

## Original Article

# Safety of long-term doxycycline administration: a retrospective study

## 長期多西環素治療的安全性：回顧性研究

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**Background:** There are concerns over the side effects and the development of resistance after long-term intake of doxycycline. **Objectives:** To evaluate the safety of long-term intake of doxycycline in Korean patients. **Methods:** In patients who were taking doxycycline, demographic and clinical data were analysed retrospectively. **Results:** Among the total of 569, low therapeutic effect was claimed in 6.3% and true adverse effects were seen in 6.5%. The rate of cessation due to a true adverse event was 2.0%. **Conclusions:** Since the occurrence of side effects was low and the majority of the side effects were well-tolerated, doxycycline is a fairly safe medication.

**背景：**人們對長期服用多西環素，有著副作用和耐藥性產生的擔憂。**目的：**評估韓國患者長期服用多西環素的安全性。**方法：**回顧性分析被處方多西環素的患者之人口統計學及臨床數據。**結果：**569例中，6.3%患者認為療效低，真實不良反應個案亦佔6.5%。由於真正不良反應而導致停藥的比率只有2.0%。**結論：**由於出現副作用的比率低，而且病人對當中大多數副作用的耐受性都不錯，因此多西環素還是相當安全的藥物。

**Keywords:** Doxycycline, drug resistance, long-term use, safety, side effect

**關鍵詞：**多西環素、耐藥性、長期服用、安全、副作用

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## Introduction

Second generation tetracyclines such as doxycycline and minocycline have a better pharmacokinetic profile and lesser toxicity compared to tetracycline.<sup>1</sup> Doxycycline is widely prescribed for chronic dermatological conditions including acne, rosacea, and folliculitis. Doxycycline is considered to be fairly safe, due to lesser and milder side effects than tetracycline.<sup>2</sup> However, since it is often taken for a long period of time, there are concerns over the development of side effects and potential resistance. Side effects of doxycycline 100 to 200 mg daily reported so far consist mostly of gastrointestinal (GI) problems such as oesophageal erosions, gastritis, nausea and vomiting. However, in rare cases, central nervous system (CNS) problems (intracranial hypertension, dizziness), genitourinary symptoms (vaginitis, inflamed vulva), rhinitis, hypoglycemia, anosmia, minor laboratory abnormalities, tooth discolouration, and temporary bone growth inhibition can occur.<sup>3</sup> Photosensitivity has also been fairly commonly reported, of which the relationship between the development of phototoxicity and doxycycline has been shown to be dose dependent.<sup>4</sup>

In the present retrospective study, we set out to determine how safe and well-tolerated doxycycline actually is in Korean patients, as well as the incidence of its side effects.

## Materials and Methods

We enrolled consecutive patients who were taking doxycycline (100 mg/tablet) between 1 January 2010 and 24 February 2014, from the Department of Dermatology of Boramae Hospital. Sex, age, underlying skin conditions, total amount of doxycycline given, duration of prescription, and side effects were assessed by reviewing medical records. We also recorded whether the patients who complained of side effects actually stopped doxycycline or were able to continue with their

medication. We analysed the demographics and employed  $\chi^2$  test to compare the group with and without side effects by SPSS software, version 21. A *p* value of less than 0.05 was considered statistically significant.

## Results

A total of 569 patients were included (311 male and 258 female, mean age:  $42.8 \pm 0.7$  years). A mean of  $20.7 \pm 1.2$  grams (average of  $0.2 \pm 0.0$  g/d) was prescribed for an average period of  $4.0 \pm 0.2$  months (range: 0.03-40.8 months). Out of many indications, the majority were seborrheic dermatitis (44.0%), acne (20.7%), folliculitis (16.0%) and rosacea (13.4%). Low therapeutic effect was claimed or demonstrated in 6.3% of patients (36/569), and out of these 36 patients, 24 had acne, 3 had seborrheic dermatitis, 4 had folliculitis, 3 had rosacea, one had flushing, and one had chronic cutaneous ulcer, respectively. Of the group who claimed low effect, acne patients were younger ( $24.0 \pm 1.2$  vs  $38.6 \pm 4.8$ ,  $p=0.012$ ) and were prescribed for a shorter period of time ( $42.4 \pm 8.9$  vs  $90.3 \pm 26.1$  days,  $p=0.038$ ) than the others. True side effects were seen in 6.5% (37/569), most of which were GI symptoms (73.0%, 27/37), followed by rare liver function test abnormalities (8.1%, 3/37), finger pain (2.7%, 1/37), facial swelling (2.7%), generalised erythematous macules (2.7%), prolonged menstruation (2.7%), dizziness (2.7%), fixed drug eruption (2.7%) and photoallergic reaction (2.7%). Among all patients, GI side effects were observed in 4.7% and liver function abnormalities in 0.53%. The prescription period was significantly shorter in the group with side effects compared with the group without ( $57.8 \pm 17.5$  days vs  $126.0 \pm 7.3$  days,  $p=0.001$ ). It was also consistent with grams taken in total ( $11.2 \pm 3.5$  grams vs  $21.3 \pm 1.2$  grams,  $p=0.008$ ). The group who complained of low effect took less grams of doxycycline ( $11.5 \pm 2.1$  grams vs  $21.3 \pm 1.2$  grams,  $p<0.001$ ) for a shorter period of time ( $58.4 \pm 11.0$  days vs  $125.8 \pm 7.3$  days,  $p<0.001$ ), and also

