CHAPTER V

DISCUSSION AND CONCLUSION

Discussion

Retrospective study showed that CAP was widely used for prophylaxis treatment of anaerobic infection in Ramathibodi Hospital (especially in the department of surgery). It was also widely used in the Department of Pediatrics to treat Haemophilus influenzae meningitis and brain abscess from anaerobic organism, because of its well-penetration into cerebrospinal fluid, and its effective bactericidal activity against Haemophilus influenzae. This evidence agreed with the study of antimicrobial drug usage by Lolekha, S, et al.[11] Eventhough there are several new antimicrobial drugs effective against anaerobic organism at the present time, the popular antibiotics used for these organisms in Ramathibodi Hospital were PGS, CAP. CAP was widely used because of its low cost.

Seven types of ADR were found in restrospective study, but only two of them (gastro-intestinal and hematological side effects), in some patients, were known to be directly caused by CAP treatment. Other ADR were caused by either CAP or other antibiotics. For example; drug fever and rashes occurred when CAP was given with penicillin group antibiotics, thus it was possible that these concomitant agents might be, rather than CAP itself, the cause of drug fever and rashes. Oral moniliasis and fungal UTI were the common superinfection, often occurred when several antibiotics were given for prolonged period of time. Most of bacterias;

included normal flora, were killed by broad spectrum property of these antibiotic combination, while the fungi were not, so superinfection from fungi occurred. Diarrhea frequently occurred when CAP combined with PGS or ampicillin and aminoglycoside antibiotics, the concomitant antibiotics, especially ampicillin, were known to be common cause of diarrhea rather than CAP itself. Since ampicillin was not well absorbed from gastrointestinal tract and little amount of CAP was excreted in bile.

Thrombophlebitis usually occurred in patients who received intravenous infusion for a long period of time, especially in those who were treated with PGS combined with other antibiotics (included CAP) infusion. This ADR was not occurred when CAP was given orally.

Elevated BUN during PGS and CAP treatment, in some patients, may be due to dehydration or increased nitrogen element in food intake, or impaired renal function due to some antibiotics, or interference in laboratory test of nitro group in CAP structure, but the latter was less possible because only little amount of nitro group involved in each dose of CAP. Impaired renal function caused by PGS or CAP was unlikely as well. There were many evidences showed that patients, who devleoped the sign of aminoglycoside nephrotoxicity, could be safely treated with CAP. Inactive CAP (especially unchanged CAP succinate and inactivated metabolites), not active CAP itself, was mostly excreted in urine.

Nausea, vomiting seemed to be the most common ADR directly caused by CAP (table 7), when given in high dose (4g/day) for more

than two weeks. It generally appeared in pediatric and geriatic (50-65 years of age) patients rather than other aged groups. This could be explained that the liver function in infant and children was not yet well-developed. Liver impairment would probably developed in old patients who had drunk alcohol for a long period of time, or those who has other liver diseases. Active CAP could not be metabolized completely by liver enzyme, resulted in a longer half-life CAP and/or high CAP concentration in serum, when high dose of CAP was given for a long period of time.

Hematological side effect seemed to be the ADR caused by CAP, in 2 aged-groups of less than 15 years and 40-60 years, when CAP was treated for more than 2 weeks. Liver impairment, as well as, hematologic abnomalities (such as, slight anemic from iron deficiency, nutrition and hemolysis) might enhance the hematologic effect of CAP in some cases. It infrequently occurred when CAP was treated for a short period. This could be explained by the extended half-life and probably high serum concentration of CAP in liver-impaired patients as well as the abnormality of bone marrow cells in hematologic abnormal patients.

From this study the total incidence of ADR due to CAP was approximately 11.1%. Some of these ADR may be due to other concomitant drugs. Only 1.9% of total studied-patients (2 cases in nausea, vomiting and 4 in hematological side effect) were direct ADR of CAP. The incidences of all ADR in this study were minor and reversible.

In prospective study, comparable peak serum levels were achieved by the studied patients, following the administration of CAP by the IV CAP-S, IV CAP-G, IM CAP-G and oral routes, with mean values of 15.07, 18.2, 16.08, 13.55 mcg/ml respectively.

Pickering et al[71] recently reported higher peak serum CAP levels following intravenous administration as compared to oral administration, although the mean areas under the curves for serum concentration were not significant different. But, in our prospective study, one possible explanation for the lower peak serum levels observed following intravenous CAP-S administration might be the rapid renal excretion of CAP-S[72] so that less drug was available for hepatic hydrolysis to active CAP. However, the time after administration at which the peak values were observed might differ from patient to patient. Peak serum levels after IV administration (CAP-S or CAP-G) were supposed to be at 30 to 45 minutes after completion of the IV infusion. It is possible in our patients and then in a previous study[73], that blood samples obtained earlier than 45 minutes after completion of the infusion showed lower levels of active CAP than these 45 to 60 minutes after completion of the infusion. The reason for this delay in reaching the peak serum level may include the time required for drug equilibrium to be reached, and more importantly, the time required for hepatic hydrolysis of the injected CAP-S ester to the active form of the drug. The peak serum levels following IV CAP-G administration were significantly higher than those following IV CAP-S administration (monitored at the same time), and there was no significant difference of peak serum levels in IV CAP-S

and IM CAP-G; these results suggested that CAP-G may not be hydrolyzed by the same pathway (or enzyme) as in CAP-S. An even longer delay in achieving peak serum levels was observed following oral administration. This appeared to be due to the time required for absorption from gastro-intestinal tract. Kelly et al[74] also reported that CAP was readily absorbed form the gastrointestinal tract and that peak serum levels were usually reached within 2 hours. The data, obtained from our study, also showed that peak serum levels at 2 hours following oral administration compared to the peak serum levels achieved following IV administration, suggesting virtually complete absorption from the gastrointestinal tract.

