Tetracyclines: Nonantibiotic properties and their clinical implications

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Tetracyclines are broad-spectrum antibiotics that act as such at the ribosomal level where they interfere with protein synthesis. They were first widely prescribed by dermatologists in the early 1950s when it was discovered that they were effective as a treatment for acne. More recently, biologic actions affecting inflammation, proteolysis, angiogenesis, apoptosis, metal chelation, ionophoresis, and bone metabolism have been researched. The therapeutic effects of tetracycline and its analogues in various diseases have also been investigated. These include rosacea, bullous dermatoses, neutrophilic diseases, pyoderma gangrenosum, sarcoidosis, aortic aneurysms, cancer metastasis, periodontitis, and autoimmune disorders such as rheumatoid arthritis and scleroderma. We review the nonantibiotic properties of tetracycline and its analogues and their potential for clinical application. (J Am Acad Dermatol 2006;54:258-65.)

Tetracyclines were discovered in 1948 as natural fermentation products of a soil bacterium, *Streptomyces aureofaciens*. The first chemically purified tetracycline was chlortetracycline (1954).[1] Currently, 3 groups of tetracyclines are available: tetracycline natural products, tetracycline semisynthetic compounds, and chemically modified tetracyclines (CMTs).[2,3] Perusal of the literature suggests that tetracyclines, besides acting as antibiotics, may also affect inflammation, immunomodulation, cell proliferation, and angiogenesis.[4,5]

Abbreviations used:

CMT: chemically modified tetracycline
IL: interleukin
MMP: matrix metalloproteinase

CHEMISTRY

Tetracyclines and analogues with biological effects on bacteria and mammalian targets show a basic chemical structure consisting of a tetracyclic naphthacene carboxamide ring system (Fig 1). Tetracyclines with antibiotic activity have a dimethylamine group at carbon 4 (C4) in ring A. Removal of the dimethylamino group from C4 reduces its antibiotic properties, but enhances nonantibiotic actions.[3] Utilization of this strategy was the basis for the development of several chemically modified tetracyclines.[2]

The ring structure of tetracyclines is surrounded by upper and lower peripheral zones. These contain various chemical functional groups and substituents.[6] Synthetic modification of the lower peripheral region reduces both antibiotic and nonantibiotic properties. On the other hand, biological targets may be enhanced by modifying the upper peripheral zone, particularly in positions C7 through C9 of the D ring. This has been accomplished with tetracycline semisynthetic compounds such as minocycline and doxycycline.[3]

TETRACYCLINES AS IONOPHORES

Ionophores are organic compounds capable of forming lipid-soluble complexes with metal cations.[7] Transportation of these cations across hydrophobic barriers, such as artificial or biological membranes, is an important function of these compounds. Tetracyclines bind divalent metal cations, mostly along the lower peripheral region, and circulate in blood plasma primarily as Ca^{++} and Mg^{++} chelates.[3] Their role as calcium ionophores has important biologic implications. After its intracellular incorporation, Ca^{++} can act as a secondary messenger and affect pathways such as secretory processes, receptor activation or inhibition, cell division, and metabolic reactions.[3]

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NONANTIBIOTIC PROPERTIES OF TETRACYCLINES

The nonantibiotic properties of tetracyclines are summarized in Fig 2 and discussed in detail below.

Inhibition of inflammation

Both laboratory and clinical studies have investigated the anti-inflammatory properties of tetracyclines. Table I summarizes inhibitory effects of tetracyclines on inflammation.

Proteolysis

Tetracyclines and their analogues inhibit matrix metalloproteinases (MMPs). MMPs are zinc-dependent endopeptidases that play an important role in the remodeling of the connective tissue and are involved in embryogenesis, wound healing, rheumatoid arthritis, and tumor invasion and metastasis.[18] There are MMPs that break down fibrillar collagens known as collagenases (MMP-1, MMP-8, MMP-13) and those that can affect basement membrane collagen (collagen IV) known as gelatinases (MMP-2, MMP-9). Tetracycline and its analogues can inhibit both collagenases and gelatinases.[5,19,20]

Angiogenesis

Angiogenesis, the formation of new blood vessels, occurs in many diseases. These include benign conditions (eg, rosacea) and malignant processes (eg, cancer). Matrix-degrading enzymes, present in the extracellular matrix of tissues, facilitate angiogenesis by allowing new blood vessels to penetrate into the matrix. MMPs represent one such class of enzymes involved in this process.

