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Pharmacological actions of tetrandrine in inflammatory pulmonary diseases

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ABSTRACT

Tetrandrine is a principle from a traditional Chinese medicine of the root of *Stephania tetrandra* S Moore approved by State Drugs Adminstration of China as a new drug for the treatment of silicosis. Except for its antiinflammatory, antifibrogenetic, immunomodulating effects and antioxidant effects, tetrandrine presents anti-allergic effects, inhibitory effects on pulmonary vessels and airway smooth muscle contraction, and platelet aggregation *via* its nonspecific calcium channel antagonism that suggested its potential in the treatment of asthma, pulmonary hypertension and chronic obstructive pulmonary disease (COPD). In general, the clinical results to date with tetrandrine in asthma and pulmonary hypertension have been exciting. The last 10 years have witnessed great leaps forward in our understanding of the molecular biology and biochemistry of chronic inflammatory diseases as well as the treatment drugs, which may create opportunities for future therapeutic innovation, development of tetrandrine derivatives or new extracts from other Chinese medicine. The current article briefly reviews the basic and clinical pharmacology of tetrandrine as well as the *in vitro* and *in vivo* data supporting the view that tetrandrine is as a novel drug for the treatment of silicosis, asthma and pulmonary hypertension.

INTRODUCTION

Tetrandrine (Tet) was isolated from the root of *Stephania tetrandra* S Moore, belongs to bisbenzylisoquinoline alkaloids, which was recognized to possess anti-inflammatory, antiallergic, antioxidant, antifibrogenetic activities, as well as immunomodulation and inhibition of platelet aggregation. Throughout the past several decades, a number of studies have demonstrated that Tet could improve the pulmonary function and structure *via* different mechanisms, including the modification of calcium metabolism in many cell types. Among the bisbenzylisoquinoline alkaloids, Tet was particularly noted for its effect on experimental silicosis and allergic models. In China, Tet has been used to treat patients with silicosis as a new anti-silicosis drug. In addition, the clinical results to date with tetrandrine in asthma and pulmonary hypertension have created exciting thoughts and opened new opportunities for its therapeutic use. This review focuses on the pharmacology of its therapeutic potential in the treatment of pulmonary diseases.

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PHARMACOLOGICAL BASIS

Antiallergic effects Antiallergic effects of Tet were first found and reported in our laboratory[1]. Our

results suggested that antiallergic mechanism of Tet might be related to inhibition of calcium influx in inflammatory cells and airway smooth muscle actions[2-4].

Tet has a broad-spectrum of inhibitory activity on type I-IV allergic reaction and allergic mediators[5]. Tet by iv or ig inhibited type I allergy, such as passive cutaneous anaphylaxis in rats, allergic contraction of isolated ileum, trachea and lung strips in sensitized guinea pigs, and by aerosol protected against antigen-induced increase of lung resistance (R_L) and decrease of dynamic lung compliance (C_{dyn}) in sensitized rats. In the study using the murine model of allergic conjunctivitis induced by ragweed pollen, Tet significantly reduced conjunctival eosinophil infiltration and the number of intact and degranulating mast cells, similar to topical antiallergic drugs, such as cromolyn and nedocromil[6]. Tet by ig inhibited type II, III and IV allergy, such as Forssman cutaneous vasculitis in guinea pigs, Arthus reaction in rats and rabbits[7], sheep erythrocytes-induced delayed-type hypersensitivity (DTH) responses and 2,4-dinitrofluorobenzene-induced contact dermatitis in mice.

Tet greatly inhibited the release of allergic mediators induced by antigen or anaphylaxis of slow reaction substance (SRS-A) in lung of sensitized guinea pig[5]. Tet inhibited the degranulation and histamine release of rat peritoneal mast cells and lung tissues induced by antigen, dextran or compound 48/80. The action mechanism may be related to supress the $[^{45}Ca]^{2+}$ uptake of sensitized mast cells challenged by antigen[2]. Tet also inhibited the histamine release from peritoneal mast cells induced by dextran, ovalbumin-IgE and concanavalin A[1,8]. However, Tet failed to inhibit histamine release from mast cells by non-specific stimulants such as aspirin, calcimycin or adenosine triphosphate (ADP). The inhibition was reversible by washing the mast cells, showing that Tet does not bind tightly to the cell membrane or cytoplasmic components[8].

