010). A 6-week, open label study in 10 patients with schizophrenia and also with body mass index (BMI) $> 27 \text{ kg/m}^2$ found that

adjunctive salsalate treatment (2grams, twice per day) led to a significant reduction in levels of triglycerides and hemoglobin A1c; in addition, there was a trend decrease in levels of various cytokines that are indicative of immune activation (interleukin-1 β , interleukin-2 and IL-6); the effects of salsalate on clinical symptoms and function were not reported in that study (Keller et al 2013).

Future studies with a larger sample size, longer treatment time duration, and double-blind, placebo-controlled design are needed to further examine potential benefits of salsalate treatment to improve psychiatric symptoms and metabolic problems in patients with schizophrenia, especially in the early phase of illness. In addition, future studies need to examine the potential mediating role of NF- κ B or other immune/inflammation related biomarkers to predict therapeutic response of salsalate treatment in schizophrenia.

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Table 1

Clinical outcome measures after 12-week salsalate treatment (N=8)

Variable	Baseline	Week 12	t	df	p
	Mean (SD)	Mean (SD)			
PANSS total	58.3 (11.4)	53.5 (11.9)	2.12	7	0.072
PANSS Positive	13.0 (5.4)	10.9 (4.4)	1.71	7	0.132
PANSS Negative	18.5 (6.5)	17.4 (6.1)	1.23	7	0.259
PANSS General Psychopathology	26.8 (5.6)	25.3 (6.3)	1.66	7	0.142
MATRICES composite score	27.9 (11.9)	31.6 (15.2)	-1.86	7	0.105
CDRS	1.4 (1.8)	1.3 (2.4)	0.31	7	0.763
UPSA-B Communication	33.3 (10.7)	33.8 (14.6)	-0.08	7	0.942
UPSA-B Finance	36.4 (8.4)	40.9 (8.4)	-2.16	7	0.067
UPSA-B total	69.7 (18.2)	79.1 (15.9)	-2.01	7	0.084
QLS total	74.0 (20.8)	76.9 (22.7)	-2.04	7	0.080
WBC (th/mm ³)	6.8 (1.3)	6.0 (1.2)	2.93	7	0.022
hsCRP (µg/ml)	3.0 (1.2)	2.0 (1.2)	1.68	7	0.144
IL-6 (pg/ml)	2.2 (0.87)	2.3 (1.0)	-0.21	7	0.845

Notes: 1) Paired-samples t test was performed to compare the change over time in outcome measures; 2) PANSS: the Positive and Negative Syndrome Scale; 3) MATRICS: the Measurement and Treatment Research to Improve Cognition in Schizophrenia; 4) CDRS: the Calgary Depression Rating Scale; 5) UPSA-B: the Brief University of California San Diego Performance-based Skills Assessment; 6) QLS, the Heinrichs-Carpenter Quality of Life Scale; 7) WBC, white blood cell count; 8) hsCRP, high-sensitivity C-reactive protein; 9) IL-6, interleukin-6.