PHARMACOTHERAPY OUTCOMES AND COST EVALUATION OF PAEDIATRIC EPILEPSY IN PENANG HOSPITAL

by

MUHANNAD R. M. SALIH

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DEDICATION

This thesis is lovingly dedicated to my parents, Dr. Riadh Mohammed Salih and Eman Abdullah. Their support, encouragement, and constant love have sustained me throughout my life and always will.

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LIST OF ABBREVIATIONS

ABC	Activity-based costing
AEs	Adverse events
AEDs	Antiepileptic drugs
BP	British pharmacopeia
BTZ	Breakthrough seizure
CAD	Canadian dollar
CBA	Cost-benefit analysis
CEA	Cost-effectiveness analysis
CER	Cost-effectiveness ratio
CMA	Cost-minimisation analysis
CNS	Central nervous system
COI	Cost of illness
CT	Computed tomography
CUA	Cost-utility analysis
DALYs	Disability-adjusted life years
DARR	Dose above the recommended range
EEG	Electroencephalography
FDA	The U.S. Food and Drug Administration
GDD/ID	Global developmental delay/intellectual disability
HYEs	Healthy year equivalents
ICER	Incremental cost-effectiveness ratio
ILAE	International League Against Epilepsy
IMR	Institute for Medical Research
JM	Jururawat Masyarakat
KUB	Kidneys, ureters, and bladder

LIST OF ABBREVIATIONS

MREC	Medical Research Ethics Committee
MRI	Magnetic resonance imaging
NIH	National Institutes of Health
PASW	Predictive Analytics SoftWare
PPK	Pembantu Perawatan Kesihatan
QALYs	Quality-adjusted life years
RM	Ringgit Malaysia
SFDs	Seizure-free days
SPSS	Statistical Package for the Social Sciences
TDM	Therapeutic drug monitoring
UFEME	Urine full examination microscopy elements
U/S	Ultrasound
WHO	World Health Organisation
WHO-ART	WHO Adverse Reaction Terminology
WHO-CHOICE	World Health Organisation through the programme of CHOosing Interventions that are Cost Effective

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PENILAIAN HASIL DAN KOS FARMAKOTERAPI EPILEPSI PEDIATRIK DI HOSPITAL PULAU PINANG

ABSTRAK

Epilepsi, lebih kerap terjadi dalam kalangan kanak-kanak berbanding dengan orang dewasa, dan ia boleh mempunyai kesan kognitif dan sosial yang memudaratkan. Dalam pediatrik, epilepsi biasanya mempunyai kerintangan terhadap drug kerana pembentukan dan perkembangan sebenar epilepsi terbentuk di atas elemen-elemen dan urutan isyarat yang berbeza dengan perkembangan otak. Justeru, epilepsi dalam kalangan kanak-kanak adalah suatu dilema kerana ia tidak boleh dirawat sebagai sebahagian daripada epilepsy dalam kalangan dewasa. Banyak sekali isu yang memberi kesan terhadap penyebab, pengurusan serta hasilan daripada epilepsi di Asia, termasuk faktor-faktor seperti psikososial, budaya, ekonomi, politik dan organisasi. Objektif am kajian ini adalah untuk menilai pengurusan pesakit pediatrik dengan epilepsi berstruktur-metabolisme, dari sudut klinikal dan ekonomi, di Klinik Pesakit Luar Neurologi Pediatrik, Hospital Pulau Pinang, Malaysia.

Bahagian pertama daripada kajian retrospektif membujur ini melibatkan pemerhatian klinikal. Pemerhatian susulan pada kanak-kanak yang terlibat dalam kajian ini dijalankan sehingga satu tahun selepas lawatan pertama. Data yang diperlukan diambil daripada rekod perubatan. Dalam bahagian kedua pula, kajian ekonomi berasaskan prevalens tahunan dijalankan. Kos pengurusan epilepsi dianggar daripada perspektif penyedia (pihak hospital) dengan menggunakan analisis mikrokos bawah-atas, Data bil / carta perubatan (laporan kes) yang diperoleh daripada pihak hospital (penyedia) dikumpul untuk menganggar sumber yang digunakan. Di samping itu, analisis kos-keberkesanan dijalankan untuk menilai kegunaan pemantauan drug

terapeutik, dan drug antiepilepsi (AED) baru sebagai terapi tambahan dalam pengurusan pesakit pediatrik dengan epilepsi berstruktur-metabolisme.

Dalam kalangan kanak-kanak dengan epilepsi berstruktur-metabolisme, bangsa Melayu, perempuan, berumur < 4 tahun, kanak-kanak dengan perkembangan yang lambat / ketidakupayaan intelek, dan pesakit bermanifestasi dengan sawan setempat 'sawan seizure' adalah lebih bergerakbalas terhadap rawatan AED berbanding dengan pesakit sub-kumpulan lain. Tambahan pula, pesakit dengan rawatan politerapi biasanya lebih sukar dan mempunyai kekerapan serangan yang tinggi berbanding dengan mereka yang menjalani rawatan monoterapi. Kadar menggunakan AED dengan dos melebihi dos yang disarankan adalah rendah (hanya 10.83% daripada pesakit). Dari segi kawalan sawan yang lebih baik, penggunaan AED dengan dos melebihi dos yang disarankan tidak menunjukkan sebarang faedah berbanding dengan penggunaan agen tersebut pada dos yang disarankan. Sekitar dua pertiga daripada pesakit mengalami kesan mudarat dalam tempoh susulan. Kadar kesan mudarat hanya berhubung kait dengan umur pesakit.

