Pharmacoepidemiological Study on Adverse Reactions of Antiepileptic Drugs

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The relationship between the occurrence of side effects (SEs) and drug factors, such as antiepileptic drugs (AEDs), daily dose, duration of treatment, drug combination pattern, total and free serum concentrations, metabolite per parent level ratio as an index of metabolism ability, and co-medicated drugs except AEDs were evaluated in 227 outpatients with epilepsy. The possible influences of certain physiological and/or the pathophysiological factors were also evaluated. SEs with 19 clinical signs were observed in 66.1% of all patients. There was no definite dose- or serum concentration-dependent increase in the incidence of SEs. Stepwise discriminant function analysis revealed that benzodiazepines (BZN) polytherapy with AEDs produced a higher incidence of somnolence and general fatigue than did any other AED or drug combination. The effects of various drug combination patterns on the incidence of SEs were also evaluated on the basis of observed frequencies. The incidence of somnolence was significantly higher in patients taking phenytoin (PHT) plus carbamazepine (CBZ) therapy, and in patients taking BZN plus either PHT, phenobarbital (PB) or CBZ therapy compared with patients taking either PHT, PB or CBZ therapy. Other responsible drug combination patterns were PHT plus valproic acid (VPA) therapy for mental function impairment, acetazolamide (AZM) polytherapy with PB or PHT for dry mouth, and CBZ plus BZN therapy for constipation. In this study, the stratifying points (occurrence limits) of SEs were detected in various variables such as the number of prescribed drugs, daily dose and serum concentrations. Interestingly, these limits are within the commonly accepted "therapeutic range" or "usual daily dose," and some of these limits shifted down when another AED was co-medicated. Furthermore, additional risk factors for patients who had clinical SEs, even though their serum concentrations or daily dose stayed below the limits, were evaluated. However, this study confirms that variables related to drug therapy are more closely involved in the occurrence of SEs than variable patient characteristics, especially the number of prescribed drugs and the AEDs polytherapy with BZN. The incidence of almost SEs (*e.g.* somnolence, weakness) significantly increased when three AEDs were co-medicated with BZN or AZM. Thus, it is emphasized that one or at most two AEDs, including psychopharmacological drugs, should be given to minimize the risk of SEs.

Keywords antiepileptic drug; side effect; pharmacoepidemiology; risk factor; discriminant function analysis

Introduction

Over the past 20 years the development of techniques for the blood concentration monitoring of antiepileptic drugs (AEDs) has facilitated a trend towards a more simplified and effective use of the drugs. One of the primary objectives of AED concentration measurement is to avoid the occurrence of side effects (SEs). There is general agreement that a direct relationship exists between AED serum concentrations and the degree of clinical intoxication.[1,2] However, it was found in a clinical setting that SEs were often observed even in the therapeutic range, and there have been frequent complaints from patients who are not clearly toxic but who complain about the medication slowing them down and making then function less efficiently.[3–5] The clinical manifestations and management of AED side effects have been amply discussed in some literature,[6,7] but little is known about the factors that lead to this state. Identifying and defining the causative factors of AED SEs could lead to a decrease in the incidence of SEs and also in common complications of the pharmacological treatment of seizures.

Recently, a new scientific discipline, pharmacoepidemiology,[8,9] has been employed in order to quantitate the incidence of known SEs and beneficial effects of drugs. The many important factors regarded as contributing to the development of SEs in frequently used drugs, *e.g.* non-steroidal anti-inflammatory drugs and neuroleptics, were reviewed in depth. However, there is still a lack of information about the epidemiology of SEs due to AEDs in Japan.

The goals of the present study were (1) to evaluate the correlation between the incidence of SEs and the prescribed drugs or the patients' characteristics; and (2) to identify probable causes for an increased incidence of SEs in patients whose serum AEDs concentrations were still within a "therapeutic" or even "subtherapeutic range." A preliminary results of some of the findings was published previously.[10,11]

Materials and Methods

Patients Data was collected from April 1988 to September 1990 on 227 ambulatory compliant adult epileptic patients (115 males), treated at the Department of Neuropsychiatry of Kyushu University Hospital.

