Treatment effects of traditional Chinese medicines Suoquan Pill and Wuling Powder on clozapine-induced hypersalivation in patients with schizophrenia: study protocol of a randomized, placebo-controlled trial

Chia-Chun Hung1, Pin-Kuei Fu1, Hsuy-Yi Wang1, Chin-Hong Chan1, Tsuo-Hung Lan1,3,4
1. Psychiatry Department, Taichung Veterans General Hospital, Taichung, Taiwan, China
2. Nucleic Medicine Department, Taichung Veterans General Hospital, Taichung, Taiwan, China
3. Institute of Genome Science, National Yang-Ming University, Taipei, Taiwan, China
4. Division of Mental Health and Substance Abuse Research, National Health Research Institute, Miaoli County, Taiwan, China

Background: It is reported that 30% to 80% schizophrenia patients suffered from hypersalivation when taking clozapine. Some investigations of the use of formulas of traditional Chinese medicine (TCM) to treat clozapine-induced hypersalivation suggested their potential treatment effects. In these formulas, Suoquan Pill (SQP) and Wuling Powder (WLP) were suggested to have therapeutic effects in improving clozapine-induced hypersalivation.

Methods and design: A prospective, double-blind, randomized, placebo-controlled study will be conducted to test the therapeutic effects of SQP and WLP in relieving hypersalivation in patients taking clozapine. A total of 45 patients will be enrolled into this study with 15 in each treatment group. Patients will receive medication according to their assigned group. Either SQP 10 g per oral dose twice daily, WLP 10 g per oral dose twice daily or placebo powder 10 g per oral dose twice daily will be prescribed to the patients for 8 weeks. The Drooling Severity Scale, Nocturnal Hypersalivation Rating Scale and sialoscintigraphy will be used as the primary outcome measures; the Clinical Global Impressions Severity, the Positive and Negative Syndrome Scale, the Abnormal Involuntary Movement Scale, the Simpson-Angus Scale and the TCM constitutional scale will be used as the secondary outcome measures.

Discussion: It is hypothesized that SQP and WLP will have a beneficial effect in controlling clozapine-induced hypersalivation symptoms. It may also improve the life quality of psychotic patients by improving their mental status.

Trial registration: ClinicalTrials.gov (Identifier: NCT01045720).

Keywords: clozapine; schizophrenia; sialorrhea; therapeutic methods, traditional Chinese medicine; Suoquan Pill; Wuling Powder; study protocol

DOI: 10.3736/jcim20110506
http://www.jcimjournal.com


Correspondence: Tsuo-Hung Lan, MD, PhD. Associate Professor; Tel: +886-4-2359-2525 ext. 3460; E-mail: thlan@ym.edu.tw, tosafish@gmail.com
Clozapine, one of the atypical antipsychotics, has been used in treating schizophrenia for decades. Due to the tendency of clozapine to combine with many receptors of neurotransmitters, it has several side effects. Large studies revealed that sedation and hypersalivation are the most common side effects among patients who were undergoing clozapine treatment[11]. It was estimated that 30% to 80% of patients receiving clozapine have hypersalivation[2,4]. Clozapine-induced hypersalivation may also be dose-related[5, 6], not tolerated[7] and may persist for long periods of time, at times for several years[8]. Hypersalivation is stigmatic and can cause several complications, such as symptomatic aerophagia due to increased swallowing[9], parotitis[10] and painful swelling of the salivary glands[11], sleep disturbance[12] and an increased risk of choking and aspiration pneumonia[13, 14]. For long-term clozapine use in patients, especially in the elderly, the risk of hypersalivation and complications should not be neglected.