tended to be younger than the others ( $28.9 \pm 2.1$  years vs  $43.7 \pm 0.8$  years,  $p < 0.001$ ). Photoallergic reaction was observed only in one patient, indicating that it is very uncommon in Korean patients. Although a total of 12.8% of patients complained of ineffectiveness or true side effects, the eventual rate of cessation of prescription due to a true adverse event was 2.0% (11/569), compared to 6.0% (34/569) due to low therapeutic effect; 29.7% (11/37) of those with true adverse events discontinued medicine in comparison to 94.4% (34/36) of those with low effect. The demographics of and the reasons for discontinuing doxycycline in the 11 patients are described in Table 1.

## Discussion

In the present study, only 6.5% of patients complained of true side effects and 6.3% complained of low therapeutic effect after doxycycline intake. Both the group with true side effects and the group with low therapeutic effect took fewer pills than the remainder of patients. On the other hand, the group which complained of ineffectiveness was younger compared with the others. However, the actual percentage of those who stopped doxycycline due to side effects excluding those who claimed or demonstrated low effect was only 2.0%.

In the literature, most of the side effects of doxycycline are GI, CNS and genitourinary system-related and have been reported in cases who took less than three weeks of doxycycline.<sup>2</sup> In the present series, patients who complained of true side effects took  $11.2 \pm 3.5$  grams for  $8.3 \pm 2.5$  weeks. Even though 12.8% of patients complained of side effects or ineffectiveness, 98.0% of total patients (70.3% of those with true adverse events) were able to continue with doxycycline. Because low therapeutic effect cannot be categorised as a true side effect of a medicine, our results support that most of side effects of doxycycline are tolerable.

The reason that most of the patients were able to continue with doxycycline is because GI discomfort, the most common side effect of doxycycline can be circumvented by immediate intake after a meal. Oesophagitis and oesophageal ulceration are known to occur usually when the medication is taken before bedtime and with little or no water.<sup>5</sup> This is because the ulceration results from the physical contact of the tablet with the epithelial lining of the oesophagus.<sup>3</sup> Therefore, the risk of esophageal ulceration reported with the use of doxycycline can be minimised with adequate fluid intake and avoiding lying down after oral intake of the capsule or tablet.<sup>6</sup>

Among the 11 patients who actually stopped doxycycline due to adverse events, one patient had underlying acute myeloblastic leukemia, one was under excess stress and on a food binge before and during doxycycline intake, and one had concurrent medication (Terbinafine 250 mg daily) and he complained stomachache after taking doxycycline. After cessation of doxycycline, this problem resolved. These facts indicated that the actual cessation rate purely due to doxycycline may have been even lower (Table 1).

A three to four week course of oral tetracycline is generally required to achieve substantial improvement in signs and symptoms of inflammatory skin diseases like rosacea where this drug is indicated.<sup>7</sup> The effect of doxycycline can be explained by its anti-microbial and anti-inflammatory properties. The anti-microbial effect results from selection pressure against sensitive commensal flora, transient flora, and selected bacterial pathogens. Even though doxycycline has an anti-microbial effect, the effect of doxycycline in inflammatory skin diseases is not definitively associated with eradication or reduction of a bacterial pathogen in most cases. In a study by Del Rosso et al, the signs and symptoms of inflammatory skin diseases consistently improved throughout a four-month period on an anti-inflammatory dose of doxycycline 40 mg daily.<sup>8</sup>