There was no correlation of serum levels to age of children as well as to period of treatment. Wide interindividual variation in peak serum levels of CAP and lack of corrlation between dose and serum concentration were observed in our study. This observation has also been reported recently by other investigators[10,75]. However, peak serum levels estimates from this study were subject to several sources of error; some of the data were obtained following different dosage forms of CAP, so the difference in rate of hydrolysis of esters might be encountered, the analytic method used was not very sensitive and it could measured only concentration more than 5 mcg/ml of CAP, influence of delayed hydrolysis of CAP succinate (CAP-S) on CAP serum concentration was not considered, and some patients were received liver enzyme inducer (phenobarbital) and/ or antipyretic drug (paracetamol) during the CAP therapy; these 2 medicines might also make change in CAP concentration in serum by drug interaction, as mentioned in chapter II.

Slow prolonged hydrolysis of CAP-S in serum during the dosing interval in some patients also helps explain why serum concentration at the time of peak level in our study produce the level below the desirable range.

In the present study, the average CAP concentration in CSF following IV CAP-S administration was approximately 5 mcg/ml (the number of study was small), this value was similar to those studied by Yogev[5], which trough CSF level was 4.2 mcg/ml, measured exactly before CAP-S was administered. Therefore it was surprising that in our study CAP levels in CSF was measured at ½, 2, 4, 5 hours following IV administration in 3 patients (table 11), were approximately unchanged. CAP level in CSF if possible, should be measured not only at trough level but also at some other times after administration. Therefore, further studies should be performed in future to demonstrate whether there is any significant difference in trough and peak CSF levels, and whether CAP levels in CSF were 35% - 50% of the simultaneous serum levels concentration following oral administration and approximately 50% following IV administration as in other reports[10]. However, emphasis was given to both levels of 4.2 and 5 mcg/ml. The lowest CAP level would exceed the MIC of CAP against most strains of Haemophilus influenzae (MIC = 1.56 mcg/ml) such as; in isolated strain from Yugev's study.[5]

Urine levels of active CAP varied from patient to patient when given in 3 different dosage forms with 3 different route of administration in different patients (table 11). CAP-S (IV) seemed to provide the lowest

active CAP level in urine while CAP-G (IM) seemed to provide the highest level. However the lowest value of active CAP from CAP-S was higher than MIC of most micro-organism. It would be more than enough to treat urinary tract infection. Other studies[3] suggested a significant and variable fraction of the administered dose of CAP-S, excreted unchanged in the urine and was not bioavailable in active form. However, CAP levels in urine from our study were subject to some sources of error; the levels were not measured at the same timing in each patient, and the population was too small. So further studies should be performed to evaluate if the data concerned in this study is significant and if there is significant difference in active CAP level in urine when CAP-S and CAP-G were administered.

The incidences of leukopenia and neutropenia from data in chapter IV (table 13). Demonstrated that bone marrow suppression occurred when CAP was treated for a period of time. Duration of CAP therapy before bone marrow suppression occurred varied from 15 to 78 days, with the average of 38.17 $\pm$ 24.36 days. The peak serum levels were 19.5 to 21.5 mcg/ml before the sign of bone marrow suppression occurred. This data suggested that there was a correlation between bone marrow suppression and duration of treatment. The correlation between bone marrow suppression and serum levels could not be evaluated because of unadequate data, eventhough the peak serum levels tend to rise up higher than desirable range, before bone marrow suppression could be detected. Further studies, should be performed in Thai patients in the future.

Other incidences of ADR; thrombophlebitis and superinfection, occurred in much the same way as in the retrospective study.

The incidence of bone marrow suppression in prospective study was higher than those in retrospective study. Prospective study was done only in children. The incidence of bone marrow suppression seemed to occur in case with impaired liver function. However, aplastic anemia; the severe and irreversible side effect, gray syndrome; ADR of high dose CAP, were not seen in our studies. These unseen ADR can be explained that aplastic anemia is idiosyncratic reaction and is estimated to occur with an incidence of one in 25,000 (0.004%) to one in 100,000 (0.001%) after the use of CAP. It is possible that aplastic anemia cannot be found in small population study. Gray syndrome usually occurred when peak serum levels were very high, about 70 mcg/ml, but our study peak serum levels were not exceeded 40 mcg/ml, therefore gray syndrome could not be found.

Conclusion

Retrospective and prospective studies showed that ADR of CAP seem to be minor and reversible. However, risk and benefit should be considered before using this agent. For example; it should be very useful in serious infection, such as; Haemophilus influenzae meningitis and brain abscess. But it should not be used in mild infection, such as; upper respiratory tract infection, because its ADR is predominant is such case. It should be used in the lowest effective dose for the shortest period of time. It should be used with caution in a patient with a history of previous hematologic abnormalities or impaired liver function.

Monitoring blood levels should be performed, especially in patients with liver impairment in order to minimize toxicity and maintain therapeutic concentrations. It is suggested that serum CAP concentration, as well as reticulocyte count, white blood cells count, platelet count and hemoglobin concentration, should be monitored in patients receiving this agent if therapy is continued beyond 2 weeks. Reticulocyte count, to a much greater extent than the leukocyte count, is a good prognostic criterian for the course of aplastic anemia.

Chloramphenicol glycinate gave higher serum chloramphenicol level than chloramphenicol succinate when both were given intravenously. Moreover chloramphenicol glycinate can be given intramuscularly and give similar serum concentration as intravenous chloramphenicol succinate.