The mechanism of clozapine-induced hypersalivation is not clear. The hypothesis include: (1) affect of clozapine blocking α1 or α2 nor-epinephrine receptors, resulting in increased blood flow to salivary glands and increased saliva secretion[15, 16]; (2) clozapine blocked M1 muscarinic cholinergic receptors and relatively increased activity of M1 muscarinic cholinergic receptors which could stimulate saliva secretion[17, 18]; (3) clozapine reduced larynx swallowing function and esophagus motility, which could increase saliva pooling into the mouth and drooling[19, 20]. Previous studies have focused on several interventions for treating clozapine-induced hypersalivation, including central acting α2-adrenergic receptor agonists (such as clonidine[21, 22], lofexidine[23] and guanfacine[24]), anticholinergic or antimuscarnic drugs (such as pirenzepine[25, 26], atropine[27, 28], trihexiphenidyl[29, 30], biperiden[31], ipratropium bromide[32, 33], glycopyrrolate[34, 35] and scopolamine[36]), antipsychotics[37, 41, 42] and antidepressants[43, 44], or diphenhydramine[45]. Botulinum toxin injection[46, 47] and septoplasty[48] were also reported. Though many interventions were studied, however, the effects were not conclusive[49, 50, 51].

In traditional Chinese medicine (TCM), saliva is one type of the body fluid. Hypersalivation was reported to be more prevalent in children with frequent enuresis. There are several traditional Chinese medicinal herbs being used to treat the symptoms of hypersalivation. Some investigations of using formulas of TCM to treat clozapine-induced hypersalivation suggested the potential treatment effects[49, 52]. In these formulas, Suoquan Pill (SQP) and Wuling Powder (WLP) seemed to have treatment effects in improving hypersalivation in patients who kept using clozapine. SQP was first reported in the Southern Song Dynasty (between 1127—1279 CE). It comprises of three kinds of herbs including Wuyao (Radix Linderae Aggregatae), Shanyao (Rhizoma Dioscoreae Oppositea) and Yizhihun (Fructus Elettariae Majoris), and is used to warm kidney yang and expel cold while relieving frequent urination by stopping leakage. WLP was first reported in the Han Dynasty (206 BCE—220 CE). It comprises of five herbs including Zhuling (Polyborus), Fuling (Poria), Zexie (Rhizoma Alismatis), Rougui (Cortex Cinnamomi Cassiae) and Bailihu (Rhizoma Atractylodis Macrocephalae), and is used to balance body fluid distribution and is considered to have bidirectional effects. The two formulas are still widely used in current TCM clinical practice.

A prospective, double-blind, parallel, placebo-controlled study will be conducted to investigate the treatment effects of SQP and WLP in treating clozapine-induced hypersalivation in patients with schizophrenia. The primary goal of this study is to determine the efficacy of SQP and WLP in reducing clozapine-induced hypersalivation, as per the Drooling Severity Scale and the Nocturnal Hypersalivation Rating Scale, and may through image study of sialoocintigraphy. The hypothesis is that SQP and WLP use will result in a significant reduction in clozapine-induced hypersalivation.

1 Methods and design

1.1 Participants

1.1.1 Sample size Forty-five patients are planned to be enrolled in this study, with 15 patients in each group. We estimated 60% improvement of the primary end points (sialocintigraphy, the Drooling Severity Scale and the Nocturnal Hypersalivation Rating Scale) after taking the trial drugs for 8 weeks, while 0 to 5% improvement in the placebo group, with α = 0.05 and β = 0.2. The SQP and WLP groups would be compared with the placebo group independently, with hypothesis supporting superior efficacy to placebo effect.

1.1.2 Entry procedures The patients or the patients’ authorized legal representatives will sign an informed consent document approved by the Institutional Review Board of Taichung Veterans General Hospital (Protocol No/IRB TCVGH No: C082000) prior to the patient’s participation in the study.

1.1.3 Inclusion criteria Patients may be included in the study if they meet the following criteria: (1) age: more than 18 years; (2) gender: both; (3) diagnosis of schizophrenia or schizoaffective disorder as per the Diagnostic and Statistical Manual, 4th edition-text revised (DSM IV-TR)[53] criteria; (4) have the capacity to provide voluntary informed consent; (5) subjective or objective symptoms of hypersalivation.

