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Decreased Bioavailability of Tamoxifen after Rectal Administration

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TAMOXIFEN (Nolvadex®*) is widely used in the management of breast cancer, and is relatively well-tolerated after oral administration. The most common side-effects are mild nausea and vomiting occurring in approx. 10% of patients [1]. This pilot study was designed to develop a fatty rectal suppository as a possible alternative for the oral dosage forms and to establish the bioavailability of tamoxifen after adminstration of 40 mg as a single dose in these suppositories. The suppositories were prepared by grinding the tablets and mixing with the molten fatty base.

Six healthy male volunteers (age 23–30 yr) participated in this study after approval by the local ethical committee and written informed consent.

Three dosage forms, commercially available tablets (Nolvadex® 20) and two types of suppositories, were administered in this study to the volunteers; only the results for the most favourable suppository will be discussed in this note. In each session the equivalence of 40 mg tamoxifen (two tablets or one suppository) was administered. Between the treatments was a sampling and wash-out period of 28 days.

Tamoxifen is metabolised in man to two major metabolites, 4'-OH-tamoxifen and *N*-desmethylamoxifen. After a single dose, only the latter metabolite, besides the parent compound, can be detected in the plasma of the volunteers. Both metabolites are supposed to be pharmacologically active, but are omitted in the estimation of the bioavailability.

Plasma samples were assayed for tamoxifen and its major metabolites by a modified HPLC-procedure with a post-column fluorescence activation [2]. From the plasma values the bioavailability was calculated per volunteer, and the theoretical steady-state level after chronic dosing was estimated. After oral administration, peak levels for tamoxifen of 64–100 ng/ml (95% confidence interval) are detected at t = 4–6 hr after administration (Fig. 1). After rectal administration a mean peak level of approx. 15 ng/ml is found at t = 8 hr.

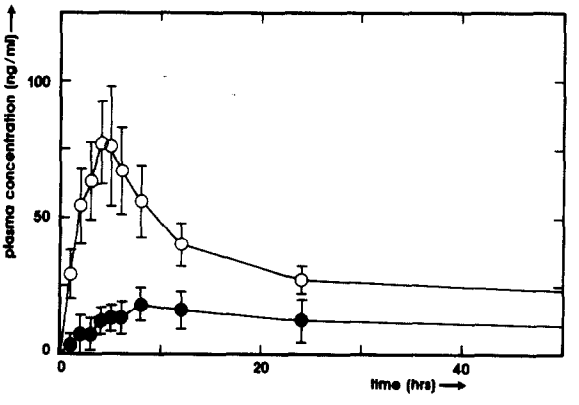

Fig. 1. Mean plasma levels of tamoxifen after administration to six male volunteers in a 40 mg *dose* (± *S.D.*); 0 = *tablet*; 0 = *suppository.*

Rectal administration is not only resulting in delayed but also incomplete absorption, as reflected in the area under the curve for tamoxifen: after tablets 15.85 ± 4.65 nmol.hr/ml and after suppositories 4.43 ± 2.41 nmol.hr/ml.

This result indicates that the relative bioavailability of tamoxifen in suppositories is approx. 30% compared to tablets. Consequently the theoretical steady-state level after chronic administration of tamoxifen in suppositories will be at 30% of the oral level: in this group of volunteers a mean steady-state after repeated dosing of 250 ng/ml for

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tablets and 70 ng/ml after suppositories can be calculated. A more detailed description of this study, including the details of the analytical procedure will be published elsewhere [3]. Despite the fact that no correlation has been found between plasma values and clinical effect, the rectal administration of tamoxifen in fatty suppositories to breast cancer patients cannot be recommended without further investigations.

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