

## Letter to the Editor

# Preliminary Efficacy Study of a Bioadhesive Vaginal Metronidazole Tablet in the Treatment of Bacterial Vaginosis

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Bacterial vaginosis is a common cause of vaginitis, characterized by replacement of lactobacilli-dominated flora with a mixed flora containing *Gardnerella vaginalis*, various anaerobic bacteria and *Mycoplasma hominis*.

Metronidazole is the drug of choice in the treatment of bacterial vaginosis, but dosage and duration of therapy are still controversial. The current recommendation is a treatment with metronidazole orally with 500 mg twice daily for seven days (Centers for Disease Control 1989), but a 2-g single-dose oral metronidazole regimen has been shown to be as effective (Lugo-Miro et al 1992). However, metronidazole has some unpleasant side-effects and is contraindicated in the first trimester of pregnancy. Alternative therapy has been sought as a clindamycin vaginal cream (Schmitt et al 1992). Recently, an increasing interest in the development of vaginal bioadhesive tablets has been shown because of the advantages of maintaining a certain drug level locally and enabling lower dosing frequency and a lower amount of drug administered (Brannon-Peppas 1993).

This study has been designed to evaluate the efficacy of a single vaginal metronidazole bioadhesive tablet application vs a standardized oral treatment with metronidazole. The bioadhesive formula has already successfully been used as a buccal bioadhesive tablet containing miconazole nitrate to treat candidiasis (Bouckaert et al 1992).

In a double-blind study the patients were randomly allocated to receive a bioadhesive vaginal tablet (weight 1 g; diam. 20 mm) with 100 mg metronidazole or a placebo vaginal tablet. The bioadhesive matrix consisted of a modified starch/polyacrylic acid mixture (Bottenberg et al 1991). Both groups were compared with a third arm of the study where patients were given the conventional oral metronidazole treatment consisting of two 500-mg doses daily of Flagyl over seven days. In the case of treatment with the bioadhesive tablet, a single tablet was applied to the cervix at the out-patient clinic. The bioadhesive tablet was fixed on the portio uteri previously cleaned with a dry tampon. The tablet was applied with tweezers or forceps. Patients were asked to record the loss of a tablet. The patient's complaints,

the results of the clinical evaluation and the results of the direct microscopic examination were recorded on an evaluation sheet. A clinical, microscopic and bacteriological evaluation was performed after one and four weeks. If patients were still infected after four weeks an oral treatment was started immediately.

Out-patients aged 18-50 years were included. The patients were informed about the objective of the study and the approval of the Medical Ethical Committee of the University Hospital was obtained. Exclusion criteria were evidence of other specific vulvovaginitis (candidiasis, *Trichomonas vaginalis*), cervicitis due to *Neisseria gonorrhoeae* or *Chlamydia trachomatis*, pregnancy, antibacterial medication and the presence of an intrauterine device. The diagnosis of bacterial vaginosis was based on the following criteria: presence of clue cells (microscopic examination and Gram staining), flor vaginalis and two of the following criteria: positive amine test, observation of vaginal discharge, and a vaginal pH > 4.5. Endocervical cultures for sexually transmitted pathogens were obtained at every visit. Patients were considered cured if none of the above mentioned diagnostic criteria was fulfilled and no bacterial vaginosis could be detected by microbiological tests. The results were statistically evaluated using a  $\chi^2$ -test. Statistical significance was regarded as having been reached when  $P < 0.05$ .

Table 1 shows the results. A total of 30 patients were enrolled in the study. Six women were excluded (3 in the placebo group and 3 in the metronidazole group). After one week none of the patients receiving the placebo bioadhesive tablet was cured, while 8 out of 10 orally treated patients and 6 out of 7 patients who received the metronidazole bioadhesive tablet showed no signs of flor vaginalis. After four weeks a trend towards higher prevalence of bacterial vaginosis occurred in the group treated with the bioadhesive metronidazole tablet in comparison with the orally treated group (four of the patients treated with the bioadhesive carrier were cured compared with seven cures in the orally treated group). No significant difference in clinical efficacy was observed after one and four weeks between the group treated orally and the group treated with the bioadhesive carrier ( $0.5 < P < 0.7$  and  $0.05 < P < 0.1$ , respectively). The cure rate was significantly lower in the group receiving the

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Table 1. Cure rates for the different formulations.

	After 1 week		After 4 weeks	
	Cured	Not cured	Cured	Not cured
Placebo bioadhesive tablet (n = 7)	0	7	0	7
Bioadhesive tablet with 100 mg metronidazole (n = 7)	6	1	4	3
Flagyl (n = 10)	8	2	7	3

placebo bioadhesive tablet ( $0.001 < P < 0.01$ ) as compared with the two other treatment groups.

In this study where a single 100-mg metronidazole bioadhesive vaginal tablet was administered, similar cure rates were obtained as for the orally treated group, although only one-seventieth of the drug was administered locally. After four weeks a certain recurrence incidence was observed in both treated groups. Recurrence of infection is an important problem in the treatment of bacterial vaginosis. The recurrence could be due to the presence of microorganisms remaining after the period of treatment, failure of restoration of the normal lactobacilli flora after infection and reinfection via sexual contact.

Although further research is required to define the optimal tablet geometry and drug-loading limits on the residence time, the use of a bioadhesive tablet opens new perspectives in the local treatment of bacterial vaginosis, especially with a dramatic reduction in the amount of drug administered. An optimization study is continuing, to investigate the influence of drug loading, the geometry of the

tablet and the polymer/drug ratio on residence time and the cure rate.

### References

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## Book Review

### Crystallization Technology Handbook

Edited by A. Mersmann

Published 1994, Marcell Dekker, Inc., New York

xii + 691 pages

ISBN 0 8247 9233 5 \$195.00

The stated aim of this book is to describe not only the science of crystallization, but also the design procedures of crystallizers. I believe that the book fulfils that aim.

The first chapter deals with fundamentals in a reasonable manner, however, I don't think it was targeted for the novice reader; for example Miller's indices are used but not explained.

The second chapter is entitled 'Interaction Between Balances, Processes and Product Quality'. This is a chemical engineering, and often mathematically based, section dealing in some considerable detail, with everything from mass balance, through size distribution and growth rate, classified product, agglomeration and abrasion, habit, and the influence of impurities, to caking.

The third chapter is devoted to 'Design of Crystallizers and Crystallization Processes'. Not surprisingly, this is pure chemical engineering and from my perspective seems to cover all

aspects and available types of crystallizer that may be of industrial interest.

The fourth chapter is on the control of crystallizers and the fifth on reaction crystallization. The sixth is an interesting section on additives for crystal engineering, including changing morphology, aiding dissolution, polymorphism control and modelling.

Chapter seven deals with crystallization from the melt and given a comprehensive coverage of the approaches and technology which are available.

The final chapter 'Thermal Analysis and Economics of Processes' relates to aspects such as energy utilization as well as capital and other operational costs of industrial crystallization processes.

The text is presented in varying styles, some chapters being relatively easy reading (from my perspective), whilst others deal with relatively detailed mathematical concepts. In conclusion this book is suitable for people who have some scientific knowledge of the principles of crystallization which they wish to develop into a practical industrial application.

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