1.1.4 Exclusion criteria Patients may be excluded from the study for any of the following reasons:
(1) the dosage of clozapine is not stable for at least 8 weeks; (2) patients have other diseases which may influence salivation (such as Parkinson disease); (3) patients are pregnant or plan to be pregnant in 6 months, or patients are breast-feeding; (4) patients receive below medications with dosage adjusted within the 2 weeks prior to the trial: central acting α2-adrenergic receptor agonist, such as clonidine, lofexidine, guanfacine, guanabenz, α-methyldopa, and moxonidine; anticholinergic/antimuscarinic drugs, such as pirenzepine, atropine, trihexiphenidyl, benztropine, ipratropium bromide, procyclidine; local use could be allowed however (such as eye drops or inhalant medication); other medication including β-adrenoreceptor blockers, diphenhydramine and botulinum toxin injection; (5) patients have impaired liver function, defined as alanine aminotransferase over three times of normal limit; (6) patients have impaired renal function, defined as serum creatinine over 25 mg/L; (7) patients have attended other medical trials for hypersalivation one month prior to the trial; (8) patients have a known allergy to SQP or WLP. 1.2 Randomization and allocation concealment This is a prospective, randomized, double-blind, placebo-controlled study. Patients who meet the inclusion criteria and are out of the exclusion criteria will be selected into the clinical trial program and be assigned to one of the three groups (SQP, WLP and placebo) by randomization. A random number table will be generated by using Microsoft Excel software. The enrollees would be assigned to one of the three groups according to the numbers. The numbers would be divided by three, and the enrollees would enter group 1, 2 or 3 with the remainder 0 or 1 or 2, respectively.

The enrollees and the rating physicians (including psychiatrist and TCM doctor) will be informed neither about the randomization nor the intervention drugs. The three intervention drugs are all 10 g powder manufactured by the same company (Sun Ten Pharmaceutical Company, Taiwan), with opaque medicine bags of the same appearance. The intervention drugs are stored in the pharmacy of Taichung Veteran General Hospital, General Clinical Research Center. The study nurse would bring the intervention drugs to patients while visiting. The enrollees should bring back the opaque medicine bags to the study nurse to ensure compliance. 1.3 Intervention Patients would receive medication according to their assigned group. Either SQP 10 g per oral dose twice daily, or WLP 10 g per oral dose twice daily, or placebo powder 10 g per oral dose twice daily would be prescribed to the patients for 8 weeks. SQP used in this study is composed of herb extract granules of Wuyao, Shanyao and Yizhiren with the composition ratio of 1:1:1. The approved number (by Department of Health, Executive Yuan, Taiwan) of the three herb extract granules were 046855, 046909 and 001711, respectively. WLP used in this study is a Chinese patent drug with the approved number 045196 by Department of Health, Executive Yuan, Taiwan. The placebo powder was 10 g of starch in each granule. 1.4 Statistical analysis Paired t test will be used for before-after test of each enrollee to evaluate the improvement of drooling severity with the drug intervention. To evaluate the efficacy of WLP and SQW, one-way analysis of variance (ANOVA) and post-hoc analysis between groups by LSD-t test would be performed. 1.5 Outcome measures 1.5.1 Primary outcome measure 1.5.1.1 Drooling Severity Scale The Drooling Severity Scale57, 58 is a rating scale used by subjective and care givers’ observation. The drooling severity is divided into 9 grades in this scale. 1.5.1.2 Nocturnal Hypersalivation Rating Scale The Nocturnal Hypersalivation Rating Scale59 is designed to evaluate the severity of hypersalivation at night. The severity is divided into 4 grades in this scale. 1.5.1.3 Sialoscintigraphy Sialoscintigraphy60, 61 evaluates the uptake and excretion of salivary glands and provides a quantitative description of the salivary function. Patients undergo a salivary gland scan after receiving Tc-99m pertechnetate injection. Tc-99m pertechnetate is an isotope which can be uptake by salivation glands and excreted to the month. The tool is useful in evaluating salivary gland function in patients with Sjögren’s syndrome or salivary tumor clinically. 1.5.2 Secondary outcome measure 1.5.2.1 Clinical Global Impressions Severity The Clinical Global Impressions Severity62 will be used by the clinician to record the severity of schizophrenic illness at the time of assessment. The score ranges from 1 (normal, not at all ill) to 7 (among the most severely ill patients). 1.5.2.2 Positive and Negative Syndrome Scale The Positive and Negative Syndrome Scale63 is a 30-item rating instrument evaluating the presence, absence and severity of positive, negative and general psychopathology of schizophrenia. The scale is developed from the Brief Psychiatric Rating Scale and the Psychopathology Rating Scale. All the 30 items are rated on a 7-point scale (1=absent; 7=extreme). 1.5.2.3 Abnormal Involuntary Movement Scale Abnormal Involuntary Movement Scale (AIMS)64 is a 12-item instrument assessing abnormal involuntary movements associated with antipsychotic drugs, such as tardive dystonia and chronic akathisia, as well as “spontaneous” motor disturbance related to the illness itself. Scoring of the AIMS consists of rating the severity of movement in three main anatomic areas (facial/oral, extremities, and
trunk), based on a 5-point scale (0 = none, 4 = severe).