Minocycline and doxycycline inhibit angiogenesis induced by implanted tumors in rabbit cornea.[21] Doxycycline and, to a lesser degree, CMTs inhibit synthesis of MMPs (MMP-8, MMP-9) by endothelial cells. This inhibition, noted at the protein and mRNA levels, may affect migration of endothelial cells during angiogenesis.[22] The antiangiogenic effect of tetracyclines may have therapeutic implications in inflammatory processes accompanied by new blood vessel formation (eg, autoimmune disorders, rosacea, cancer invasion). Well-controlled studies must be performed, at both the laboratory and clinical levels, to investigate this potential.

Apoptosis

Apoptosis, programmed cell death, is of fundamental importance for the homeostasis and development of any organism. Disease states such as cancer and neurodegenerative disorders may result from its deregulation. Crucial components of the apoptotic pathway have been elucidated. A family of proteases termed caspases (*c*ysteinyl *a*spartate-

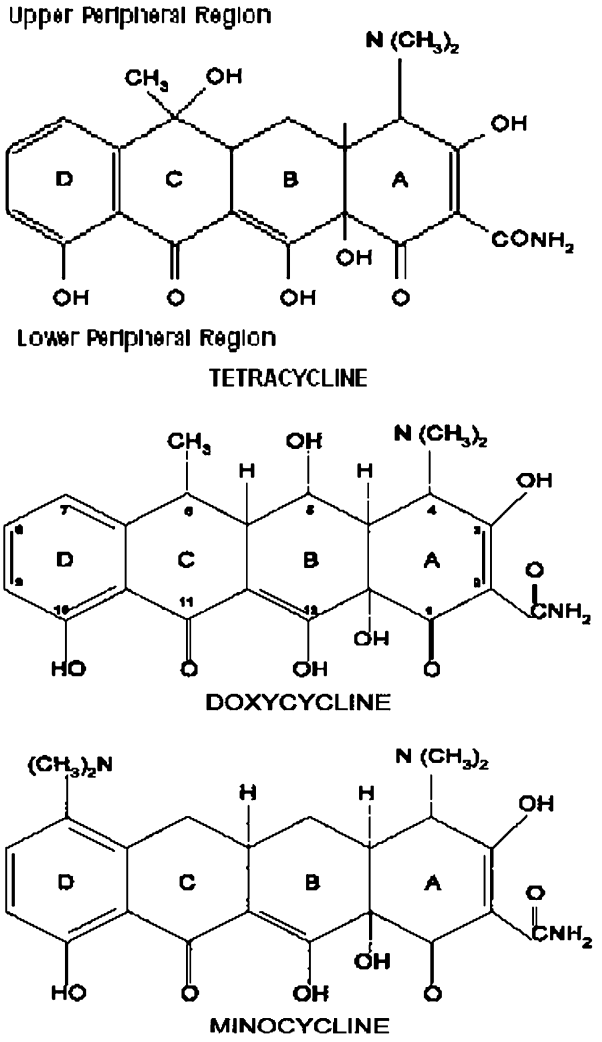

Fig 1. Chemical structures of tetracycline, doxycycline, and minocycline.