The patients ranged in age from 17.0 to 80.1 with an average age of 42.8 (S.D.; ±12.5). Their body weight ranged from 31.0 to 82.5 kg with an average of 56.6 (±10.3). The daily dose (mg/d) was phenobarbital (PB) 8.3—133.3 (mean±S.D.; 66.8±28.0, $n=143$), phenytoin (PHT) 30.0—500.0 (211.5±68.5, $n=176$), valproic acid (VPA) 200.0—1800.0 (849.1±380.1, $n=57$), carbamazepine (CBZ) 200.0—1200.0 (603.4±252.2, $n=117$), primidone (PRM) 200.0—1500.0 (495.7±380.2, $n=23$), nitrazepam (NZP) 2.0—15.0 (7.0±3.2, $n=18$), clonazepam (CZP) 0.2—6.0 (2.6±1.8, $n=45$), diazepam (DZP) 2.0—15.0 (9.0±5.5, $n=8$), acetazolamide (AZM) 20.0—250.0 (121.3±74.2, $n=26$), sultiame (SLM) 50.0—400.0 (210.0±147.8, $n=15$), chlordiazepoxide (CDP) 2.0—30.0 (13.8±8.1, $n=11$). Twenty patients were receiving AED monotherapy, and other patients were receiving from two to seven different prescriptions from among the four major AEDs: -PB, PHT, CBZ and VPA-, and other less commonly used AEDs and/or psychopharmacological drugs (*e.g.* benzodiazepines, BZN)—on average 3.1 per patient.

Seizure type was classified as generalized tonic–clonic in 85 patients. Complex partial seizures were diagnosed in 74 patients. The remaining 68 patients had simple partial seizures, 61 of whom had secondarily generalized seizures.

Data concerning the duration of treatment and the seizure frequency was obtained from medical records as well as from information from the

patients and their relatives. The patients had a seizure frequency varying from daily seizures to once a year. However, 90 patients had been seizure-free for at least one year before this study. The duration of treatment with each AED also varied considerably among patients, from 1 month to 20 years.

The observations were made at the routine visits to the clinic, and no attempt was made to control for the sampling time in relation to the time of day or the most recent time of medication. The elapsed time from the previous dose ranged from 2 to 6.5 h with an average of 4.2 h, indicating that venipuncture was performed at approximately a maximum point of serum levels throughout the day. It was confirmed that the patients on polytherapy, including psychopharmacological drugs, did not change their co-medications for at least 1 month prior to this study. All patients were informed about the object of the study and gave consent to it.

Toxicity Determination The side effects were sought at the routine visit to the clinic. The clinical signs in the skin and the connective tissue (gingival hyperplasia, rash and hypertrichosis), the digestive tract (dry mouth, constipation, anorexia, nausea and vomiting), the nervous system (somnolence, mental function impairment, slowness of mentation, headache, vertigo, diplopia and another ocular disorder: nystagmus, tremor and ataxia) and miscellaneous SEs (general fatigue, weakness and dysmenorrhea) were assessed.

The following methods were used to determine SEs.

1. The patients answered questionnaires about episodes with subjective evaluations: definitely yes, probably yes, possibly, probably not, or definitely not, during the time they were waiting for consultation. The verbal expression of the questions was aimed at the appropriate social background and age of the patient.

2. Each sign or symptom was found by anamnesis, based on a previously devised questionnaire in which all SEs attributed to AEDs were included. The details of each SE, duration and degree, were evaluated by ranking them from none (0) to grade III (3+) at each consultation. All objective evaluations were performed by the physicians who were responsible for the clinical management of the patients.

Grade I toxicity was defined only by subjective complaints, but without impairment to usual daily activities. Grade II toxicity included one or some combination of complaints, but with no strong objective evidence of toxicity upon neurological examination.[12] Patients with grade III toxicity had the same subjective toxicity as did patients with grade I or II toxicity, but they also had objective evidence of toxicity and needed to reduce or discontinue the treatment.

As study patients arrived at the clinic, one blood sample was taken for the estimation of serum AEDs concentration and clinical laboratory tests (electrolyte levels, renal and liver functions and plasma protein concentrations, *etc.*).

Serum Drug Concentration Measurements The AED concentrations were determined by fluorescence polarization immunoassay (TDx® analyzer, Abbott Laboratories, Chicago, IL). Venous blood (10 ml) was collected in a plane syringe, and the serum was separated at room temperature. Three milliliters of serum were centrifuged for 10 min at 3000 rpm (10 °C) using the ultrafiltration technique (Amicon Micropartition MPS3 System, Amicon Co., Danvers, MA) to obtain unbound AEDs. The degree of protein binding was calculated as the ratio of drug in the ultrafiltrate to that in serum, and was expressed as a free fraction (FF).

Carbamazepine-10,11-epoxide (CBZE) and 5-(4-hydroxyphenyl)-5-phenylhydantoin (5-HPPH) concentrations in serum, one of the main metabolites of CBZ and PHT, were measured in duplicate by high performance liquid chromatography according to the methods of Chelberg *et al.*[13] and Sauchuk *et al.*,[14] respectively. CBZE/CBZ and 5-HPPH/PHT serum concentration ratios were used as the indices of drug metabolism ability.

