ORIGINAL ARTICLE

PROSPECTIVE STUDY OF ADVERSE REACTIONS OF ANTIEPILEPTIC DRUGS IN THAI OUTPATIENTS

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SUMMARY

Adverse reactions of antiepileptic drugs were being monitored prospectively in 560 outpatients (52.9% male) suffering from convulsive disorders in two major Bangkok Metropolitan hospitals. The patients were interviewed by trained observers using an open-ended question and a check list of known adverse reactions at least twice after receiving the drugs. Patients' medical records were also reviewed. Six different anti-epileptic drugs were being prescribed in the descending order : phenobarbital (42.5%), phenytoin (38.8%), carbamazepine (8.6%), clonazepam (6.4%), primidone (3.0%), and sodium valproate (0.7%). Nineteen percents of the patients reported some adverse effects of which 25% were sedation. Other adverse reactions were also related to central nervous system e.g. dizziness drowsiness,headache. No serious adverse effects were noted.

Epilepsy is a collective designation for a group of chronic central nervous system disorders having in common the occurrence of sudden and transitory episodes of abnormal phenomena of motor, sensory, autonomic or psychic origin (1). The ideal antiepileptic drug would obviously suppress all seizure without causing any unwanted effects. Unfortunately, the drugs used currently not only fail to control seizure activity in some patients, but they frequently cause a considerable array of adverse effects that range in severity from minimal impairment of the central nervous system to death from aplastic anemia (1).

As far as we know, comprehensive prospective surveillance programs to determine the incidence and severity of adverse reactions of antiepileptic drugs in outpatient populations have not yet been conducted in Thailand. The outpatients setting would be a better representative of the

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general population. Patients frequently do not follow direction carefully, so that overdose toxicity may result from the intake of much larger amounts of drugs than have been prescribed. The prospective nature of the study should provide more accurate data on adverse drug reactions than the retrospective studies.

MATERIALS AND METHODS

All patients in this study were outpatients visiting a medical clinic at the Outpatient Departments of Ramathibodi and Prasart Neurological Hospitals during July 1-November 30, 1983. The drugs used were prescribed by specialists at standard doses. The patients were interviewed by the trained observers at least twice after receiving the drugs. The questions being asked were both open-ended questions and a check list of possible adverse effects. All patients were free of cancer diseases and psychiatric problems. The patients who were seriously ill and unable to communicate were excluded.

Adverse drug reactions noted in this study were classified according to the criteria suggested by Irey (2).

Definite - a reaction which follows a reasonable temporal sequence from administration of the drug : which follows a known response pattern to the suspected drug. This reaction can be confirmed by improvement on stopping the drug (de-challenge); and reappearance of the reaction on repeated exposure (re-challenge).

Probable - a reaction which follows a reasonable temporal sequence from administration of the drug : which follows a known response pattern to the suspected drug. This reaction could be confirmed by de-challenge and could not be reasonably explained by the known characteristics of the patient's clinical state.

Possible - a reaction which follows a reasonable temporal sequence from administration of the drug : which follows a known response pattern to the suspected drug. This reaction could have been produced by the patient's clinical state or other modes of therapy administered to the patient.

Conditional - a reaction which follows a reasonable temporal sequence from administration of the drug : which dose not follow a known response pattern to the suspected drug. This reaction could not be reasonably explained by the known characteristics of the patient's clinical state. The function of this category is to retain temporarily those cases which may be manifesting a yet undescribed adverse drug reaction and allow later reclassification of the case when more information becomes available. This category prevents the loss of previously unsuspected drug reactions and help identify new adverse drug reactions.

Doubtful - any reaction which dose not meet the criteria above.

The severity of adverse drug reactions was classified according to Schimmel (3).

Minor adverse drug reaction - if the clinical manifestation was short and no specific treatment is needed.

Moderate adverse drug reaction - if the specific treatment were given or caused prolongation of hospitalization.

Table 1 Age and sex distribution.

Age(years)	Male		Female		Total	
	Number	%	Number	%	Number	%
15-20	76	25.7	68	25.7	144	25.7
21-30	120	40.5	85	32.2	205	36.6
31-40	56	18.9	73	27.6	129	23.0
41-50	23	7.8	16	6.1	39	7.0
51-60	11	3.7	15	5.7	26	4.6
61-70	8	2.7	2	0.8	10	1.8
71-80	2	0.7	5	1.9	7	1.3
Total	296	52.9	264	47.1	560	100

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Severe adverse drug reaction - if it was life threatening or cause organ damage and lost of functions. Sometimes adverse drug reaction may result in death.