*s*pecific *p*rotein*ases*) play an important role in the regulation of mammalian apoptotic cell death.[23] Caspase-1, also known as the interleukin 1β (IL-1β)-converting enzyme for its ability to convert the precursor IL-1β into mature IL-1β, is important in mediating neuronal cell death after experimental traumatic brain injury in mice. Decreased mature IL-1β production may be correlated with a reduction in tissue injury and an improvement in neurological function.[23-25]

Recent experimental data indicate that tetracyclines have antiapoptotic properties.[26,27] Intraperitoneal administration of minocycline 12 hours before or 30 minutes after traumatic brain injury was shown to prevent neuronal cell death in mice by inhibiting caspase-1.[28] This effect had clinical implications since it reduced tissue injury and neurological deficits. Improved neurological function correlated with decreased lesion size and decreased capsase-1

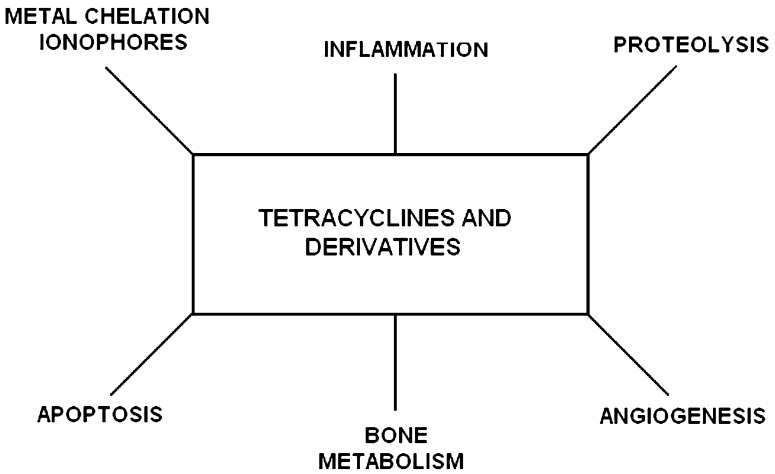

Fig 2. Nonantimicrobial properties of tetracycline and its derivatives.

Table I. Inhibitory effects of tetracyclines on inflammation

Drug	Inhibitory effects on inflammation
TCN, DCN	Inhibition of mitogen-induced human lymphocytic proliferation by blockage of blast transformation[8]
TCN	Suppression of neutrophilic migration and chemotaxis[9,10]
MCN	Inhibition of transmigration of T lymphocytes and production of MMP-9 in a murine model of autoimmune encephalitis[11]
TCN	Inhibition of inflammatory response following application of potassium iodide[12]
MCN	Inhibition of T-lymphocyte activation with resultant inhibition of T-cell proliferation[13]
MCN, DCN	Inhibition of phospholipase A2[14]
MCN	Up-regulation of anti-inflammatory cytokine IL-10 in synovial explants[15]
MCN, DCN, CMT	Inhibition of the expression of nitric oxide synthetase[16,17]
DCN, CMT-3	Accelerated degradation of nitric oxide synthetase[17]

CMT, Chemically modified tetracycline; *DCN,* doxycycline; *IL-10,* interleukin 10; *MCN,* minocycline; *MMP,* matrix metalloproteinase; *TCN,* tetracycline.

activity, as measured by mature IL-1β production. Minocycline may also have beneficial effects in chronic neurodegenerative diseases such as Huntington disease[29] and amyotrophic lateral sclerosis.[30]

Bone metabolism

Prophylactic administration of doxycycline reduces the severity of canine osteoarthritis in the dog anterior cruciate model.[31] Levels of active and total collagenase activity in extracts of cartilage from osteoarthritic knees of untreated dogs are significantly higher than the levels in doxycycline-treated dogs. This effect is accompanied by inhibition of proliferation and hypertrophy of chondrocytes and by a reduction in MMP activity.

Recent experimental evidence indicates that minocycline, by stimulating new bone formation, prevents the decrease in mineral density (osteoporosis) observed in ovariectomized old rats.[32] This model mimics the accelerated bone loss commonly experienced by postmenopausal women. The effect could be related to a reduction in osteoclast function by tetracycline and CMTs.[33,34] Additional well-controlled studies must be performed to more clearly elucidate the cellular and molecular mechanisms involved.

CLINICAL STUDIES

Diseases, both dermatologic and nondermatologic, that have been investigated for the therapeutic use of tetracyclines are listed in Table II.