Pelaksanaan perkhidmatan pemantauan tahap AED serum merupakan suatu wadah berkuasa dalam mengurangkan kekerapan serangan. Walaupun banyak kesan mudarat berkaitan dengan kepekatan didokumenkan dalam fail pesakit oleh pegawai perubatan pelatih atau neurologis pediatrik, namun "Ketoksikan dijangka" tidak pernah dianggap sebagai satu alasan bagi permohonan pemantauan drug terapeutik dalam kajian semasa. " Tahap periksa' dan " Tahap periksa semula" adalah alasan bagi 52% dan 14% daripada permintaan asei, masing-masing. Secara keseluruhannya, terdapat persetujuan di antara saranan ahli farmasi klinikal dengan tindakan neurologis pediatrik terhadap pengurusan terapeutik. Sebahagian besar pemantauan tahap AED adalah sesuai. Dalam perkaitan dengan masa pensampelan,

lebih setengah daripada tahap AED serum diambil dengan betul. Penggunaan AED baru sebagai terapi tambahan secara signifikannya tidak meningkatkan kawalan serangan dalam pesakit yang dikaji.

Perkara yang paling mahal dalam senarai kos adalah AED, sementara pemeriksaan ultrabunyi adalah yang termurah. Kemasukan ke hospital dan drug bukan antiepilepsi adalah item kedua dan ketiga termahal. Kos TDM merupakan sebahagian kecil daripada keseluruhan perbelanjaan tahunan. Akhirnya, kos tahunan keseluruhan daripada pengurusan epilepsi adalah RM 1690.13 bagi setiap pesakit setahun dan ia secara positifnya berkaitan dengan kekerapan serangan.

Analisis peningkatan nisbah kos-keberkesanan bagi kedua-dua langkah pengukuran keberkesanan (iaitu perkadaran pesakit mencecah ≥50% pengurangan dalam kekerapan serangan, dan perkadaran pesakit yang 3 bulan bebas daripada serangan) mendapati pemantauan drug terapeutik adalah perkhidmatan yang paling kos-berkesan. Dengan kata lain, penggunaan AED generasi lama adalah dominan berbanding dengan penggunaan AED baru sebagai terapi tambahan.

PHARMACOTHERAPY OUTCOMES AND COST EVALUATION OF PAEDIATRIC EPILEPSY IN PENANG HOSPITAL

ABSTRACT

Epilepsy is more common in childhood than in adulthood, and it may have destructive cognitive and social effects. In paediatrics, epilepsy is usually drug resistant because the developmental progressions underlying epilepsy build on signalling elements and cascades that are distinctive to the development of the brain. Thus, epilepsy in children is a particular dilemma that cannot be treated as a subset of adult epilepsy. Numerous issues greatly affect the causation, management and outcome of epilepsy in Asia, including psychosocial, cultural, economic, political, and organisational factors. The general objective of this study was to evaluate the management of paediatric patients with structural-metabolic epilepsy. This included both clinical and economical standpoints in the Out-patient Paediatric Neurology Clinic at Hospital Pulau Pinang, Malaysia.

In the first part of this retrospective longitudinal study, an observational clinical evaluation was conducted. The recruited children were followed up for one year after the first visit. The required data were extracted from the medical records. In the second part, an annual prevalence-based economic study was conducted. The total costs of epilepsy management were estimated from the provider (i.e., hospital) perspective, using a bottom-up, microcosting analysis. Medical chart/billing data (i.e., case reports) obtained from the hospital (i.e., provider) were collected to estimate the resources used. In addition, cost-effectiveness analysis was performed to assess the use of therapeutic drug monitoring, and new antiepileptic drugs as add-on

therapies in the management of paediatric patients with structural-metabolic epilepsy.

Among children with structural-metabolic epilepsy, Malays ethnicity, females, patients less than 4 years of age, patients with GDD/ID, and patients manifested with focal seizure are more responsive to AED therapy than other subgroups of patients. Moreover, patients with polytherapy treatment are more complicated and have higher frequency of seizure attacks than those on monotherapy treatment. The rate of using antiepileptic drugs at doses above the recommended range was low (only 10.83% of the patients). In term of better seizure control, uses of antiepileptic drugs at doses above the recommended range shows no benefit over using these agents at the recommended doses. Around two-thirds of the patients experienced adverse events during the follow-up period. The rate of adverse effect was only associated with the patients' age.

The implementation of the monitoring services of serum antiepileptic drug levels found to be as a powerful tool in reducing the patient's seizure frequency. Although many concentration-related adverse effects were documented in the patient's file by the house medical officer or paediatric neurologist, "Suspected toxicity" was never rated as a reason for therapeutic drug monitoring request in the current study. "Check level" and "Recheck level" were the reasons in 52% and 14 % of the requested assays, respectively. By and large, there was a great agreement between the recommendations of clinical pharmacist and the actions of paediatric neurologist toward therapeutic management. An overwhelming proportion of the monitored antiepileptic drug levels were appropriately indicated. In relation to the time of sampling, more than half of the serum antiepileptic drug levels were appropriately

sampled. The use of new antiepileptic drugs as add on therapy did not significantly improve seizure control in the studied patients.

The most expensive item in the costs list was antiepileptic drugs, whereas ultrasound examination represented the cheapest item. Hospitalization and non-antiepileptic drugs were the second and the third most costly items, respectively. The cost of TDM made-up only a small proportion of the total annual expenditure. Ultimately, the total annual cost of epilepsy management was RM 1690.13 per patient per year and it was positively correlated with seizure frequency.

The analysis of incremental cost-effectiveness ratio for both of the effectiveness measures (i.e. the proportion of patients that achieved ≥50% reduction in seizure frequency, and the proportion of patients with 3-months seizure free) found therapeutic drug monitoring to be a cost-effective service. On the other hand, the use of old generation antiepileptic drugs was dominant over the use of new antiepileptic drugs as add on therapy.

CHAPTER ONE: GENERAL INTRODUCTION

1.1 Background

1.1.1 Epidemiology

Epilepsy is a central nervous system (CNS) disorder that is characterized by a continued predisposition to seizures and by their cognitive, neurobiological, social, and psychological consequences (Fisher *et al.*, 2005). The World Health Organisation (WHO) estimates that eight people per 1000 worldwide have epilepsy. Moreover, developing countries exhibit higher prevalence of epilepsy than developed countries (Commission on Tropical Diseases of the International League Against Epilepsy, 1994; Burneo *et al.*, 2005; Preux and Druet-Cabanac, 2005). Even though Asia has experienced considerable economic expansion and development of health services, it is a diverse and resource-constrained continent. More than half of the 50 million epileptic patients worldwide are living in Asia. Although a large number of studies have been conducted in Asia, information regarding the disease burden is limited (Mac *et al.*, 2007).