1.5.2.4 Simpson-Angus Scale The Simpson-Angus Scale\cite{65} is a 10-item instrument used to evaluate the presence and severity of parkinsonian symptomatology. It is the most commonly used rating scale for parkinsonism in clinical trials over the past 25 years. The 10 items focus on rigidity rather than bradykinesia, and do not assess subjective rigidity or slowness. Items are rated for severity on a 0-4 scale, with definitions given for each anchor point.

1.5.2.5 TCM constitutional scale In TCM, there is the concept that everyone has a different "constitutional type" and thus has different tendencies towards certain symptoms or diseases. Thus the "Classification and Determination of Constitution in TCM"\cite{67} scale is used to evaluate the constitutional type of enrollees in this study and to evaluate the association between drug response and the constitutional types.

1.5.3 The safety monitor The enrollees have to receive blood sampling on the screening, and visits 3, 4, and 5, including cell blood counts, differential counts, liver function, and renal function. Also, the adverse effects will be evaluated and reported with detailed severity, frequency and relatedness. Table 1 displays the study visit schedule.

<table>
<thead>
<tr>
<th>Item</th>
<th>Visit 1 (7 d before the study starts)</th>
<th>Visit 2 (Day 1)</th>
<th>Visit 3 (Day 8)</th>
<th>Visit 4 (Day 29)</th>
<th>Visit 5 (Day 57)</th>
<th>Visit 6 (Day 58 and after)</th>
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<tr>
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<td>Questionnaire (6)</td>
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<td>Sialoscontigraphy</td>
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<td>Blood sampling</td>
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<td>Adverse effect record</td>
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<td>Concomitant drug</td>
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<td>Data key-in</td>
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</table>

This table illustrates the visiting schedule of this study. "X" stands for the test or exam or data would be done or collected on the visit, and "-" means that the item would be skipped on that visit.

2 Discussion

World Health Organization launched the first global strategy on traditional and alternative medicine in 2002 and encouraged the research of traditional medicine by scientific methods\cite{68}. There are still many limitations in clinical medicine, propagating the search for alternative treatments in TCM to address the problem of clozapine-induced hypersalivation.

Clozapine was introduced to clinical psychiatry in the 1960s and used in treating schizophrenia and affective psychosis. Clozapine has a complex pharmacology. It has antagonistic activity at the D_1, D_2, D_3 and D_4 dopamine receptors, α₁ and α₂ adrenergic receptors, 5-hydroxy tryptamine-2 receptor, H₁ histamine receptors and M₁, M₂, M₅ and M₆ muscarinic receptors, with agonist activity at the M₅ muscarinic receptor\cite{69}. Compared with other antipsychotics, clozapine has low affinity to D₁ dopamine receptors and has low risk of extra-pyramidal symptoms. It has been revealed that 40% to 60% receptors are blocked under clinical effective dosage of clozapine, much lower than haloperidol which could antagonize about 80% D₂ receptors\cite{70,71}. It is unclear whether and why clozapine is more effective than other antipsychotic agents. There is abundant evidence in well-designed clinical studies that clozapine is more effective in treating schizophrenia and relapse prevention than other typical and second generation antipsychotics\cite{72,73}. It is also wellknown that clozapine is obviously more effective in treating schizoaffective disorder and refractory bipolar mania\cite{74,75}. Clozapine is proved to reduce suicidal risk\cite{76}; for there are nearly no side effects of extra-pyramidal symptoms, it could be used tolerably in Parkinson disease patients with psychosis\cite{77,78}. Also psychotic patients who are sensitive to antipsychotic-induced extra-pyramidal symptoms can be treated by clozapine\cite{79}.