Skin

The mechanisms of action of the tetracyclines and tetracycline derivatives in the treatment of various skin diseases discussed in this section are summarized in Table III.

Acne. Tetracycline, minocycline, and doxycycline are effective in the treatment of acne, particularly during the inflammatory stage. It has previously been suggested that the beneficial effect of tetracycline is due to the inhibition of *Propionibacterium acnes* accompanied by a reduction in sebum free fatty acids and extracellular lipases.[35] However, it is currently believed that the inflammatory reaction plays an important role in the pathophysiology of acne.[36] The exact cascade of events that is responsible for inflammation in acne is not known. However, there is evidence of chemotaxis of

Table II. Therapeutic use of tetracyclines in dermatologic and nondermatologic disease

Disease	Reference(s)
Dermatologic	
Acne	10,37,38
Rosacea	39-41
Bullous dermatoses	43-53
Sarcoidosis	54
Kaposi's sarcoma	58
Pyoderma gangrenosum	59
Hidradenitis suppurativa	60
Sweet's syndrome	62
α_1-Antitrypsin deficiency panniculitis	63
Pityriasis lichenoides chronica	64
Nondermatologic	
Rheumatoid arthritis	66-69
Scleroderma	70
Cancer	72-76
Cardiovascular diseases	
Abdominal aortic aneurysm	77,78
Acute myocardial infarction	79
Periodontitis	19,82-84

Table III. Mechanisms of action of tetracycline and tetracycline derivatives in the treatment of skin disease

Skin disease	Proposed mechanism of action
Acne	Down-regulation of *P acnes* lipase Inhibition of neutrophil chemotaxis Inhibition of proinflammatory cytokines and MMP-9
Rosacea	Inhibition of angiogenesis Inhibition of neutrophil chemotaxis Inhibition of proinflammatory cytokines and MMP-9
Bullous dermatoses	Inhibition of MMP-2 and MMP-9 Inhibition of neutrophil chemotaxis
Cutaneous sarcoidosis	Inhibition of granuloma formation by inhibition of protein kinase C
Kaposi's sarcoma	Inhibition of MMP-2 and angiogenesis
Neutrophilic dermatoses	Inhibition of neutrophil chemotaxis

MMP, Matrix metalloproteinase.

neutrophils,[37] which are known to store MMP-9. Thus the therapeutic effect of tetracyclines in acne may at least in part be due to reduction in neutrophilic chemotaxis[10] as well as their inhibitory effect on proinflammatory cytokines and MMP-9. This contention is supported by a recent study that showed that subantimicrobial-dose doxycycline (20 mg taken twice daily) reduced the number of both inflammatory and noninflammatory lesions in patients with moderate facial acne.[38] No detectable antimicrobial effect on the skin flora was demonstrated.

Rosacea. Tetracyclines and their analogues are effective in the treatment of rosacea and related disorders, such as perioral dermatitis, ocular rosacea, and steroid-related rosacea.[39,40] A single daily dose of doxycycline may be effective for ocular rosacea.[41] The anti-inflammatory effects of tetracyclines already mentioned may explain, at least in part, their beneficial effects in rosacea. Inhibition of angiogenesis may be a contributory factor in the therapeutic effect of tetracyclines in this group of disorders. Features that favor angiogenesis may contribute to the telangiectasia of rosacea. These include protease-triggered release of angiogenetic factors stored in the extracellular matrix, release of inhibition of endothelial factors, and release of angiogenic factors from activated macrophages.[42]