The prevalence of epilepsy ranges widely among Asian countries, from 1.5 to 14 per 1000 (Li *et al.*, 1985; Aziz *et al.*, 1994; Aziz *et al.*, 1997; Lee *et al.*, 1997; Loh *et al.*, 1997; Su *et al.*, 1997; Mani *et al.*, 1998; Radhakrishnan *et al.*, 2000; Asawavichienjinda *et al.*, 2002; Huang *et al.*, 2002; Ray *et al.*, 2002; Wang *et al.*, 2002; Bharucha, 2003; Fong *et al.*, 2003; Mori, 2003; Rajbhandari, 2003; Wang *et al.*, 2003; Murthy *et al.*, 2004; Cuong *et al.*, 2005; Chen *et al.*, 2006; Rajshekhar *et al.*, 2006; Tran *et al.*, 2006). This broad variation may be partially a consequence of the implementation of different questionnaire styles and/or different study methods (Cuong *et al.*, 2005; Tran *et al.*, 2006). The median prevalence for Asian countries is estimated to be 6 per 1000, which is much lower compared with other developing

countries in different areas of the world (15 per 1000 in sub-Saharan Africa and 18 per 1000 in Latin America (Burneo *et al.*, 2005; Preux and Druet-Cabanac, 2005)).

Information on the incidence of epilepsy in Asia is limited. Only five estimates are available, mainly for China and India (Li *et al.*, 1985; Mani *et al.*, 1998; Sawhney *et al.*, 1999; Ray *et al.*, 2002; Wang *et al.*, 2002). In China, the reported incidence rates were low, from 28.8 per 100,000 person-years (Wang *et al.*, 2002) to 35 per 100,000 person-years in the general population (Li *et al.*, 1985). India has a higher incidence of 60 per 100,000 person-years (Sawhney *et al.*, 1999). On the whole, these rates are not different from the reported results in developed countries, where the incidence of epilepsy is 24-53 per 100,000 person-years (Jallon, 2002).

Demographic characteristics may be driving factors for the incidence and prevalence of the disease. Two peaks ages have been found. Childhood is one of the peak ages for disease incidence (Aziz *et al.*, 1997; Tran *et al.*, 2006), and young adulthood is the other peak age for prevalence (Li *et al.*, 1985; Radhakrishnan *et al.*, 1999; Sridharan and Murthy, 1999; Radhakrishnan *et al.*, 2000; Ng *et al.*, 2001; Fong *et al.*, 2003; Mannan, 2004; Tran *et al.*, 2006). A Chinese study that was conducted in Shanghai illustrated two prevalence age peaks: one between 10 to 30 years old and one in people over 60 years old (Huang *et al.*, 2002). Both the incidence and prevalence of epilepsy in developed countries reflect a bimodal distribution, with a primary peak in childhood and the other peak in old age (Sander *et al.*, 1990; Jallon, 2002; Lim, 2004). The most plausible explanation for the absent peak in the elderly in Asian regions is the younger population compared with that of developed countries (Mac *et al.*, 2007). Generally, Asian male and female prevalence rates of epilepsy are not dramatically different. However, the disease tends to be more common in males than in females (Aziz *et al.*, 1997; Lee *et al.*, 1997; Mani *et al.*,

1998; Sridharan and Murthy, 1999; Ng *et al.*, 2001; Huang *et al.*, 2002; Fong *et al.*, 2003; Rajbhandari, 2003; Tran *et al.*, 2006).

Two Asian studies (in Pakistan and India) found a higher prevalence of epilepsy in rural areas than in urban areas (Aziz *et al.*, 1997; Rajshekhar *et al.*, 2006). Consistently, an Indian meta-analysis study showed the same trend in the prevalence of epilepsy. The prevalence in the rural areas was 5.5 per 1000 compared with 5.1 per 1000 in urban areas (Sridharan and Murthy, 1999). Several clinical studies have been conducted in Asia (some in Malaysia), but few have described the distribution of seizure types in community-based settings. Moreover, the assessment of outcomes from various studies is not easy because the disease classifications are not harmonised (Win, 1993; Loh *et al.*, 1997; Manonmani and Tan, 1999a; Radhakrishnan *et al.*, 2000; Ling Kwong *et al.*, 2001; Ng *et al.*, 2001; Wong, 2001; Fong *et al.*, 2003; Thomas *et al.*, 2005; Tran *et al.*, 2006).

The prevalence rates of idiopathic, cryptogenic and symptomatic epilepsy in Asia were 4-42%, 13-60%, and 22-53% respectively (Manonmani and Tan, 1999a; Ling Kwong *et al.*, 2001; Ng *et al.*, 2001; Wong, 2001; Fong *et al.*, 2003; Tran *et al.*, 2006). The ranges of partial and generalised seizures in Asian epileptic patients were 31-50% and 50-69%, respectively (Loh *et al.*, 1997; Radhakrishnan *et al.*, 2000; Ling Kwong *et al.*, 2001; Tran *et al.*, 2006). The dominance of generalised epilepsy and the broader range of cryptogenic syndrome can be attributed to the dissimilarities in the level of imaging researches and to the clear shortage of standardised classification and terminology in Asian studies. Electroencephalographic information is frequently not obtainable, which could also have affected the prevalence of the idiopathic epilepsy described in a number of studies. The accurateness of the clinical

classification of epilepsy in Asia necessitates population-based studies with electroencephalographic recording (Mac *et al.*, 2007).

1.1.2 Aetiology

The causes of epilepsy in the Asian population appear to be head injury, birth trauma, and intracranial infections. Few publications describe the aetiology of epilepsy, and these are mostly case-control or cohort studies. Usually, head trauma and stroke are the primary causes of epilepsy in areas of higher socioeconomic development (Li *et al.*, 1985; Rajbhandari, 2003; Hui and Kwan, 2004; Shichuo *et al.*, 2004).

