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部分訳　酒さとニキビにメトロニダゾールが有効である
メトロニダゾールがニキビに効果を示すのは、メトロニダゾールの抗菌作用によると言うよりも、むしろ別の生物活性である坑炎症作用によると思われる。

**抗炎症作用**

資料3号 (3)

ニトロイミダゾール　古川文献　＃1

**Metronidazole, its Bioactive Metabolites and Acne**

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**［メトロニダゾール：活性代謝産物とニキビ］**


要旨

酒さとニキビにメトロニダゾールが有効であることはよく知られたことである。一方、最近の研究から,メトロニダゾールを含む一部の抗菌剤の代謝物が親化合物を凌ぐ抗菌活性を示すことが明らかになった。そこで、ニキビの病理発生の根幹に関っているpropionibacterium acnes に対する抗菌活性について再検討を行った。その結果、この菌はhydroxy 体に対して marginally more sensitive であった（メトロニダゾールの MIC 100mic g/ml に対して hydroxy 体の MIC は 50mic g/ml）が、尚、通常の使用時に得られる濃度範囲からは外れた高いものであった。

メトロニダゾールがニキビに効果を示すのは、メトロニダゾールの抗菌作用によるというよりも,むしろ別の生物活性である抗炎症作用によると思われる。


（代謝物の提供は Rhone-Poulenc）

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# Metronidazole, its Bioactive Metabolites and Acne

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Key words: *Metronidazole – Acne*

## Summary

*Metronidazole's activity has been established in both acneform rosacea and acne vulgaris. Recent research indicating that the breakdown products of several antibiotics, including metronidazole, may have considerably greater activity than the parent compound, prompted a re-examination of the susceptibility of* Propionibacterium acnes, *the organism involved in the fundamental pathogenesis of acne vulgaris. Although the organism was marginally more sensitive to the hydroxy derivative, MIC levels were still outside the readily attainable therapeutic range. The beneficial effects of metronidazole in acne vulgaris are attributable to its anti-inflammatory activities, rather than its antibacterial ones.*

## Introduction

The activity of metronidazole in acne is well known. It is one of the recommended drugs in acneform rosacea[1–3], and displays antibacterial activity and anti-inflammatory activity in acne vulgaris[4–6]. Although the antibacterial activity of metronidazole against *Propionibacterium acnes* in acne vulgaris is of a modest degree, recent data suggest that the breakdown products of metronidazole may be more powerful than the parent compound[7–8]. In view of these findings, the bioactivity of the hydroxy derivative of metronidazole was examined for its anti-*P. acnes* effects.

## Material and Methods

Twenty-four dermatological isolates of *P. acnes* were selected for testing. All strains were characterised as *P. acnes* by standard microbiological tests. They were recovered from lyophilised vials by subculture to horse blood agar and checked for purity prior to testing. Metronidazole, its hydroxy metabolite 1-[2-hydroxy-ethyl]-2-hydroxymethyl-5-nitroimidazole and its acid metabolite 2-methyl-5-nitro-imidazolyl acetic acid were supplied by Rhone-Poulenc Pharmaceuticals. Each was dissolved in *N,N*-dimethyl formamide and diluted in distilled water to produce a stock concentration of 10 000 µg/ml.

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Working standards from 5.0 µg/ml to 100 µg/ml were prepared by further dilution in 0.02 M phosphate-buffered saline and incorporated in brain–heart infusion agar enriched with 5% horse blood. Susceptibilities of *P. acnes* were prepared from 48-hour blood agar cultures in Penassay broth and adjusted on a Spectronic 20 spectrophotometer so that an inoculum of $7 \times 10^6$ cfu was delivered per spot with a Steers replicator. Control plates without antibiotic and a control strain of *Bacteroides fragilis* ATCC 25285 were included in the test series. Plates were incubated at 37°C for 48 hours in anaerobic jars in an atmosphere of 95% nitrogen and 5% carbon dioxide. The minimum inhibitory concentration (MIC) for each drug was defined as the lowest concentration permitting no growth.

## Results

All strains were resistant to metronidazole and the acid metabolite (MIC > 100 µg/ml). The lowest MIC for the hydroxy derivative of metronidazole for three of the 24 strains was 50.0 µg/ml.

## Discussion

Antibiotics have played a central role in the treatment of both acne rosacea and acne vulgaris for decades[1–3,6]. Metronidazole is currently one of the drugs of choice for acne rosacea[1–3] and exhibits anti-inflammatory properties in acne vulgaris. However, its role against *P. acnes*, the anaerobe fundamentally implicated in the pathogenesis of acne vulgaris, is less firmly established because of its modest activity[4–5]. Recent information has prompted a second look at the latter situation. It is now recognised that the breakdown products of several antibiotics, such as desacetylcefotaxime[9], hydroxy-clarithromycin[10] and, significantly, metronidazole[7,8], may have greater activity than the parent drug against certain organisms. Applying this rationale we re-examined the susceptibility of a number of stralns of *P. acnes* to hydroxymetronidazole and the parent compound. Although the organism was marginally more sensitive to the hydroxy derivative, MIC levels were still outside the readily attainable therapeutic range[11]. It is likely that the salutary effects of metronidazole in acne vulgaris derive from its anti-inflammatory activities rather than its antibacterial ones.

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