Bullous dermatoses. Subepidermal bullae are frequently accompanied by splitting or dissolution of the basement membrane accompanied by an inflammatory reaction involving lymphocytes and neutrophils. The mechanism of action may include inhibition of neutrophil and eosinophil chemotaxis or inhibition of protease release from granulocytes. Tetracycline or minocycline, alone or in combination with nicotinamide, were shown to be effective in bullous dermatoses affecting the dermoepidermal junction, such as bullous pemphigoid, cicatricial pemphigoid, linear IgA disease, and lichen planus pemphigoides.[43-53] These reports are generally uncontrolled, and it is possible that a selection bias toward patients with milder disease or spontaneous remission may be operative. Additional studies are also necessary to evaluate whether tetracycline in combination with nicotinamide is more effective than either of the two drugs administered as monotherapy. Nevertheless, this therapeutic option represents an attractive alternative to systemic corticosteroids in the initial treatment of bullous dermatoses affecting the dermoepidermal junction. While avoiding the potential complications of immunosuppressive agents, the combination of tetracycline and nicotinamide offers obvious advantages for older patients who may have concomitant osteoporosis, diabetes mellitus, or hypertension. Finally, if the administration of an immunosuppressive agent is deemed necessary, tetracycline may be administered concomitantly as combination therapy so that the dosage of the immunosuppressant may be tapered more rapidly.

Cutaneous sarcoidosis. More recently, the use of minocycline for the treatment of sarcoidosis was reported.[54] Minocycline, 200 mg daily for 12 months, was administered to 12 patients. The median follow-up period was 26 months. Eight patients

demonstrated complete clearing of their lesions, whereas 2 patients showed a partial response. The duration of response ranged from 10 to 41 months. No relapse occurred during the 12-month treatment period. However, maintenance of remission required concomitant administration of corticosteroids in several of the patients. In addition, a moderately severe hypersensitivity reaction to minocycline was experienced by one patient in the study.

It is interesting to note that tetracyclines, minocycline and doxycycline inhibit in vitro granuloma formation by monocytes exposed to dextrin beads.[55] This effect is thought to be due to inhibition of protein kinase C by tetracycline. These in vitro results provided the rationale for the successful use of minocycline in the treatment of other granulomatous dermatoses, such as silicone-induced subcutaneous granulomas[56]and granulomatous cheilitis.[57]

Kaposi's sarcoma. Kaposi's sarcoma is characterized by proliferation of endothelial cells and increase in MMP activity. A preliminary clinical trial involved 18 patients with AIDS-related Kaposi's sarcoma who were treated with a chemical modified tetracycline, COL-3.[58] After receiving 25, 50, or 70 mg/m^2 per day for 25 weeks, one patient showed complete resolution and 7 demonstrated partial improvement of skin lesions. The overall response rate was 44%, and median time to response was 4 weeks. There was also a reduction in MMP-2 serum levels. On the basis of these preliminary data, additional studies investigating the use of COL-3 as monotherapy in patients with early Kaposi's sarcoma and in combination with other therapies in patients with more severe disease seem warranted.

Miscellaneous dermatoses. There have been isolated reports describing the effectiveness of tetracyclines in pyoderma gangrenosum,[59] hidradenitis suppurativa,[60] neutrophilic disease,[61] Sweet's syndrome,[62] α_1-antitrypsin deficiency panniculitis,[63] and pityriasis lichenoides chronica.[64] Evaluation of larger numbers of patients in well-controlled studies is necessary before any conclusions can be drawn regarding the efficacy of tetracycline and its derivatives in the treatment of these conditions.

Autoimmunity

The immunomodulatory and anti-inflammatory properties of minocycline suggested that this drug might be effective in the treatment of autoimmune disorders.

Rheumatoid arthritis. Rheumatoid arthritis is a chronic inflammatory disease affecting about 2 million Americans. Although the cause of rheumatoid arthritis is not entirely known, it has been shown that joint destruction is at least in part due to enhanced collagenase activity in synovial fluid and synovial fibroblasts.[65] Oral administration of minocycline in adjuvant and collagen-induced arthritis in rats reduced the incidence of arthritis.[66] Furthermore, minocycline administration reduced collagenase activity in the synovial fluid derived from patients with rheumatoid arthritis.