Tet antagonized the action of allergic mediators. For example, Tet noncompetitively antagonized contraction of isolated guinea-pig ileum induced by histamine or acetylcholine, human trachea and lung strips induced by anaphylaxis of slow reaction substance (SRS-A)[9], and isolated guinea-pig trachea and lung strips induced by carbachol, histamine, and leukotriene (LT) A_4[10,11]. Tet by iv obviously suppressed SRS-A induced lung overflow indicating that Tet could reduce the increased airway resistance in guinea pig[5]. Tet failed to influence the basic Ca^{2+} influx of airway smooth muscle in guniea pig and dog, but could completely block the $[^{45}Ca]^{2+}$ influx excited by histamine and high potassium *via* potential-operated channel (POC) and receptor-operated channel (ROC). Furthermore, Tet 60 mg/L first blocked the POC, equivalent to verapamil 50 mg/L[3]. The relaxation was not directly origined from airway smooth muscle *per se*, and not related with β-receptor[11]. Tet 10 μmol/L could reverse and inhibit SRS-A bioactivity in bronchial alveolar lavage fluid (BALF)[12]. Tet significantly inhibited guinea pig airway microvascular leakage induced by platelet-activating factor (PAF), bradykinin, LTD_4 or histamine, and cutaneous vascular leakage enhanced by histamine and serotonin in rats[5,13]. Tet by aerosol inhibited histamine and acetylcholine or SRS-A-induced asthma in guinea pigs[1,9], and histamine-induced airway hyperresponsiveness in conscious and unbridled guniea pig[14].

Inhibition of platelet aggregation Tet had a nonselective inhibitory effect on platelet aggregation not solely due to its Ca^{2+} antagonism and may act on other pathways[15], such as the reduction of endogenous PAF generation[16], anti-calmodulin properties[17], or suppression of thromboxane (TX) B_2 formation[18].

Our studies indicated that Tet inhibited rabbit and pig platelet aggregation by PAF, arachidonic acid (AA) and ADP *in vitro* and *in vivo,* the effect of Tet is approximately 2-10 times as potent as that of verapamil [19]. Afterward, Du ZY *et al* also reported that Tet inhibited the production of LTB_4 and TXB_2 in rabbit whole blood stimulated with calcimycin *in vivo* and *in vitro*. In the presence of exogenous AA, the inhibitory effects of Tet were markedly lessened[20]. Tet blocked the release of AA from platelet phospholipids and TXA_2 generation in rabbit platelet-rich plasma (PRP) stimulated by collagen[17]. In Ca^{2+}-free medium, Tet still inhibited platelets aggregation induced by ristocetin 2.5 g/L. Lower concentrations of Tet (30 nmol/L to 3 μmol/L) failed to inhibit the aggregation (requiring Tet 10-300 μmol/L), but strongly suppressed ATP-release induced by ADP 10 μmol/L[15]. Tet also markedly inhibited platelet adhesion and thrombosis, but failed to change thrombin coagulation time and plasma coagulation time[21].

Tet also inhibited PAF, thrombin, collagen, ADP, epinephrine, AA and calcimycin-induced human platelet aggregation by interfering with the intracellular messengers system and suppression of TXA_2 formation, but not by inhibiting the binding of PAF to PAF-receptor on the platelet membrane directly[22].

Anti-inflammatory effects The mechanism of Tet might be related to antagonism on calcium–calmodulin system, interleukin (IL)-1, lipoxygenase, or inhibition on PGEs synthesis, or the activation and release of PLA_2 of inflammatory cells, but far from fully understood. Our laboratory early work showed that the anti-inflammation mechanism of Tet might be related to the suppression of AA metabolism. Tet 375 μmol/L had a weak inhibitory effect on cyclooxygenase of sheep seminal vesicle than that of indomethacin, but Tet 125 μmol/L had a potent inhibitory effect on 5-lipoxygenase of pig polymorphonuclear leukocytes (PMNs). These evidence indicated that Tet had more powerful suppressive effects on lipoxygenase than cyclooxyenase[5] .

