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## NEW INSIGHTS INTO THE TAMOXIFEN PHARMACOKINETICS CONSTITUTE A BASIS FOR A LOADING DOSE SCHEME.

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The aim of the present study was to obtain more data on the single dose pharmacokinetics of tamoxifen and to evaluate the results in view of the clinical tamoxifen posology.
A dose of 40 mg of Tamoplex® tamoxifen has been administered to 12 healthy male volunteers. Plasma samples have been drawn up to 360 hours after dosing. Tamoxifen (T) and its main metabolite N-desmethyltamoxifen (N-desMeT) have been determined by HPLC of the irradiated samples with fluorimetric detection.
The maximal concentration of T of 63.8 ng/ml was found 5.1 hrs after dosing, that of N-desMeT of 29.2 ng/ml 12.8 hrs after dosing. The 24 hr concentrations of T and N-desMeT were 20.7 and 20.3 ng/ml. The concentration of T resp. N-desMeT decayed to 4.6 and 9.6 ng/ml respectively after 360 hrs. The average plasma concentrations have been analyzed by the Nonlin program: a three compartment open model with first order absorption gave an excellent fit. The absorption rate constant of T was 0.11 $hr^{-1}$, the distribution half-life of T was 14.0 hrs, the elimination half-life of both T and N-desMeT was 208 hrs.
Contrary to known data 1° T has a long half-life already after the first single dose and not only after repeated dosing, 2° the half-life of N-desMeT equals that of T, whereas it was reported to be twice as long. On the basis of this study the use of a single loading dose of T has been justified.

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## A PILOT STUDY ON A LOADING DOSE TAMOXIFEN: TOLERANCE AND EFFICACY

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Following the results of the study in volunteers and the steady state level study in breast cancer patients we investigated a loading dose scheme tamoxifen in breast cancer patients. Based on the 24 hour level in the volunteer study a loading dose of 160 mg tamoxifen ( on day one ) was chosen to achieve the same 24 hour level as in the steady state study. This loading dose was followed by 30 mg once daily. The first aim was to assess the tolerance of a loading dose of 160 mg. Besides that, the response rate and side effects were compared to literature data.
36 patients with inoperable or metastatic breast cancer were entered in the study. The mean age was 66.5 years ( 43-85 ); 27 had oestrogen receptor positive, 2 ER-negative tumours and the receptor-status of 7 was unknown.
The first 24 hours no side effect were registered. During the daily dose regimen 1 patient had transient tumour pain in the bones, 2 had a heavy feeling in the epigastric region, 3 had hot flushes and one had a calf vein thrombosis. Three patients were not evaluable for the response; 5/33 had progressive disease, 4/33 had no change, 24/33 had an objective response ( 8 complete and 16 partial response ). The mean response duration was 13.3 months ( range 3-33 months ). Eleven patients are still in remission. The side effects and response rates are comparable to literature data. Since the steady-state level is reached within 24 hours, it may become clear more rapidly whether tamoxifen is of benefit to a patient. The above-described regimen is recommended for routine clinical use.

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## A PLEA FOR PREOPERATIVE TAMOXIFEN WITH A LOADING DOSE FOR THE TREATMENT OF BREAST CANCER

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The anti-oestrogenic drug T is now used extensively in the management of metastatic breast cancer. In controlled trials of T as adjuvant agent in treatment of early breast cancer a significantly delayed recurrence in early breast cancer without causing toxicity was demonstrated. The pharmacological aspects of T have been studied extensively in order to reveal its mode of action and behaviour in patients. The data showed the importance of ER levels for the outcome of therapeutic efficacy while it was clearly demonstrated that with conventional T therapy, C(ss) of the parent drug and metabolites were not achieved until after 4-8 weeks.
We simulated T kinetics and metabolism using data published previously to determine MRT of T as starting-point for a loading dose concept. It was assumed that a (minimal) residence time of T at the site of the receptor and a C(ss) of 150 ng/ml is correlated with clinical response. Evaluation of plasma concentration-time data showed that mean MRT of T upon oral administrations was 41.9 ± 17 hr. From the data of moment analysis(MRT; C(ss)), $t(\frac{1}{2},z)$ of oral T together with the minimal toxicity and compliance it could be concluded that loading doses before oral maintenance T can be recommended.
Taking a possible growth stimulus upon tumour resection into account preoperative administration of T including a loading dose is recommended for the management of (early) breast cancer. The benefit of the concept will be studied firstly in an animal model.
Abbreviations used are: T: Tamoxifen; ER: Estradiol Receptor; C(ss): steady-state concentration; V(ss): steady-state Volume of distribution; MRT: Mean Residence Time; $t(\frac{1}{2},z)$: elimination half-life.

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## TAMOXIFEN AS SOLE THERAPY FOR LOCALISED BREAST CANCER

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Primary breast cancer is conventionally managed by surgery or radiotherapy. However, there is a subgroup of patients in whom these treatment options may not be suitable due, for example, to general infirmity, intercurrent illness or patient refusal. We have reviewed our experience with the use of tamoxifen as sole therapy for such patients.
The series comprises 33 women who first presented between 1979 and 1985. Patients with systemic metastases were excluded. Mean age is 79 years (range 61-92 years). The dimensions of the cancer were measured with calipers at each examination. At first presentation 3 were < 2 cms in maximum diameter, 19 were 2-5 cms and 11 were > 5 cms. 7 had palpable ipsilateral axillary nodes. 4 patients have died during the follow up period, two of breast cancer and two of unrelated causes.
Of 15 women who have been followed for more than 2 years, 8 have shown a complete response and remain alive and well (mean follow up 37 months, range 24-49 months). A sustained partial response occurred in one patient. Three demonstrated an initial partial response of mean duration 25 months but subsequently relapsed and were managed by mastectomy (n=1), radiotherapy (n=1) and medroxy progesterone acetate (n=1). No response to tamoxifen occurred in the remaining 3 patients, 2 of whom have had mastectomies and one refused any further treatment. Side effects were limited to one complaint of transient vaginal bleeding.
In summary, tamoxifen appears to have a definite place as a sole treatment for breast cancer in selected patients with more than half achieving a useful response and side effects are minimal. Conventional therapy should be proceeded with rapidly if complete response is not obtained.