CHAPTER I

INTRODUCTION

Background and Rationale

Chloramphenicol (CAP) was the first "broad spectrum" antibiotic, with activity against most gram positive and many gram negative bacteria, anaerobic bacteria and rickettsiae.(1)

Shortly after its introduction, CAP was incriminated as a cause of serious blood dyscrasias, and probably become better known for its undesirable side effects than for its broad spectrum of activity. In 1958 the unique toxic effect of CAP on the newborn infant which came to be known as the "gray baby syndrome", was first recognized, and the use of the antibiotic was curtailed further.(2) The introduction of other broad spectrum antibiotics (primarily ampicillin and the aminoglycosides) in the late 1950s and early 1960s provided attractive alternatives to CAP and reduced its use to a minimum.(1)

A resurgence in use of CAP occurred in the 1970s and can be attributed to several developments. The emergence of ampicillin-risistant Haemophilus influenzae is unquestionably a major factor in reintroduction of CAP to treat childhood meningitis and other serious infections caused by this bacterium. Recent interest in an increased awareness of anaerobic infection have also contributed to an increased use of CAP.(1) Equally important has been the development of better analytical methods to measure the drug, leading to

an improved understanding of the metabolism and excretion of CAP in infants and children.[12,13] This change has stimulated renewed interest in the pharmacology of this antibiotic in infants and children[3] and also allowed the drug to be used effectively and safely for treatment of selected serious infections in all age groups.[1]

The metabolism and elimination of CAP vary widely among patients, and the drug has a relatively narrow therapeutic range. Therefore, it is desirable to monitor peak and trough CAP levels early in the course of therapy and also to monitor for signs of hematopoietic toxicity during therapy.[1]

Recently, peak serum levels achieved following treatment with intravenous CAP were reported to be comparable to the levels obtained after oral administration of the same dose of this drug.[4,5] So it is also interesting to compare the peak serum levels of CAP after various route of administration. (eg: intravenous, intramuscular, and oral)

It is well known that CAP is a toxic drug producing bone marrow and mitochondrial change at concentrations as low as 12 mcg/ml.[7] Gray baby syndrome[6,8] or gray toddler syndrome[9] have occurred with serum concentration greater than 25 mcg/ml. The concentration of CAP required for therapeutic efficacy is dependent on the susceptibility of the infecting organism, serum concentration between 10 and 20 mcg/ml are generally regarded as effective against susceptible pathogen.[3] Therefore, optimal dose should result in serum concentration between 10 and 25 mcg/ml.[6]

Although dosing recommendations for CAP were developed to assure avoidance of dose-related toxicity in most cases, recent studies suggest that the recommended doses may result in lower than expected serum levels

in some patients and greater than desired levels in others.[3,10]

Because of its low cost, CAP is suitable for economic status in developing countries. Thus CAP is widely used in most of the hospitals in Thailand. For example: in Ramathibodi Hospital, 340, 327 and 595 cases of hospitalized patients were treated with CAP in 1978, 1979 and 1980 respectively.[11]

Incidence of adverse drug reaction from CAP varies from country to country. In Thailand, data about serum levels and adverse drug reaction (ADR) of CAP has not been collected and reported elsewhere. Therefore, it is time to study serum levels and ADR from CAP in Thai patients.

Objective

1. To study the indication, dose and duration of treatment of CAP in Ramathibodi Hospital.

2. To determine the types of ADR of CAP in Thai Patients.

3. To find the incidence of each reaction from CAP.

4. To find the factors influence the incidence of ADR.

5. To compare peak serum level of active drug (CAP base) in patients who are treated with three different preparations of CAP. They are intravenous CAP succinate ester (CAP-S), intramuscular and /or intravenous CAP glycinate ester (CAP-G) and oral CAP base.

6. To study CAP levels in cerebrospinal fluid (CSF) and urine.

Materials and Method

The thesis is divided into two parts. They are

1. Retrospective Study

Medical records of all patients who were treated with CAP during hospitalization in the Department of Medicine, Surgery, Gynecology and Pediatrics,Ramathibodi hospital in 1980 were reviewed for evidence of toxicity and side effect of CAP.

2. Prospective Study

This part is concerned with ADR, serum levels, CSF levels and urine levels of CAP.

2.1 The subjects were 33 pediatric patients age varied from 5 months to 13 years.

2.2 Record history and physical examination of each patient.

2.3 Determine peak and trough of CAP levels in patients who were treated with CAP intravenously and/or orally every 7-10 days during the therapy.

2.4 Compare peak and trough CAP serum levels after CAP glycinate (IM or IV) and CAP succinate (IV), administered in 12 patients.

2.5 Determine CAP levels in CSF of meningitis case at 45 to 60 minutes after intravenous administration.

2.6 Measure CAP levels in urine at different time after CAP-S (IV) or CAP base (oral)

2.7 Follow complete blood count (CBC) in patients, treated with CAP more than 2 weeks, every 7-10 days.

2.8 Check liver function and renal function in patients suspected to have liver impairment or renal impairment prior to drug treatment or due to ADR during the therapy.

Significance of the Study

1. If the incidence of ADR from CAP is rarely found, CAP will become very useful in Thailand, because of its safety and low cost.

2. If the factors influencing ADR are exactly known, it will be useful for all physicians to apply this data as a guideline to avoid or minimize toxicity and maintain therapeutic concentration.

3. As we know that CAP-S will give very variable peak serum levels and it must be administered by intravenous only, if CAP-G can be used intramuscularly and provides peak serum levels approximately the same as CAP-S intravenously, it may be used in cases that we want to avoid intravenous injection.

4. Studies of CAP levels in CSF and urine are to reconfirm whether CAP levels in CSF and urine are within the same therapeutic concentration as known in many reports.