Posttraumatic epilepsy is considered to be one of the most important complications of head injury in Asia. In fact, it may account for 5% of total epilepsy, and 20% of symptomatic epilepsy results from head injuries (Shichuo *et al.*, 2004). In other parts of the world, in developing countries such as those in Latin America or sub-Saharan Africa, the high level prevalence of epilepsy may be due to CNS infections. A number of diseases have been listed by The Commission on Tropical Diseases of The International League Against Epilepsy as being causes of epilepsy, including malaria, tuberculosis, schistosomiasis, acquired immunodeficiency syndrome, and cysticercosis, but the commonest cause of epilepsy appears to be cysticercosis (Commission on Tropical Diseases of the International League Against Epilepsy, 1994).

Several studies in Latin America (Brutto *et al.*, 2005; Garcia and Del Brutto, 2005) and Africa (Preux and Druet-Cabanac, 2005) showed a correlation between neurocysticercosis and epilepsy. Some studies reported that the cause of half of the epilepsy cases was neurocysticercosis (Kamgno *et al.*, 2003; Rajshekhar *et al.*,

2003), and seizures occurred in the majority of patients with parenchymal cysticercosis (Rajshekhar *et al.*, 2003). Although several studies described the existence of cysticercosis in Asia (Veliath *et al.*, 1985; Theis *et al.*, 1994; Chung and Chi, 1998; Kuruvilla *et al.*, 2001; Erhart *et al.*, 2002; Ito *et al.*, 2003; Rajshekhar *et al.*, 2003; Willingham *et al.*, 2003; Dorny *et al.*, 2004; Joshi *et al.*, 2004; Rajshekhar, 2004; Yindan *et al.*, 2004), only a small number of studies have been conducted to examine the association between neurocysticercosis and epilepsy. Neurocysticercosis is almost certainly an imperative cause of seizures and epilepsy in areas with a high prevalence of taenia solium infection. The high prevalence is present in several Asian countries: India, Vietnam, China, Bali, Papua, and Sulawesi in Indonesia. Cysticercosis is almost never identified in highly developed Asian countries such as South Korea (Chung and Chi, 1998).

Paragonimiasis is common in several Asian countries: Vietnam, the Philippines, China, Japan, and South Korea (Tran *et al.*, 2004; Strobel *et al.*, 2005). Through migration, the lung fluke may reach the brain and cause various neurological syndromes including seizures and epilepsy (Higashi *et al.*, 1971; Kaw and Sitoh, 2001; Choo *et al.*, 2003). Nevertheless, no research has measured the significance of paragonimus infection in epilepsy.

In Asia, malaria an endemic infectious disease, with over 3 million cases per year. Cambodia, Pakistan, Burma, India, Indonesia, Papua New Guinea, and Bangladesh each have more than 50,000 cases per year (Malaria, 2005). In Thailand, a retrospective survey of patients with childhood malaria (irrespective of the existence of cerebral malaria) found that 7.7% of the patients had convulsions (Wattanagoon *et al.*, 1994). In another study, 60% of 104 cases with cerebral malaria had developed convulsions (Faiz *et al.*, 1998). Nevertheless, no systematic studies have described

the relationship between malaria and epilepsy in Asia. However, this link was recently supported by a case-control study in Gabon and a cohort study in Mali in Africa (Ngoungou *et al.*, 2006a; Ngoungou *et al.*, 2006b).

Japanese encephalitis is another endemic disorder that has several consequences, including seizures and epilepsy. A large part of China, the Indian subcontinent, and Southeast Asia are affected (Solomon *et al.*, 2000). Two-thirds of Japanese encephalitis patients experience acute symptomatic seizures, and 13% of them develop chronic epilepsy (Murthy, 2003).

1.1.3 Genetic aspects

In India, two studies have illustrated that there is no association between being a twin and having epilepsy. The twins of an individual with epilepsy was not at a significantly increased risk of epilepsy (Jain *et al.*, 1999; Sharma, 2005). Although some Chinese studies showed no significant association between susceptibility genes and epilepsy (Chen *et al.*, 2003a; Chen *et al.*, 2003b; Lu *et al.*, 2003; Ren *et al.*, 2005), some other studies have suggested that familial history of epilepsy and parental consanguinity may be risk factors. In two different Indian studies, familial history of epilepsy was two to three times higher among epileptic patients than among controls (Sawhney *et al.*, 1999; Nair and Thomas, 2004). This results was consistent with the findings of two other epileptic studies in China and Laos (Zeng *et al.*, 2003; Tran *et al.*, 2006). This degree of risk was similar to that of studies from Africa (Preux and Druet-Cabanac, 2005).

Consanguineous marriage is popular in certain Asian societies, particularly among Muslim and Indian people. Parental consanguinity is more common among patients than among controls (Nair and Thomas, 2004). Another study on epileptic patients of

Indian origin in Malaysia demonstrated that about one-third had a parental consanguineous marriage and that there was a significant association between parental consanguinity and two types of epilepsy (idiopathic and cryptogenic epilepsy) (Ramasundrum and Tan, 2004). Consanguinity could therefore be targeted for prevention of epilepsy.

1.1.4 Epilepsy management

There is wide variability in the management of epilepsy in different regions. In Asia, this variability might be attributed to many factors such as economic situation, quality of health care, and secondary services, rural or urban habitation, and the cultural frameworks of societies (Tan and Lim, 1997; Scott *et al.*, 2001). Based on the WHO Atlas Epilepsy Care (World Health Organization. International Bureau for Epilepsy. International League Against Epilepsy, 2005), the median number of hospital beds devoted to epilepsy management per 100,000 population is extremely small in Asia: 0.05 in Southeast Asia and 0.46 in the western Pacific; these figures are lower than those in Africa (0.55) and far lower than those in Europe (1.65).

