CHAPTER I

INTRODUCTION

Background and Rationale

In 1947, aminopterin (Figure 1) was synthesized by Seeger and associates as an analog of folic acid. It appeared that the compound exhibited antagonistic action against folic acid in the growth of culture of Streptococcus faecalis (Lippens, 1984). A short time later, Farber used this drug for the treatment of acute leukemia. A dramatic improvement in the course of the disease was observed in 10 of 16 children affected by acute leukemia (Farber, Diamond, Mercer, Sylvester, and Wolff, 1948). Gubner discovered aminopterin's effect on psoriasis, a non-neoplastic disease of the skin characterized by abnormally rapid proliferation of epidermal cells (Weinstein, 1977).

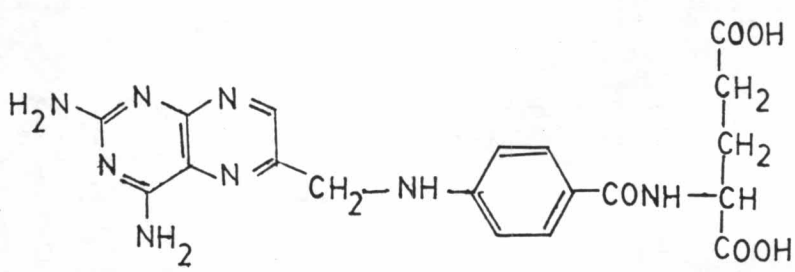

Figure 1. Chemical structure of aminopterin.

Afterwards, aminopterin was replaced in most studies by amoethopterin, which was later called methotrexate (MTX) synthesized by Seeger and his co-workers. Methotrexate could be more purified than aminopterin, it was more stable in vitro, and appeared to be less toxic in patients. Soon methotrexate became preferred over aminopterin (Lippens, 1984). After 20 years of experience, methotrexate was approved by the FDA for the treatment of severe recalcitrant psoriasis (Weinstein, 1977).

Now methotrexate is used widely for acute leukemia, non-Hodgkin's lymphoma, osteogenic sarcoma, choriocarcinoma, small-cell lung carcinoma, head and neck cancer, breast carcinoma, epidermoid carcinoma, and intrathecal chemotherapy. It is also useful in bone marrow tranplantation, rheumatic disease which do not response to other therapies, dermatomyositis, Wegener's granulomatosis, and sarcoidosis (Bleyer, 1978; Frei, Blum, Pitman, Kirkwood, Henderson, Skarin, Mayer, Bast, Garnick, Parker, and Canellos, 1980).

Although methotrexate is useful in the treatment of the diseases as stated before but there has not yet been pharmacokinetic study of methotrexate in Thais. The reason may be that how to determine serum methotrexate concentration which is the first step of the pharmacokinetic study is rather difficult. However, if serum methotrexate concentration of patients were

found out, the patients can be protected from toxicity. Hence, this research was designed to determine serum methotrexate concentration and to study pharmacokinetics of methotrexate in Thai patients suffering from head and neck cancer who did take this medicine. The determination of serum methotrexate level in patients will be also useful in drug monitoring to prevent toxicity.

Objectives

1. To develope the method to determine the concentration of methotrexate in serum samples.

2. To investigate the methotrexate pharmacokinetics after bolus intravenous administration of methotrexate in Thai patients suffering from head and neck cancer.

3. To study the clinical effect of methotrexate in Thai patients suffering from head and neck cancer.

4. To elaborate a practical pharmacokinetic equation for calculating the serum methotrexate level at any times when needed.

Significance of the Study

1. This study will provide the method to determine serum methotrexate concentration.

2. The result will provide the pharmacokinetics

of methotrexate in Thai patients suffering from head and neck cancer.

3. The pharmacokinetic equation for calculating serum methotrexate concentration will be elaborated.

4. The study will help us to know clinical effect of methotrexate in Thai patients suffering from head and neck cancer.

5. Finally, this research will be a study model for other chemotherapeutic agents studies in the future.