Other pertinent information such as age and sex were also analyzed to determine whether they would influence the development of adverse drug reactions. Descriptive statistics, paired t-test and contingency table analysis were used whenever appropriate.

RESULTS

Age, sex, disease and drugs

A total of 560 patients who suffered from convulsive disorders were monitored. Of which 47.1% were female as shown in Table 1. The patients' age ranged mostly between 15-40 years old (85.3%).

Six antiepileptic drugs used in this study were shown in Table 2. Phenobarbital and phenytoin were commonly prescribed (81.3%). Table 3 showed that 65.2% of the patients received more than one drug at a time (55.1 and 10.1% received two and more than two drugs respectively).

Adverse drug reactions

By using paired t-test to compare the results of an open-ended

Table 2 Antiepileptic drugs being prescribed.

Drugs	No. of patients	Percent
Phenobarbital	238	42.5
Phenytoin	217	38.8
Carbamazepine	48	8.6
Clonazepam	36	6.4
Primidone	17	3.0
Sodium Valproate	4	0.7

question and a check list of known side effects, we found that in order to assess the adverse reactions, the check list method significantly revealed more numbers of side effects as reported by the same patients than the open-ended question ($P<0.05$).

As shown in Table 4, 18.9% of the patients developed adverse reactions. The reactions seemed to occur most often in the age range between 51-80 years old (34.8% of the patients in this age groups). The numbers of adverse drug reactions were significantly different among each age group (Contingency table analysis $P<.05$)

Table 3 The number of drugs received according to sex.

Number of drugs received	Male Number	%	Female Number	%	Total Number	%
1	52	31.7	58	38.2	110	34.8
2	94	57.3	80	52.6	174	55.1
More than 2	18	11.0	14	9.2	32	10.1

Table 4 Incidence of adverse drug reactions (ADR) of antiepileptic drugs in patients with different age groups.

Age(years)	Male ADR/Total	%	Female ADR/Total	%	Total ADR/Total	%
15-20	14/76	18.4	12/68	17.6	26/144	18.1
21-30	18/120	15.0	14/85	16.5	32/205	15.6
31-40	12/56	21.4	14/73	19.2	26/129	20.2
41-50	6/23	26.1	0/16	0	6/39	15.4
51-60	4/11	36.4	6/15	40.0	10/26	38.5
61-70	2/8	25.0	0/2	0	2/10	20.0
71-80	2/2	100.0	2/5	40.0	4/7	57.1
Total	58/296	19.6	48/264	18.2	106/560	18.9

Table 5 Incidence of adverse drug reactions according to number of drugs received.

Number of drugs received	Male ADR/Total	%	Female ADR/Total	%	Total ADR/Total	%
1	16/52	30.8	14/58	24.1	30/110	27.3
2	12/94	12.8	9/80	11.3	21/174	12.1
More than 2	6/18	33.3	5/14	35.7	11/32	34.4

Table 6 Clinical manifestation of adverse drug reactions and the responsible drug.

Clinical manifestation	Pheno-barbital	Pheny-toin	Carbama-zepine	Clona-zepam	Primi-done	Total	Percent*
Neurological**	37	35	10	5	-	87	82.1
Lethargy	6	11	1	1	-	19	17.9
Gastro-intestinal	6	9	1	1	1	18	17.0
Cardio-vascular	3	10	1	1	-	15	14.2
Allergy	2	5	2	-	-	9	8.5
Respiration	2	3	2	1	-	8	7.5
Tremor	1	3	1	-	-	5	4.7
Urinary change	2	2	-	-	-	4	3.8
Eedema	-	2	1	-	-	3	2.8
Ear symptoms	-	3	-	-	-	3	2.8
Dryness of mouth	1	1	-	-	-	2	1.9
Total	60	84	19	9	1	173	
Percent°	34.7	48.5	11.0	5.2	0.6	100	

*Percent of total patients reported adverse drug reactions (106 patients)
o Percent of total symptoms reported by the patients (173 symptoms)
** 25% were sedation, others included dizziness, headache, restlessness, depression and confusion.