Likewise, the majority of Asian countries have a very low number of neurologists. In 2004, WHO found that there was less than one neurologist per million residents in India, Laos, and Bangladesh. However, Japan had a range of one to 50 neurologists per million people (World Health Organization, 2004; World Health Organization. International Bureau for Epilepsy. International League Against Epilepsy, 2005).

In Asia, technologies that are used in the diagnosis of epilepsy, such as electroencephalography (EEG), computed tomography (CT), and magnetic resonance imaging (MRI), are generally available. However, different geographical areas may exhibit various degrees of accessibility. In countries like Japan, South Korea,

Singapore, and Taiwan, which are considered to be more developed economic regions, high qua medical services are highly accessible and obtainable for most of the population. By contrast, in other countries such as Cambodia, East Timor, Laos, or Mongolia, facilities for EEG, MRI, or CT are mostly unavailable (Tan and Lim, 1997).

Antiepileptic drugs (AEDs) are the easiest and most harmless way to manage epilepsy. In Asia, a range of old-generation AEDs (phenobarbital, carbamazepine, valproic acid, phenytoin, clonazepam, ethosuximide, and primidone) is commonly used. The exact agent used depends on the therapeutic society and observation in each country (International League Against Epilepsy, 1985; Chen *et al.*, 2000b; Thomas *et al.*, 2001; Seneviratne *et al.*, 2002; Liu *et al.*, 2003; Rajbhandari, 2003; Silpakit and Silpakit, 2003; Gunawan, 2004; Hui and Kwan, 2004; Kariyawasam *et al.*, 2004; Krishnan *et al.*, 2004; Lim, 2004). New generation AEDs, such as topiramate, lamotrigine, vigabatrin, gabapentin, tiagabine, or felbamate, are commonly used in Singapore, Malaysia, China, and in a few of the less urbanised countries such as the Philippines and Vietnam (Nassiri and Stelmasiak, 2000; Epilepsy, 2004).

There is a wide range of drugs accessibility across Asia depending on the cultural framework (level of development, urbanisation, etc). Nonetheless, accessibility is most likely to be easier in Asia than in Africa (Mac *et al.*, 2007). Subsidisation of AEDs appears to be quite limited or not available for most parts of Asia. Even for the most popular old-generation AEDs, families or patients pay out of pocket and in some instances beyond their means. For example, the annual expenses of one of the cheapest antiepileptic agents (i.e. phenobarbital) are approximately US $30 in Laos, which is equivalent to the monthly income of a school-teacher. Consequently, not all

patients can have long-term therapeutic management if it is not supported or subsidised (Mac *et al.*, 2007). In one Indian study, the average yearly expenditure (direct and indirect) of out-patient management of epilepsy is US $47 per patient. Moreover, the yearly cost for all patients undergoing emergency and inpatient management at a secondary hospital is estimated to be US $810.50 and US $168.30, respectively. Overall, the loss of productivity was much higher than the cost of treatment, and it would be worthy for governments or societies to monopolize in epilepsy management (Krishnan *et al.*, 2004).

1.1.5 Treatment gap

The International League Against Epilepsy (ILAE) held a workshop and gave a clear definition for the term "seizure treatment gap", which was "the difference between the number of people with active epilepsy and the number whose seizures are being appropriately treated in a given population at a given point of time, expressed as a percentage". Active epilepsy is defined as "two or more unprovoked epileptic seizures on different days in the prior year that are disabling to the individual" (Meinardi *et al.*, 2001; Scott *et al.*, 2001). Ninety percent of patients with epilepsy in sub-Saharan Africa and Latin America receive insufficient treatment or no treatment by any means (Shorvon and Farmer, 1988; Anonymous, 1997b; Scott *et al.*, 2001). On the other hand, the treatment gap in Asia was 29-98%, with the ranging value of 50 to 80% in most countries. The rural areas illustrated a higher seizure treatment gap than urban areas. The shortage of AEDs and the lack of epileptic knowledge influence the treatment gap in rural areas (Bharucha *et al.*, 1988; Koul *et al.*, 1988; Aziz *et al.*, 1994; Aziz *et al.*, 1997; Mani, 1997; Pal, 1999; Sridharan and Murthy, 1999; Radhakrishnan *et al.*, 2000; Ray *et al.*, 2002; Wang *et al.*, 2002; Gourie Devi *et al.*, 2003; Wang *et al.*, 2003; Rajbhandari, 2004; Bharucha NE *et al.*, July 1997).

In conclusion, there is a range of biological diversity in epilepsy across Asia and the western countries; in particular, epilepsy affects those of a young average age and lesser physique among Asian countries. Climatic distinctions, such as those reflected in the elevated prevalence of Japanese encephalitis and malaria, remain sources of acute symptomatic seizures in several regions of Asia. Numerous issues greatly affect the causation, management and outcome of epilepsy in Asia, including psychosocial, cultural, economic, political, and organisational factors. As a consequence, the precedence should be set for these issues in research to pick up epilepsy care in Asia (Chong-Tin, 2007; Mac *et al.*, 2007).

1.1.6 Underlying type of cause

the ILAE replaced the old terms idiopathic, symptomatic, and cryptogenic with modified conceptual terms genetic, structural–metabolic, and unknown (Berg *et al.*, 2010). Genetic epilepsy is directly resulted of an identified genetic defect(s), in which seizures are the core symptom of the disorder. In structural-metabolic epilepsy there is an apparent structural or metabolic disease. Structural lesions may results from trauma, stroke, and infection or it might be of genetic origin (e.g., tuberous sclerosis). In "unknown" cases, so far, the nature of the underlying cause is unidentified.

1.2 Problem statement

A logical strategy for childhood epilepsy care obliges the scientific realisation that the various types of seizures may occur at diverse age strata and have a variety of primary causes. It is difficult to define a specific type of AEDs for these patients. For decades, epilepsy therapeutic management has been restricted to the use of several agents that are considered the old generation AEDs: phenytoin, phenobarbital,

carbamazepine, sodium valproate, primidone, and ethosuximide. Whilst the clinical application and therapeutic implementation of these different AEDs are well recognised in adult patients, these drugs are not often applicable to the seizure and epilepsy care in children. In addition to the accurate selection of the AED, physicians also must keep in mind the potential effects of the chosen AED on the biological and psychosocial development of the child patient (Rahman *et al.*, 2005).