With the clinically irreplaceable role of clozapine, much effort has been made in addressing the management of the clozapine-induced hypersalivation, including using TCM. As early as 1993, Kang et al\cite{80} reported that SQP was effective in treating clozapine-induced hypersalivation. However, the study lacked a placebo-control group for comparison and the rating scale would have bias through clinical observation. Thus a randomized, double-blind, parallel, placebo-controlled study is designed to investigate the effects of SQP and WLP on clozapine-induced hypersalivation.

Besides subjective and objective questionnaires, for evaluating the severity of hypersalivation, the nuclear medicine method sialoscontigraphy is applied. While being applied in this study, the response of the patients to the TCM treatment could be evaluated and also some useful information for further research of the mechanism of clozapine-
induced hypersalivation could be obtained.

The constitutional types of the enrollees in this study are also evaluated. In TCM, it is important to identify a patient’s constitutional type, for different constitutional types would have different vulnerability to a disease. Patients with the same symptoms but different constitutional types may need different treatments. The drug’s effects may also be influenced by a patient’s constitutional type. In Kang’s study\(^\text{[56]}\), it revealed that two constitutional subtypes (Stagnation of Phlegm-Dampness and Yin Deficiency) showed the best results with SOP. Thus in this study, a TCM assessment to differentiate the patients’ constitutional types to analyze the association between the drug response and the constitutional types is applied.

Integrative medicine is in popularity. For there is still a lack of adequate management of clozapine-induced hypersalivation in patients with schizophrenia, alternative management solutions are sought here. To apply TCM in the treatment of clozapine-induced hypersalivation, it is hoped that the patients’ quality of life could be improved, the side effects of medication could be reduced, and the complications could be managed.

3 Acknowledgements

The authors appreciate Dr. Jen-shu Wang, the chief of the Department of Traditional Chinese Medicine of Taichung Veterans General Hospital for supervising the traditional Chinese medication. The authors are also grateful to the Department of Health, Executive Yuan, Taiwan for funding this study.

4 Funding source

The study is partly funded by the Department of Health, Executive Yuan, Taiwan (No. DOH88-PAB-1001-P).

5 Competing interests

The authors declare that they have no competing interests.

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“缩丸丸和五苓散治疗氯氮平引起的精神分裂症患者唾液分泌过多的临床疗效评估”研究方案

洪嘉昀1, 傅荣芬1, 王心怡2, 陈朝航1, 蓝祥鸿1, 3, 4
1. 台中荣民总医院精神部，台湾 台中
2. 台中荣民总医院核子医学部，台湾 台中
3. 国立阳明大学遗传学研究所，台湾 台北
4. 国家卫生研究院群体健康科学研究所精神与成瘾医学研究组，台湾 苗栗县

背景：氯氮平引起的唾液分泌过多在精神分裂症患者中的发病率很高，不但影响患者外观及人际关系，也会严重影响患者的生命质量，是患者不愿意继续服药的原因。本研究旨在评估传统中药方剂缩丸丸和五苓散对氯氮平引起的唾液分泌增多的治疗作用。

方法与设计：本研究采用前瞻性、双盲、随机、安慰剂对照试验设计，共分为台湾中部一所医学中心精神部门入45名受试者，随机分配至缩丸丸组、五苓散组及安慰剂组。患者根据其所在组接受不同的治疗。缩丸丸或五苓散或安慰剂口服10 g，共8周。使用涎液严重度量表评分、夜间涎液量表评分及唾液腺造影的结果作为主要结局指标；临床总体印象量表评分、阳性与阴性症状量表评分、异常不自主运动量表评分、锥体外系副作用量表及中医体质表评分作为次要结局指标。

讨论：通过对本试验研究，希望能够证实缩丸丸和五苓散对于氯氮平引起的神精神分裂症患者唾液分泌增多有一定的疗效，并能够改善患者的精神状态而提高其生命质量。

临床试验注册：ClinicalTrials.gov (Identifier: NCT01045720)。

关键词：氯氮平；精神分裂症；涎液；中医治法；缩丸丸；五苓散；研究方案