Tet showed anti-inflammatory effects in various animal models, such as croton oil-induced ear edema in mice[23], formaldehyde-induced paw swelling in rats, experimental burns in rabbits, adjuvant arthritis in rats[24], and carrageenan-induced pleurisy in rat[25]. Tet also reduced the number of white blood cells in bronchoalveolar lavage fluid (BALF)[26]. Tet suppressed the vascular permeability, neutrophils emigration, β-glucuronidase release, and leukocyte infiltration into air pouches induced by IL-1 and tumor necrosis factor (TNF), and monocyte infiltration induced by PAF, and polymorphonuclear leukocytes (PMN) infiltration in the carrageenin induced subcutaneous air pouch inflammation in rats[27,28]. Although Tet failed to affect $[Ca^{2+}]_i$ of neutrophils in normal rat in resting state, but inhibited the rises of $[Ca^{2+}]_i$ of neutrophils induced by calcimycin, PAF, and LTB_4 via decreasing Ca^{2+} influx[3]. Meantime, Tet caused significant inhibition of random movement, chemotaxis, IL-1 production, and IL-1, TNF-α, IL-6, and IL-8 secretion from monocytes[29,30]. Tet also significantly inhibited murine IL-5 and human IL-6 activity[23].

For alveolar macrophages (AM), Tet could prevent the activation of AM induced by inhalation or intratracheal instillation of silica, suppressed monokine release from both silica and LPS-stimulated AM[31], inhibited the release of LTB_4 and O_2^- from AM, and decreased the $[Ca^{2+}]_i$ of AM[25], as well as inhibited the activation of NF-κB and NF-κB-dependent reporter gene expression induced by lipopolysaccharide (LPS), phorbol 12-myristate 13-acetate (PMA), and silica in a dose-dependent manner. At the doses used, Tet failed to interfere with Sp-1 DNA binding activity or Sp-1-dependent reporter gene expression in these cells. Western blot analysis suggests that the inhibitory effect of Tet on NF-κB activation can be attributed to its ability to suppress signal-induced degradation of I κB-α, a cytoplasmic inhibitor of the NF-κB transcription factor[32].

Tet showed inhibition on human neutrophil and monocyte adherence, Mac-1-dependent neutrophil adhesion to fibrinogen induced by *N*-formyl-methionyl-leucyl-phenylalanine (fMLP) or PMA, and PMA enhanced adherence without toxicity. Monocytes were shown to be more sensitive to Tet than neutrophils. Suppression of adherence was reversible by washing, suggesting that the drug failed to bind tightly to membrane components[33,34]. But contrary evidence suggested that Tet failed to inhibit both the secretion and the expression of the cellular adhesion molecules (soluble E-selectin, ICAM-1, and VCAM-1) of leucocytes[35].

Immunomodulating effects Tet has multiple immunosuppressive properties, particularly in celluar immunity. In humoral immunity, Tet significantly inhibited IgG secretion and synthesis by B cells[30,36].

Tet markedly reduced mitogen-induced lymphoproliferative responses, suppressed the natural killer cell-mediated lysis of K562 cells. It failed to interfere with receptor-ligand binding, but did affect the inositol triphosphate second messenger system[36]. Tet potently inhibited PMA+CD28-costimulated and CD3+CD28-costimulated activation, CD28-costimulated and PMA+calcimycin-induced T-cell proliferation, IL-2 secretion of human peripheral blood T cells, and the expression of the human peripheral blood T cells activation antigen, CD71. In addition, Tet down-regulated both Th_1 and Th_2 cytokines in $CD4^+$ and $CD8^+$ T-cell subpopulations[37]. Tet inhibited the expression of the protein kinase C-dependent IL-2 receptor α-chain and CD69 but not the expression of the Ca^{2+}-dependent CD40 ligand and CD69. This effect was relatively specific because it only targeted the protein kinase C-dependent but not Ca^{2+}-dependent signaling pathway[38].

Data from studies of mononuclear cell separated from peripheral blood of young atopic and old non-atopic asthmatic patients showed that Tet inhibited mononuclear cell proliferation, the production of IL-2, IL-4 and IFN-γ, and the expression of HLA-DR, CD23 and CD25 on CD3 positive T cells. Similar levels of inhibition in both groups of stable asthmatic patients were reported[39].