The most desirable outcome in the utilisation of AEDs is for patients to be free of seizures for the rest of their lives, but many different aspects govern the outcomes of AEDs treatment in the paediatric population: the recognition of underlying causes, the type of seizures, selection, dosing and monitoring of AEDs, and the pharmacokinetic parameters of AEDs. Each of these is necessary for successful management; however, there is a scarcity of duly-performed outcome-based studies in childhood epileptic patients.

The present AED expansion structure fundamentally renders children with epilepsy "therapeutic orphans". This is obviously seen in children with severe persistent epilepsy syndrome, a disease that does not occur in adults. Consequently, such children can only hope that through chance their diseases will gain from the therapeutic improvement projected in adult patients with partial epilepsy (Trevathan, 2003). Accordingly, the clinical application and therapeutic use of AEDs are better documented and standardised in adults than in children (Hasan *et al.*, 2010).

This revolutionisation in the treatment and the new focus on cost restraint and care management are raising the attention towards the economic features of epilepsy. Cost estimates are increasingly needed by government payers, insurance companies, and others groups that are attentive to the allotment of limited research and treatment

dollars. These cost estimates are required to show the cost of having epilepsy and to detail the assortment of features that assign the distribution of the burden across the population. Cost-effectiveness analysis (CEA) and cost-benefit analysis (CBA) are considered necessary for the assessment of health services and new treatments (Begley *et al.*, 1999b).

1.3 Rationale of the study

Whilst the types and number of AEDs are expanding, the management of epilepsy (mostly childhood epilepsy) remains a challenge. Seizure episodes affect 25% or more of the paediatric population with childhood epilepsy (White, 1997). Amongst children up to 16 years of age, approximately 4 to 10% experience at least one seizure. In epidemiology terms, research suggests that approximately 150,000 children will suffer a first-time unprovoked seizure each year, and of those, 30,000 will manifest epilepsy (McAbee and Wark, 2000).

The aim of using AEDs in treating epilepsy is to eliminate seizures without side effects (Perucca, 1996b; Guberman A and Bruni J, 1999). A considerable number of patients with epilepsy are still unable to attain this aim, even with the introduction of the new generation of AEDs (Brodie and Dichter, 1996; Mattson *et al.*, 1996). There are various rationales for this quandary, including, the wrong identification of seizure type and subsequent inaccurate AED selection, inter-patient variations in dose-response and AED tolerability, inconsistent degrees of adherence with prescribed treatment, flawed approaches in regulating medication (Duncan JS, 1996; Devinsky, 1999), and incorrect utilisation of therapeutic drug monitoring (TDM) service (e.g., misinterpretation) (Dodson, 1989; Commission on Antiepileptic Drugs. International League Against Epilepsy, 1993).

The present need for cost realisation in the context of health has called for the financial appraisal of health care services and facilities as well as pharmaceuticals to recognise those drugs which are worth the most money in caring for patients. Hence, for situations in which a number of competing drugs or amenities are present, economic analyses compare the expenditure and outcomes of treatment with services or drugs are being the criterion. In epilepsy, the establishment of TDM services and the introduction of new AEDs have also motivated economic analyses to balance the costs to outcomes. Wherever better effectiveness cannot be revealed, economic evaluations must quantify the resource implications of differing adverse-event profiles to evaluate the rationalisation for higher prices (Shakespeare and Simeon, 1998).

1.4 Significance of the study

Epilepsy is more common in childhood than in adulthood, and it may have destructive cognitive and social effects. In paediatrics, epilepsy is usually drug resistant because the developmental progressions underlying epilepsy build on signalling elements and cascades that are distinctive to the development of the brain (Ben-Ari and Holmes, 2006). Thus, epilepsy in children is a particular dilemma that cannot be treated as a subset of adult epilepsy.

The clinical findings of this study will provide the fundamental basis for health professionals to understand the logical and the appropriate utilisation of health services (e.g., TDM) in the management of childhood epilepsy in Malaysia. Moreover, these results will clarify the picture for the implementation of a new generation of AEDs as adjuvant. Consequently, the study outcomes will lead to better patient care, optimise seizure control, enhance patient quality of life, avoid

possible adverse effects and preserve the patient aptitude in conducting daily activities.

In health economics, the research is a financial appraisal, and it gives the facts of the prospective outlays and interests of health care interferences. In epilepsy, such investigations are still in their infancy, and there is an urgent call for such studies in such areas, for example, the awareness that incorrect use of a service (e.g., TDM) may result in intolerable waste of funds (Bussey and Hoffman, 1983; Chadwick, 1987; Hallworth, 1988) and even harm to patient health (Beardsley *et al.*, 1983a; Woo *et al.*, 1988; Jackson *et al.*, 1994). Likewise, expensive new AEDs are gaining popularity, and economic assessment is essential, which should counts on measures of social rehabilitation as well as seizure frequency, which is presently the standard outcome measure (Cockerell *et al.*, 1994). Hence, the results of this study will highlight the significance of optimising seizure control as a way to reduce the costs of epilepsy, not only for the hospital, but also for society.

1.5 Study objectives

The objective of this study was to evaluate the management of paediatric patients with structural-metabolic epilepsy. This included both clinical and economical standpoints in the Out-Patient Paediatric Neurology Clinic at Hospital Pulau Pinang, Malaysia.

1.6 Thesis overview

Chapter 2 describes the clinical evaluation method and its findings for assessing the actual medical practice in the management of epilepsy at the Out-Patient Paediatric Neurology Clinic in Hospital Pulau Pinang, Malaysia. The chapter details the impact

of implementing TDM services on clinical seizure outcomes. Additionally, this chapter describes the paediatricians' adherence to the TDM recommendations. In relation to the above, the assessment of the appropriateness of the determination of serum levels of AEDs is explained as well. Furthermore, the drug utilisation patterns of AEDs prescribed for the management of different types of epilepsy and the evaluation of clinical outcomes for both generations (old and new) of AEDs in paediatric population are examined.