There have been several double-blind, placebo-controlled clinical trials using 200 mg daily of minocycline in patients with rheumatoid arthritis. Kloppenburg et al [67] treated a cohort of 80 patients and noted significant improvement in joint tenderness, number of swollen joints, and levels of C-reactive protein. In another study involving 219 patients with mild to moderate arthritis treated for 48 weeks with minocycline, there was alleviation of joint swelling and tenderness, although the effect was moderate.[68] A more significant result was noted in a study involving 60 patients with early (<1 year duration) rheumatoid arthritis treated for 2 years with 200 mg daily of minocycline versus hydroxychloroquine, 400 mg daily.[69]

Scleroderma. In an uncontrolled study, minocycline 200 mg daily was administered for 12 months to 11 patients with early diffuse scleroderma. Four patients showed complete resolution.[70] Confirmation from a larger scale, controlled study would add validity to this spectacular response. It would be of interest to determine whether minocycline specifically alters the inflammatory response in scleroderma. If so, it would be worthwhile to conduct a similar study with localized scleroderma.

Cancer. Carcinogenesis is a 3-step process involving tumor cell adhesion, extracellular matrix proteolysis, and cell migration.[18] Degradation of basement membrane and its surrounding connective tissue stroma plays a major role in cancer invasion and metastasis. MMP-2 and MMP-9 (gelatinases A and B) are frequently expressed in various malignant tumors.[71] Experimental data using various carcinoma cell lines and animal carcinogenesis models showed that doxycycline, minocycline, and CMTs may inhibit tumor growth by inhibiting MMPs and by a direct effect on cell proliferation.[72-75] Few clinical trials investigating the use of tetracyclines in cancer treatment have been conducted. Recently, a phase I clinical trial of oral COL-3 (6-demethyl, 6-deoxy, 4-dedimethylaminotetracycline) was administered to 35 patients with multiple refractory metastasizing tumors. Although COL-3 appeared to have stabilized nonepithelial-type malignancies, additional follow-up studies are necessary to determine its true efficacy in the prevention of progression of cancer metastasis.[76]

Cardiovascular system. Abdominal aortic aneurysm is a chronic degenerative condition

associated with a life-threatening risk of rupture. Degradation of aortic wall elastin and collagen occurs secondary to local production of several MMPs. Doxycycline inhibits MMP-2 and MMP-9 derived from human vascular cell types and from tissue explants from abdominal aortic aneurysms.[77]

The administration of 200 mg of doxycycline for 7 days before aortic aneurysm surgery resulted in a 3-fold reduction of aortic MMP-2 expression and 4-fold reduction of MMP-9.[77] In a randomized, double-blind placebo-controlled pilot study involving 32 patients, the administration of doxycycline was associated with a significant reduction in aneurysm expansion rates as demonstrated by ultrasound surveillance.[78] Preliminary data also showed that doxycycline reduces polymorphonuclear leukocyte activity in patients with acute myocardial infarction.[79]

Periodontitis. Chronic periodontal inflammation is a common cause of irreversible loss of tooth attachment. This process involves increased apical proliferation and migration of gingival sulcular epithelial cells, an increase in periodontal microbial pathogens, and eventual destruction of collagen in the gingival, periodontal ligament, and alveolar bone. The source of the proteolytic enzymes is the gingival epithelial sulcular epithelium (MMP-2, -7, -8, -13, -14)[80] and from periodontal pathogens.[81] Early studies showed that tetracycline, doxycycline, and minocycline inhibit collagenase of gingival crevicular fluid derived from adult periodontitis.[19,82] The oral administration of submicrobial dose of doxycycline (20 mg twice daily) as an adjuvant for conventional procedures for adult periodontitis resulted in a significant improvement in tooth attachment as well as reduction of pocket depth and bleeding after probing.[83] More recently, local delivery of doxycycline showed similar effects in chronic periodontitis.[84]

CONCLUSIONS

Tetracycline and its analogues have been used in the treatment of various dermatologic and nondermatologic diseases. Although there is some evidence for anti-inflammatory and immunomodulatory effects, additional studies must be performed, at both the laboratory and clinical levels, to corroborate these properties.

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