Antioxidant effects Tet effectively blocks the ability of quartz to stimulate oxidant release from pul-

monary macrophages. Tet also markedly inhibited the lipid peroxidation induced by freshly fractured quartz[40], particle-stimulated oxygen consumption, and zymosan-stimulated oxygen consumption, superoxide anion release, and hydrogen peroxide secretion from alveolar macrophages[41,42]. Tet increased the activity of superoxide dismutase (SOD) in the lung, serum and BALF on pulmonary fibrosis mice model induced by pingyangmycinum (bleomycin), similar to cortisol[43]. In the carrageenin induced inflammation, the intracellular SOD activity on neutrophils was increased by Tet[26].

Antifibrogenetic effects Fibroblasts and alveolar macrophages play a pivotal role in pulmonary fibrotic development. The effect of Tet on alveolar macrophages has been described in antioxidant effects.

In vitro, Tet concentration-dependently decreased the synthesis of collagen on cultured human lung fibroblasts as well as the production of hyaluronic acid without obvious toxicity[44]. Tet, at its dose lower than that required to inhibit cell DNA synthesis, could antagonize the stimulating action of platelet-derived growth factor (PDGF) on cell proliferation and collagen synthesis[45]. Tet also blocks proliferation and the incorporation of [^{3}H]-thymidine into DNA by fibroblasts stimulated with a variety of growth factors such as human serum, PDGF plus plasma, fibroblast growth factor (FGF) plus plasma, or TNF plus plasma[46]. Moreover Tet could chelate copper ion, thus hamper the formation of insoluble collagen fibers[47].

In vivo, TET could inhibit the development of experimental silicosis and the synthesis of collagen in rat lung, reduced the quantity of glycosaminoglycan and lipid[47], decreased the collagen α1 (I) and α1 (III) mRNA levels, the amounts of mRNA silver grains[48], and reduced synthesis of collagen protein in silicotic tissues[49]. Tet could inhibit the increase of collagen contents in lung tissues and extra pulmonary arterial wall of rats with chronic hypoxic pulmonary hypertension[50]. Tet also reduced quantity of hydroxyproline in mice model induced by pingyangmycinum, similar to cortisol which is the tradtional antifibrosis agent[44]. Combined use of polyvinylpyridine-*N*-oxide (PVNO)-tetrandrine and quinolyl-piperazine hydroxyl phosphate (QOHP)-tetrandrine can accelerate the degradation of collagen in silicotic rats[51].

Effects on pulmonary vessels In rat with chronic hypoxic pulmonary hypretension, Tet could reduce mean pulmonary artery pressure (mPAP) and pulmonary vascular resistance (PVR), decrease the expression of β-FGF in wall of the intra-acinar pulmonary arteries (IAPA), and inhibit hypoxic structural remodeling of IAPA[52].

In monocrotaline-induced "inflammatory" chronic pulmonary hypertension model rats, Tet ameliorated the development of pulmonary vascular and lung tissue injury, inhibited monocrotaline-induced increase of PAP, the right heart index, without significant influence on the systemic artery pressure (SAP), inhibited the increase of medial thickness and cross sectional area[53], reduced the contractive pressure of pulmonary artery, right ventricle and right atrium of heart, and decreased the vacuolar degeneration of endoepithelial cells of IAPA, the endoepithelial subcavity, the collagens of medial membrane and number of smooth muscles of IAPA[54]. Cheng *et al*[55] compared a new Tet preparation, pulmonary targeting microspheres with Tet. Their results suggested that the new preparation showed more potent effect on the hypoxic pulmonary hypertension and had more selective action on the pulmonary circulation.

In addition, Tet 10-30 nmol/L inhibited the tube formation of vascular endothelial cells stimulated by IL-1α and platelet-derived growth factor (PDGF)-BB (a PDGF isoform) to a greater extent than fetal bovine serum-stimulated tube formation. The inhibitory effects of Tet on IL-1α and PDGF-BB were noncompetitive, and the inhibition by Tet was more than 100-fold greater than that by hydrocortisone[56]. Tet inhibited medial hypertrophy and reduced the percentage of muscularized intra-acinar vessels in nitrofen-induced congenital diaphragmatic hernia rats[57].

CLINICAL THERAPEUTIC USE

Based on the above effects, Tet had been used to treat the following pulmonary diseases which involve the inflammatory and immunologic processes in various cell types of the lung, and manifest analogous pathological changes.