In Chapter 3, a comprehensive demonstration is written regarding the designation and implementation of a cost methodology through the process of patient care to calculate the unit costs of each service or activity that was utilised by the studied patients, starting from the paediatric neurology clinic to the rest of the other departments in the hospital, including the pathology department, radiology department, neurology clinic, and pharmacy department.

Chapter 4 illustrates a number of CEA on the basis of information on the proportion of patients that achieved ≥50% reduction in seizure frequency, and the proportion of patients with 3 months seizure free. The chapter comprises two major sections. The first section includes the CEA of utilising TDM services. The second section demonstrates valuable comparisons of the use of new generation AEDs as adjuvant therapies versus old generation alone.

Chapter 5, the last chapter, contains concludes with a general summary of the study findings and limitations together with a set of recommendations for further work.

CHAPTER TWO: CLINICAL EVALUATION

2.1 Introduction

2.1.1 Therapeutic drug monitoring

2.1.1.1 Background and historical introduction

Until the 1960s, trial and error was the most common scenario for drug management (Barr, 1985; Robinson and Taylor, 1986). Even though the guiding principles were usually obtainable and believable to be efficient and safe, majority of practitioners implement dosing in an empirical approach. Doses were frequently started at low ranges and increased gradually until an improvement is achieved or, in spite of the guidelines, toxic effects manifested. Characteristically, over 50% of the adverse drug reactions in main teaching hospitals in the 1960s were precipitated by doses that were too high for the patients (Koch-Weser *et al.*, 1969). Recognising that several early studies in the 1950s (Sokolow and Edgar, 1950; Talbott, 1950; Geraci *et al.*, 1956; Buchthal *et al.*, 1960) had proposed that a serum concentration of a drug could be utilised to identify pharmacokinetic variations among different patients as well as to steer responses to therapy; for those reasons, researchers were concerned to develop this work to enhance drug effectiveness and safety.

With the realisation that standard dosage regimens resulted in unreliable patient outcomes, health professionals required a more systematic training about the application of scientific technology to shape drug treatment designed for the individual patients. These requirements encourage researchers to find analytical facilities that can more precisely describe the pharmacokinetic characteristics and therapeutic serum concentration ranges of the drugs. Hence, at the end of the 1960s, some initial studies were published on identifying pharmacokinetic parameters and

therapeutic serum concentration ranges for a number of drugs including antibiotics, antiepileptics, cardiac drugs, and bronchodilators (Smith *et al.*, 1969; Harrison *et al.*, 1970; Beller *et al.*, 1971; Koch-Weser and Klein, 1971; Jelliffe *et al.*, 1972; Jenne *et al.*, 1972; Lund, 1972; Ogilvie and Ruedy, 1972; Mitenko and Ogilvie, 1973; Koch-Weser *et al.*, 1974; Noone *et al.*, 1974).

Thus, the last three decades showed an obvious growth in the concept of TDM, especially in the area of pharmacokinetics and pharmacodynamics research. This development was related to the combination of interrelating and jointly strengthening pharmacokinetics and pharmacodynamics issues (Barr, 1985). Optimising drug therapy was the main goal of applying clinical pharmacokinetics and pharmacodynamics principles. The optimisation included minimising the probability of drug toxicity and maximising the benefits of achieving the desired therapeutic effect, particularly in the instances where the blood concentration of the drug could be a better predictor of the desired effect(s). Therefore, increased efficacy without unacceptable toxicity or reduced toxicity without compromising efficacy may justify the use of the principles of pharmacokinetics and pharmacodynamics to improve the clinical outcome and drug therapy. However, TDM has minimal benefit for drugs with a wide therapeutic index (i.e., drugs that do not exhibit toxicity at serum concentrations or doses required for therapeutic effect) (Michael E. Burton *et al.*, 2006).

In the 1970s and early 1980s, the extensive exploration and application of TDM occurred secondary to the increase in the interest and enthusiasm in the therapeutic serum drug range. In addition, physicians had a strong interest in monitoring more of their patients; in effect, pharmacists were given a great chance to have a real contribution in drug treatment. Pharmacists by training, have a better understanding

of drug serum concentrations, dosage adjustment calculations, and general drug monitoring. In addition pharmacists also have the eagerness and accessibility for TDM contribution, supported by the growing acceptance of the expanded responsibilities for pharmacists by other health care providers. Moreover, manufacturers of laboratory equipment were also competing to produce a faster and more precise analytic technology, ensuring nearly a 500-fold expansion in the TDM products in the last 25 years. By contrast, some researchers were queried to the development of TDM and to the question of whether its value had been exaggerated (Sjoqvist, 1985; Spector *et al.*, 1988; McInnes, 1989).

2.1.1.2 Rationale for monitoring serum concentrations of AEDs

Dose individualisation is considered to be an important element in the management of epilepsy. However, the recognition of the optimal dose solely based on clinical judgment can be complicated or tricky. There are three justifications for this. First, in view of the fact that AED therapy is prophylactic and seizures may arise at irregular periods of time, it is not usually easy to promptly determine whether the arranged dose will be satisfactory to generate long-term seizure control. Second, it is difficult to discriminate the clinical signs and symptoms of toxicity from the manifestation of causal disorders. Third, there are no obvious laboratory indicators for clinical efficiency for the most general manifestations of AED toxicity, for example, CNS adverse drug effects (Patsalos *et al.*, 2008).

The value of TDM service often shows a degree of discrepancies among different AEDs, and the value relies on their pharmacological characteristics. However, the epilepsy-interrelated grounds and certainly the indications for TDM are analogous for all AEDs. TDM is expected to be of particular importance for AEDs that display

obvious intra- or interindividual variability in pharmacokinetics. Regardless of the disparity in pharmacological properties of different monitored drugs, TDM is also likely to be useful in determining drug compliance, in pointing out toxicities to drug therapy, and in managing overdoses and drug interactions (Eadie, 1998; Patsalos *et al.*, 2008).

