Minocycline is an oral antibiotic widely prescribed throughout the world, primarily for the treatment of acne vulgaris; other uses include the treatment of rosacea and perioral dermatitis. In the United States, Propionibacterium acnes resistance is lowest with minocycline compared with other tetracyclines and with erythromycin. The availability of generic formulations of minocycline has created confusion regarding the clinical significance of brand versus generic minocycline products. This article reviews available data on minocycline use for acne vulgaris and discusses a patented brand of minocycline versus generic formulations, including evaluations of pharmacologic activity and safety.

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What data support the use of minocycline in the treatment of acne vulgaris?

Minocycline is a semisynthetic, long-acting, oral tetracycline derivative that has been used widely in dermatology since 1967, predominantly for the treatment of acne vulgaris. The highly lipophilic property of minocycline is well suited for penetration into lipid-rich tissues such as the pilosebaceous unit. From a pharmacokinetic perspective, more than 90% of minocycline is absorbed from the gastrointestinal tract; from a physiochemical perspective, minocycline is more lipid soluble than tetracycline and doxycycline. Additionally, the more favorable lipophilic/hydrophilic partition coefficient of minocycline appears to correlate with better tissue distribution compared with tetracycline and doxycycline.

Minocycline is well established as an effective oral agent in the management of acne vulgaris; minocycline also exhibits the lowest prevalence of Propionibacterium acnes resistance compared with other oral antibiotics commonly used to treat acne vulgaris, including tetracycline, doxycycline, and erythromycin. In a 4-week comparative trial of brand formulations, minocycline (Dynacin®) 100 mg twice daily produced a log decrease in P acnes almost 2-fold greater than tetracycline hydrochloride 500 mg twice daily and doxycycline monohydrate 100 mg twice daily. In a 6-week trial of minocycline (Dynacin), tetracycline, and doxycycline comparing log reductions of P acnes, minocycline exhibited a more rapid onset of effect, the greatest log reduction in P acnes, and the greatest residual reduction in P acnes at 3 weeks after discontinuation of treatment. In an 8-week, open-label, multicenter trial (n=385), combination therapy using minocycline (Dynacin) 100 to 200 mg daily and a brand formulation of benzoyl peroxide 6% gel (Triaz®) demonstrated a rapid onset of clinical effect in patients with moderate to severe acne vulgaris that usually was noted within the first 2 weeks of treatment; continued improvement was observed in most patients over the 8-week study course. In this trial, 87% of investigators rated global response to treatment as marked (57%) or moderate (30%) improvement, and 88% of patients rated their response as excellent (43%) or good (45%).

What are the reported biologic effects of minocycline that potentially may correlate with therapeutic activity?

In addition to antibiotic activity, a variety of in vitro and in vivo models have demonstrated multiple anti-inflammatory and anticollagenolytic effects of
tetracycline derivatives, including minocycline. These effects include inhibition of proinflammatory cytokines (such as interleukin α-like cytokine), inhibition of lipase, reduced fatty acids in sebum, suppression of chemotaxis, decreased granuloma formation, inhibition of protein kinase C enzymes, suppression of matrix metalloproteinase enzymes (collagenase and gelatinase), free radical scavenger activity, and suppression of mitogen-stimulated proliferative lymphocytic activity.1,5,7,8

How do manufacturing considerations, bioavailability, and pharmacokinetic profiles of minocycline formulations potentially correlate with clinical activities?

Because both brand and generic formulations of minocycline are available, the question of whether clinically meaningful differences are present between products has been considered. With regard to pharmaceutical product design and manufacturing, the use of comparable raw materials does not ensure equivalence of final products, especially from batch to batch. Specifics related to formulation design and the manufacturing process directly can affect the potency, dissolution characteristics, and bioavailability of the formulation.9 Minimum guidelines related to the manufacturing of minocycline have been established by the US Pharmacopeia (USP); the requirements include 90% potency and at least 75% release of minocycline after 45 minutes.9

How do bioavailability and pharmacokinetic profiles of minocycline formulations potentially correlate with clinical effects?