Table 5 showed that patients received two drugs concurrently had less adverse reaction (12.1%) while patients with more than two drugs had 34.4% of this reaction. The relationship of adverse reaction and number of drugs prescribed were significantly different. ($P<.0.001$)

Most of the side effects reported in this study (99.6%) were considered to be minor, no severe adverse reactions were noted. The clinical manifestations of adverse drug reactions were summarized in Table 6 along with the responsible drugs. Neurological symptoms (e.g. dizziness drowsiness, headache) were the most common adverse effects (82.1%). There was no significant difference between each drug in producing the incidence of adverse effects as reported by the patients taking different antiepileptic drugs as shown in Table 7.

DISCUSSION

In our study we found that age might be one of the important factor in developing adverse drug reactions to antiepileptic drugs. All adverse reactions were considered to be mild and the patients can tolerate quite well to medication. The reactions occurred may be classified into

Table 7 The number of adverse drug reactions of each drug

Drug	Patients with ADR	Total patients	Percent
Phenobarbital	42	238	17.6
Phenytoin	43	217	19.8
Carbamazepine	12	48	25.0
Clonazepam	8	36	22.2
Primidone	1	17	5.9
Sodium Valproate	-	4	-

Contingency table analysis of reaction rate indicated no statistically significant difference among each drug.

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possible and probable categories (2). These reactions also confirm the known pharmacological action of the drugs. No serious side effect was found.

The major factor in determining the choice of an appropriate anticonvulsant is the patient's type of epilepsy. Correct diagnosis of type of epilepsy serves narrow the choice of available anticonvulsants to a small group of appropriate drugs (4). Since most of the diagnoses noted in our study were labelled as "convulsive disorders", we did not know that the prescriptions followed the recommended guideline or not. Phenobarbital and phenytoin were the drugs most commonly prescribed in our study. These two drugs are widely used for the treatment of generalised epilepsy. So it is likely the most of our epileptic patients were of generalised type since this type of epilepsy comprises more than 85% of all incidence of epileptic seizure (4).

The traditional approach to antiepileptic drug treatment was to begin with one drug and to gradually increase its dosage until the seizures were controlled or until acute toxic symptoms developed in which case the dose was again slightly reduced. If seizures continued, then the next step was to add another drug and build its dosage up in the same way, and so on. Another approach was to begin the treatment with two drug (e.g. phenobarbital and phenytoin) in the hope that there was synergism and that small doses of two drugs were less toxic than a large dose of a single drug (5, 6). In our study more than 50% of the patients received these two drugs at a time and this group tended to have the least adverse reactions when compared to the patients received only one drug. Phenobarbital seems to be the drug of first choice in this study.

Convulsive disorder is a chronic disease which required long term treatment. The incidence of toxicity may increase and much of these toxic effects are directly related to the number of drug being given and some adverse reactions continue to emerge from time to time (6, 7). One of phenobarbital side effect is drowsiness which occurred in the first few weeks of the treatment. In our study, we found that after a period of time this drowsiness was subsided and if the drug was still used, insomnia may occur.

One of the problems in using drug combination is drug interaction which can precipitate toxicity or lead to loss seizure control (8). Many of drug interactions could and should be avoided by the use of single drug therapy whenever possible. In the case phenobarbital and phenytoin, phenobarbital which is an enzyme inducer can induce phenytoin metabolism and depress serum levels of the latter. Phenytoin itself can also raise serum levels of phenobarbital probably by inhibition of hydroxylation enzymes (9). The clinical significance of this drug interaction has not been well established.

The widespread practice of anticonvulsant polytherapy has many undersirable consequences and there is little evidence of clinical benefit (6). But in our study, using two drugs in combination had least side effects. For all the patients being studied, only nearly 20% had adverse reactiond and most of them were considered to be mild and confirmed by the known pharmacological actions. Patients can tolerate quite well with these reactions. However, in general treatment of epilepsy, the disease should be treated in the simplest and most effective way with one or at the most, two drugs.

In recent years, newer anticonvulsant, valproic acid or sodium valproate has been associated with a worrying incidence of serious liver and pancreatic toxicity (7). In our study only 1% of the patients received sodium valproate. The number of the subjects were too small to assess the risks of this agent.

In this study, we did not detect any rare or unusual side effects. However, it can never be assumed that this same picture will be found in general pratice or elsewhere. Since in the hands of specialists, proper selection and suitable titration of dosage may play a vital role in the safe uses of the drugs.

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