2.1.1.3 Monitoring free drug concentrations

Serum or plasma is deemed to be the best mediums for TDM in which the concentration may be monitored. Both biospecimen can be used interchangeably; however, in terms of consistency, it is better to use one or the other (Patsalos *et al.*, 2008). Saliva is a matrix of restrictedly rising usefulness for some AEDs. In the majority of clinical situations, the monitoring of total serum concentrations are sufficient; undeniably, the most regular technique for measuring AEDs in sera do not differentiate between the elements of the monitored drug that is free (unbound) and that is bound to serum or plasma proteins (Eadie, 1998; Patsalos *et al.*, 2008).

Nevertheless, because only the free drug exists to shift across the blood-brain barrier where the pharmacological effect will occur, in specific clinical situations whereby the extent of protein binding is changing, patient therapy with AEDs would be most appropriately tailored based on free serum concentrations (Eadie, 1998; Patsalos *et al.*, 2008; Salih *et al.*, 2010).

Different clinical settings may exhibit alterations in the plasma protein binding of AEDs, including hypoalbuminemia (patients with burns, old age, pregnancy, acquired immunodeficiency syndrome, etc.) (Levine and Chang, 1990; Fedler and Stewart, 1999); patients with uremia (Peterson *et al.*, 1991); drug-drug interactions; displacement of the drug from its plasma protein binding by another drug (Kilpatrick

et al., 1984; Burt *et al.*, 2000); and patients with chronic liver disease (Dasgupta, 2007).

In some situations, monitoring of total serum concentrations may be unreliable. This is typically observed when the free fraction of the AEDs increases. As a consequence, the therapeutic and toxic effects will be seen at total drug concentrations that are lower than usual (Perucca *et al.*, 1981; Barre *et al.*, 1988; Salih *et al.*, 2010).

On the whole, drugs that highly bind to plasma proteins (Table 2.1) are the most vital candidates for monitoring free drug concentrations because the variation in protein binding creates a clinically noteworthy effect in changing the free drug concentrations. However, free drug concentrations of old generation AEDs, such as phenytoin, valproic acid, and carbamazepine are still the most requested by clinicians (Perucca, 1984; Dasgupta, 2007; Patsalos *et al.*, 2008; Salih *et al.*, 2010).

Table 2.1: Pharmacokinetic parameters of the most commonly used antiepileptic drugs (Patsalos *et al.*, 2008)

Drug	Oral bioavailability (%)	Serum protein binding (%)	Time to peak concentration (h)	Time to steady-state[l] (days)	Half-life in the absence of interacting comedication (h)	Half-life in patients comedicated with enzyme inducers (h)	Comment	Reference range (mg/L)
Carbamazepine	≤85	75	2–9[a]	2–4[b]	8–20[b]	5–12[b]	Active 10,11 epoxide metabolite contributes to clinical effects	4–12
Clobazam	≥95	85	1–3	7–10[c]	10–30	?	Active N-desmethyl-metabolite contributes to clinical effects	0.03–0.3 (clobazam) 0.3–3 (desmethyl metabolite)
Clonazepam	≥95	85	1–4	3–10	17–56	11–35	7-amino metabolite retains some pharmacological activity	0.02–0.07
Ethosuximide	≥90	0	1–4	7–10	40–60	20–40		40–100
Felbamate	>90	25	2–6	3–4	16–22	10–18		30–60
Gabapentin	<60[d]	0	2–3	1–2	5–9	5–9		2–20
Lamotrigine	≥95	55	1–3[a]	3–6 (5–15 with valproic acid comedication)	15–35 (30–90 with valproic acid comedication)	8–20 (15–35 with valproic acid comedication)		2.5–15

Table 2.1: Continued

Drug	Oral bioavailability (%)	Serum protein binding (%)	Time to peak concentration (h)	Time to steady-state[l] (days)	Half-life in the absence of interacting comedication (h)	Half-life in patients comedicated with enzyme inducers (h)	Comment	Reference range (mg/L)
Levetiracetam	≥95	0	1	1–2	6–8	5–7		12–46
Oxcarbazepine	90[e]	40[e]	3–6[e]	2–3[e]	8–15[e]	7–12[e]		3–35[e]
Phenobarbital	≥95	55	0.5–4	12–24	70–140	70–140		10–40
Phenytoin	≥80[f]	90	1–12[f]	5–17	30–100[g]	30–100[g]		10–20
Pregabalin	≥90	0	1–2	1–2	5–7	5–7		?[h]
Primidone	≥90	10	2–5	2–4	7–22	3–12	Metabolically derived phenobarbital contributes largely to clinical effects	5–10[i]
Tiagabine	≥90	96	0.5–2	1–2	5–9	2–4		0.02–0.2
Topiramate	≥80	15	2–4	4–5	20–30	10–15		5–20
Valproic acid	≥90	90[j]	3–6[k]	2–4	11–20	6–12		50–100
Vigabatrin	≥60	0	1–2	1–2	5–8	5–8		0.8–36
Zonisamide	≥65	50	2–5	9–12	50–70	25–35		10–40

Table 2.1: Continued

[a]Immediate-release tablets; [b]at the initiation of treatment, time to reach steady-state may be up to 5 weeks due to autoinduction. Reported half-lifes refer to patients on chronic therapy (half-lifes are considerably longer after a single dose); [c]includes time to steady state for active metabolite N-desmethyl-clobazam; [d]bioavailability decreases with increasing dosages; [e]pharmacokinetic parameters, reference range and conversion factor refer to the active mono-hydroxy-derivative (MHD) metabolite; [f] bioavailability and rate of absorption depends on formulation; [g]elimination is not first order, and half-life increases with increasing serum concentration; [h]not established; [i]phenobarbital concentrations should also be monitored; [j]fraction bound to serum proteins decreases with increasing drug concentration; [k]enteric-coated tablets ingested in a fasting state; [l]these values are based on half-life values in the absence of interacting comedication.