Opening Remarks

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Honvan was developed in the ASTA laboratories in the early 50's following a suggestion of H. Druckrey, and its therapeutic value was soon acknowledged and reported throughout the world by leading urologists. It was the original idea of Druckrey and Raabe [1] that a highly reactive drug should not be administered directly, but instead given as a 'prodrug' in a chemically masked, inert transport form (drug latention). This 'prodrug' would then be converted into the active form in the body – preferably in the tumour cell itself. Honvan – diethyl-stilbestrol diphosphoric ester – was, therefore, one of the earliest prodrugs for the treatment of cancer. As a disodium salt it can safely be administered at high doses as a water-soluble, pharmacologically inert drug. Due to a high level of acid phosphatase in prostatic and cancerous prostatic tissue, it then undergoes dephosphorylation, thereby releasing the active cytotoxic form, stilbestrol; in other body tissues where the biochemical conditions do not prevail, this cleavage is minimal. This enabled the selectivity of estrogen treatment, which had numerous side effects, to be markedly increased. Even patients who no longer responded to the usual treatment with free estrogens showed a definite improvement in one third of the cases, as reported by Gaca et al. [2], McKinnon et al. [3], and Wilmanns [4]. With its special mechanism of action Honvan became the model for a whole series of new drugs, but this concept has proved especially successful in one particular group of substances, namely the oxazaphosphorine cytostatics.

The first practical result of the above theoretical concept aroused a good deal of controversy in the early 60's. While its advantage of solubility in water, its local and systemic tolerance, and its therapeutic potency were recognized, the following points of the mechanism of action of Honvan were doubted: (1) the cleavage in vivo;

(2) the organospecific accumulation of the liberated estrogen in the prostatic cancer cell, and (3) the direct cytostatic effect.

These critical points were also the focus of scientific discussions on Fosfestrol at the International Symposium on the Treatment of Carcinoma of the Prostate held in Berlin in 1969 [5]. According to Dr. Marberger, the local cytotoxic effects are far less evident than the systemic effects. He stressed that: 'We had very very good therapeutic effects from water-soluble stilbestrol in our patients. We still use it and we like the drug very much, and we have quite a series of patients, but we do believe that the mode of action is on another basis. Maybe the dosage plays a role, different pharmacological effects resulting from high blood levels over a short period compared with low dosage and low blood levels or compared with long continuous blood levels.'

This problem has continued to occupy our minds over the last decade. It was, therefore, fortuitous that a number of study groups decided to conduct new investigations on the

mechanism of action and on the pharmacokinetics of Honvan using modern methods. Oelschläger et al. [6–8] and Rothley and Oelschläger [9] recently have made extensive pharmacokinetic studies with the aid of a homogeneous ion-pair extraction methods. They have found important Honvan metabolites in the blood plasma of patients with carcinoma of the prostate, thereby gaining a major insight into its pharmacokinetic behaviour (enterohepatic circulation). These findings provided a clinical and pharmacological basis for the testing of new administration regimens (e.g., continuous slow intravenous infusion) which will be discussed with our clinical colleagues during this workshop. Further information about the mechanism of action of Honvan will probably be available when this group

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achieves the main aim of their investigations, namely the detection of the individual metabolites in the actual prostatic and prostatic cancer tissue. In the experimental section of this workshop Oelschläger et al. will present their 'New results on the pharmacokinetics of Fosfestrol', and Schulz et al. their report on 'Evaluation of the cytotoxic activity of diethylstilbestrol and its phosphorylated derivatives towards prostatic carcinoma, non-prostatic neoplastic and non-transformed cells. The paper by Schneider and Schönenberger on the 'Effects of diethylstilbestrol and its mono- and diphosphate on experimental mammary and prostatic tumors' will undoubtedly also be of particular interest.

The second part of this workshop is concerned with the therapeutic significance of Fosfestrol in prostatic carcinoma, and the papers presented will assess the special clinical position of Honvan in relation to the antiandrogens (luteinizing hormone releasing hormone analogues) and functionally substituted estrogens developed over the last 10 years. The two parts of the workshop – experimental and therapeutical – are closely linked, since the elucidation of the mechanism of action and of the pharmacokinetics of Honvan is essential to its optimal therapeutic application and since the difficult and expensive task of investigating the pharmacokinetics and mechanism of action is worthwhile only if the therapeutic value of the product for its vital indication is undisputed.

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