The extent of minocycline bioavailability, which is correlated directly with dissolution and active ingredient release from the drug’s oral formulation (tablet, capsule), is a factor that may influence clinical efficacy because greater drug availability is more likely to produce higher follicular drug concentration.9 The dissolution rate of minocycline from its oral solid formulation influences how quickly the rise in serum level occurs. A more rapid spike in the serum level of minocycline may influence the potential for vestibular effects (eg, vertigo, dizziness).9

A summary of pharmacologic and pharmacokinetic studies of minocycline, including comparative analyses, are depicted in Table 1.9-13 One minocycline brand (Dynacin®) has a defined quality assurance program that specifies batch-to-batch consistency using specifications for minocycline manufacturing that are more stringent that those indicated by the USP.9 The program mandates that each minocycline batch meet a 95% potency specification and a dissolution profile of at least 90% release of drug within 45 minutes.9 In addition, the brand formulation produces a more favorable initial progressive release of minocycline over the first 15 minutes compared with the rapid release and quick spiking of minocycline serum level observed with some generic formulations.9,10 The Figure illustrates the results of USP dissolution

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*USP indicates United States Pharmacopeia; P acnes, Propionibacterium acnes.
†The brand minocycline was Dynacin®, the original pelletized minocycline and original brand capsules were Minocin®.
studies comparing a brand formulation of minocycline (Dynacin) 100-mg tablet with 4 generic formulations of minocycline 100-mg capsule. The rapid rise in serum levels observed within 10 and 15 minutes with some of the generic formulations appears to correlate with an increase in vestibular effects, as discussed below.9,14

What clinical differences have been observed in studies comparing brand and generic minocycline formulations?

A blinded cross-over study of female patients (n=32) aged 21 to 55 years was performed to compare the incidence of general, vestibular, and gastrointestinal effects with brand (Dynacin) versus generic formulations of minocycline.9,14 Minocycline was administered on an mg/kg dose basis at the same time each day over 4 days, with a 14-day intervening washout period. The weight-based dosing schedule was: 50 to 69 kg, 100 mg daily (n=20); 70 to 89 kg, 150 mg daily (n=7); and 90 kg or more, 200 mg daily (n=5). Study subjects were educated regarding maintenance of a side effect diary, specifically noting the severity (mild, moderate, severe) and duration of reactions. The adverse reactions evaluated were general (headache, malaise), vestibular (vertigo, dizziness, blurred vision), and gastrointestinal (nausea, vomiting, diarrhea, cramping, flatulence). The study rating system recorded the number of days a subject experienced specific adverse events (ie, general vs vestibular vs gastrointestinal effects), as well as the number of individual episodes for each symptom area.

No significant differences were noted between the brand and generic minocycline formulations for any reported adverse events or symptoms other than for vestibular effects. A statistically significant (P=.0003) difference was noted with vestibular symptoms reported on day 5 with the brand formulation and on day 20 with the generic formulation. The ratio of individual episodes between the brand and generic formulations was 1:5.4. Five and 27 vestibular reaction episodes were noted with the brand and generic formulations, respectively.

The greater frequency of vestibular effects with the minocycline generic formulation compared with the brand formulation appears to be explained by the differences in dissolution rate, drug release, and rate of rise in serum level.9 Based on USP dissolution study parameters, the brand formulation exhibited a progressive dissolution rate of minocycline, with 90% release within 45 minutes. As a result, initial rapid spiking of serum level is obviated while still achieving complete dissolution and optimal bioavailability. The generic formulation exhibited a rapid release of minocycline, with 100% release in less than 15 minutes. This probably accounts for the significantly higher (P=.0003) reported incidence of vestibular effects associated with use of the generic formulation (Table 2).9

Conclusion

Minocycline is a semisynthetic oral tetracycline agent. The high lipophilic properties of minocycline likely correlates with marked follicular penetration
confirmed by skin biopsies using UV light techniques that demonstrate the drug’s presence within follicles after oral ingestion of a brand formulation. Minocycline is associated with the lowest prevalence of resistant *P acnes* strains compared with other oral antibiotics used to treat acne vulgaris, including tetracycline, and is reported to produce the highest log reduction of *P acnes* organisms. As with pharmacologic products in general, differences in manufacturing standards and specifications may produce a marked effect on the pharmacokinetic, pharmacodynamic, and clinical properties of individual minocycline formulations. Comparisons of a brand versus generic formulation of minocycline and original comparator pelletized and powder capsule formulations demonstrate differences in dissolution rates, drug release, serum level profiles, and side effect profiles. Dissolution rate and drug release of minocycline appear to correlate with the reported incidence of vestibular effects.

REFERENCES


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<td>Ratio of individual episodes of vestibular effects were 1:5.4 with brand vs generic formulations, respectively; vestibular symptoms reported on day 5 with brand formulation and on day 20 with generic formulation (<em>P</em>= .0003)</td>
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*USP indicates US Pharmacopeia.

†The brand minocycline was Dynacin®; the generic minocyclines were Barr and Warner-Chilcott formulations.