Silicosis The effect of of Tet on silicosic rats was first reported in China in 1975. The therapeutic effect of Tet in silicosis patients was also first reported in 1977. In the past several decades, it was widely used to treat various of silicosis patients in China. Three large-scale clinical trial data in China suggested that Tet had specific action on silicosis, therapeutic scheme of 300 mg and 200 mg were appropriate. Combination with the antifibrotic drugs QOHP or PVNO showed obvious inhibition on the process of fibrosis formation

and improvement of clinical symptoms and lower side effect than Tet alone, and showed a certain long-term therapeutic effect. Repeated and maitained treatment with a lower dosage were suggested[58-60] (Tab 1).

Asthma For Tet has broad antiallergic and anti-inflammatory actions, Yu XX [61], our co-workers investigated the clinical effect of Tet aerosol to confirm this action. In the study, 146 patients with bronchial asthma or asthmatic bronchitis were selected and treated with metered dose-inhaler of Tet. The immediate relief of asthma was achieved with a total effective rate up to 84 %. The rate of excellent response of Tet was 48.63 % and was equivalent to the isoprenaline + glyceryl guaiacolate control group, and significantly superior to the blank control group. Forty patients in Tet group were measured the pulmonary function (vital capacity, forced expiratory volume in first second, mean maximum expiratory flow, forced expiratory volume 75 %~85 % before and after treatment, the mean value were slightly, but not significant increased (P>0.05) after treatment. This result indicated that the relief of asthma by Tet aerosol was indubitable and the absence of statistical significance was probably due to emphysema which may be present in many patients. The aerosol of Tet did not elicit any serious side effect, such as tachycardia and arrhythmia, supporting its safety and efficacy.

Pulmonary hypertension Tet had improved action on pulmonary hypertension in some animal models, but there were seldom clinical study on this profile. Two small-scale clinical studies in patients with pulmonary hypertension secondary to chronic obstructive pulmonary disease indicated that Tet significantly reduced the total pulmonary resistance, mPAP and pulmonary artery systolic pressure and significantly improved artery blood gas and right ventricle function, but the reductions of total systemic circulation resistance was slight, while the changes on blood gas, transport of oxygen, consumption of oxygen and heart rate were not significant[62,62]. So Tet might be a good drug for pulmonary hypertension in patients with chronic obstructive pulmonary diseases.

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Tab 1. Clinical effect of tetrandrine on silicosis (data compiled from references 58-60).

Group	Chest X-ray films			Symptom
	Improved rate	Stable rate	Aggravating rate	improved rate
1. Silicosis I-III phase from 1977 to 1982 (n=240)				
Tet (100 mg, qd, n=52)		46.2 %	53.8 %	17 %-50 %
Tet (100 mg, bid, n=117)	24.8 %	62.3 %	12.8 %	63.5 %-78.1 %
Tet (100 mg, tid, n=71)	32.6 %	61.3 %	4.2 %	31.3 %-85.7 %
2. Silicosis I-III phase from 1991 to 1995 (n=389)				
QOHP+Tet (100 mg, bid×6) (n=152)	11.8 %	81.6 %	6.6 %	73.3 %
PVNO+Tet (100 mg, bid×6) (n=53)	9.4 %	77.4 %	13.2 %	80.7 %
Control (n=73, n=27)	0	66.7 %, 75.3 %	24.6 %, 33.3 %	13.9 %, 59.2 %
3. Silicosis I-III phase from 1996 to 2000 (n=150)				
QOHP+Tet (100 mg, bid×6) (n=21)	23.8 %	33.3 %	42.9 %	4.2 %-38.1 %
QOHP+Tet (100 mg, tid×1) (n=21)	4.8 %	85.7 %	9.5 %	4.8 %-19.1 %
QOHP+Tet observed group (n=22)	4.6 %	59.1 %	36.4 %	9.1 %-27.3 %
PVNO+Tet (100 mg,bid×6) (n=6)	33.3 %	33.3 %	33.3 %	16.7 %-50.0 %
PVNO+Tet (100 mg,tid×1) (n-=6)	0	50.0 %	50.0 %	16.7 %-50.0 %
PVNO+Tet observed group (n=7)	0	71.4 %	28.6 %	14.3 %-28.6 %
Control (n=50)	0	68.0 %	32.0 %	6.0 %-22.0 %

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