**Table 1.** Demographics of patients who discontinued doxycycline and reasons for the discontinuation

Case	Sex	Age (years)	Diagnosis	Total period of prescription before side effects (Days)	Total amount of prescribed pills before side effect (g)	Underlying condition	Side effect
1	M	57	Rosacea	1	0.1		Fixed drug eruption on legs
2	F	44	Seborrheic dermatitis	37	7.4		Finger pain
3	F	80	Rosacea	14	2.8		Facial swelling (refused all oral medication)
4	F	29	Acne	126	25.2		Photoallergic reaction (face and neck eruption)
5	F	50	Seborrheic dermatitis	21	4.2	Acute myeloblastic leukaemia (M3)	LFT abnormality (+) GOT(AST) 40 IU/L ▲ GPT(ALT) 85 IU/L ▲
6	F	28	Rosacea	63	6.3	Body weight gain (10 kg in 4 months) Excess stress and binge	GI symptoms
7	F	25	Acne	89	17.8		Vomiting
8	F	52	Seborrheic dermatitis Folliculitis	28	5.6		Generalised erythematous macules with pruritus Follow-up loss thereafter
9	M	49	Folliculitis	14	2.8	Poor adherence, Misperception about fever as cause of disease	Heartburn Follow-up loss thereafter
10	F	32	Acne	14	2.8		Prolonged menstruation Follow-up loss thereafter No gynaecological exam done
11	M	28	Seborrheic dermatitis	28	5.6	Concurrent medication: terbinafine 250 mg qd, bepotastine 10 mg bid, ebastine 10 mg qd, bismuth/ranitidine/sucralfate	Abdominal discomfort

The anti-inflammatory effect of doxycycline is known to be due to reduced activity of reactive oxygen species, inhibition of nitric oxide synthase, decreased cytokine expression, inhibition of activity of several matrix metalloproteinase (MMP) and MMP precursors, inhibition of protein kinase C activity,  $Ca^{2+}$ /calmodulin pathway and reduced proinflammatory activity of phospholipase  $A_2$ .<sup>8</sup> Doxycycline seems to be more effective than other tetracyclines because doxycycline not only inhibits MMP activity but also reduces enzyme expression at the transcriptional level, and it is most potent in inhibiting the mitogen-induced proliferative response of human lymphocytes *in vitro* by blocking blast formation.<sup>9</sup> Also in the *in vitro* system, doxycycline was proven to have a 10-fold stronger inhibitory activity against granuloma formation than the parent drug tetracycline.<sup>9</sup> As mentioned earlier, a three to four week course of tetracycline is needed for clinical improvement,<sup>7</sup> and anti-inflammatory effect of doxycycline lasts throughout four months or more.<sup>8</sup> In the present study, patients who complained of low effect took the medication for  $58.4 \pm 11.0$  days (7-265 days) or  $8.3 \pm 1.6$  weeks (1.0-37.9 weeks), which means that some of them were not treated long enough for proper evaluation of the efficacy of doxycycline.

Concern over bacterial resistance after long-term intake of doxycycline has been a hot issue, and bacterial resistance may be a possible reason for low effect. It seems that antibiotic therapy longer than three to six months brings little additional effect but increases the risk of resistance.<sup>10</sup> Risk factors identified for resistant *P. acnes* are prescribing habits, a long-term antibiotic treatment, repeated administration of antibiotics, and poor compliance.<sup>10</sup> Prevention methods consist of correct indication, avoiding long-term treatment (maximum of six months), improving compliance and, in the case of acne, combining with benzoyl peroxide once weekly, either continually or as interval treatment.<sup>10</sup> Of 36 patients with low therapeutic effect, 66% (24/36) had acne. Therefore, there is also a possibility

that true bacterial resistance developed as time went by. In the present study, seven out of 36 patients who complained of low therapeutic effect took doxycycline for more than three months. Among the seven patients, three had acne, two had folliculitis, one had seborrheic dermatitis, and one had rosacea. All three acne patients were in their twenties and the duration of acne was longer than two years. In a previously reported Korean study, there were no statistically significant differences in the resistance of *P. acnes* strains depending on age, disease duration or severity of acne, and the actual rate of resistance in Korea was lower than that in European countries.<sup>11</sup> However, we cannot neglect the possibility of bacterial resistance as the reason for the low efficacy of doxycycline.

In summary, the occurrence of side effects with doxycycline was low even after long-term intake, and the majority of the side effects were well-tolerated. Therefore, we can conclude prudently that doxycycline is a fairly safe medication even when taken long-term. In the present series, doxycycline was continuously administered safely and effectively for a maximum length of 40.8 months. In patients who claim low therapeutic effect of doxycycline, insufficient duration of administration, as well as bacterial resistance, should be taken into consideration.

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