Statistics One way analysis of variance (ANOVA) combined least-significant-difference method (LSD) was used to compare the daily dose and serum concentrations between patients with and without SEs.

To compare the causative factors between patients with a specific SE and without SEs, stepwise discriminant function analysis (DFA) was performed. Some exercise variables were treated as the categorical variables shown in Table I. At each step, the improvement in χ^2 test was used to check whether the variable entered at that step significantly improved discrimination. The object of this analysis is to conveniently predict the occurrence of SEs by using the given variables or risk factors, or the probability that a patient would develop SEs due to AEDs.

The χ^2 test was used for assessing the influence of drug combination patterns on the incidence of each SE. Because numbers were inadequate for monotherapy using the seven specific drugs, -PB, PHT, CBZ, VPA, AZM, PRM and BZN-, the following treatments were done instead; 1) the observed frequency was compared between patients without SEs and patients who complained not only of one specific SE but also of other kinds of SEs; and 2) all of the 2 × 2 tables from these 7 drugs were combined into one 2 × 2 table, forming a "composite of co- medication pattern" variable (*e.g.*, PHT ± other drugs *vs.* PHT + CBZ ± other drugs).

TABLE I. Variables Used for Stepwise Discriminant Function Analysis

Variable	Treatment (category)
Sex	1 = female, −1 = male
Seizure frequency	1 = seizure free over 1 year, 2 = 1—2 times/year, 3 = 3—11 times/year, 4 = 1—3 times/month, 5 = 1—6 times/week, 6 = >1 times/d, 7 = >10 times/d
Age	1 = <20, 2 = 20—<30, 3 = 30—<40, 4 = 40—<50, 5 = 50—<60, 6 = 60—<70, 7 = >70
Classification of epilepsy	1 = SPS, 2 = CPS, 3 = SGS, 4 = GS, 5 = Mixed
No. of prescribed drugs	Crude data
PHT	1 = absent
PB	2 = present
CBZ	
VPA	
PRM	
NZP	
CZP	
5-HPPH/PHT level ratio	Crude data
CBZE/CBZ level ratio	Crude data

SPS, simple partial seizure; CPS, complex partial seizure; GS, generalized seizure; SGS, secondarily generalized seizure; Mixed, mixed types of seizures.

The χ^2 test was also applied to obtain the limit (stratifying point) of the occurrence of SEs with Yates' correction for small samples. The stratifying point was calculated for 6 variables such as daily dose, total and free serum drug concentrations, free fractions, metabolite/parent drug level ratios and the number of prescribed drugs on the basis of observed frequencies. The extent of changes in significance of occurrence rate was checked while the variable was scanned from its minimum to maximum value, and the point at which the variable indicated the lowest level with a significant frequency exceeding $p = 0.05$ was defined as a stratifying point. In addition, the effects of drug combination pattern, drug combinations of two of the four major AEDs on the stratifying point, were evaluated.

Finally, patients whose level stayed below each stratifying point were divided into two groups, without SEs and with each SE, and their drug factors and patient characteristics (laboratory tests *etc.*) were compared using a simple t test (Student's or Welch's t test) based on the mean and variance.

With these techniques, the high-risk variables associated with SEs in patients whose serum AEDs concentrations were within and/or below the "therapeutic range" could be evaluated.

All data is expressed as mean ± S.D., and the probability values greater than 5% are considered nonsignificant.

Results

Incidence of SEs and Their Relationship with Dosage and Serum Concentrations SEs were observed in 150 patients (66.1%). The types of SEs in patients treated with PHT, PB, CBZ, VPA, AZM, PRM and BZN, together with the doses and serum concentrations at which the effects occurred, are shown in Table II. Since several SEs, such as neurologic and digestive, can occur in the same patient, the sum of each subdivision in Table II may be higher than the number of patients with SEs. The average number of prescribed drugs, including not only AEDs but also psychopharmacological drugs such as BZN, in patients with SEs were higher than those of the 77 patients without SEs. However, clearly significant differences in the daily doses were not found between patients with and without SEs.

The most frequently observed nervous system disorders

TABLE II. Frequency of Side Effects: Daily Doses Used and Serum Concentrations Reached by the Patients with Each Side Effect

Side effect	n	%	No. of prescribed drugs	PB n	PB Dose (mg/kg)	PB TL[a] (μg/ml)	PHT n	PHT Dose (mg/kg)	PHT TL (μg/ml)	PHT FL[b] (μg/ml)	CBZ n	CBZ Dose (mg/kg)	CBZ TL (μg/ml)	CBZ FL (μg/ml)	VPA n	VPA Dose (mg/kg)	VPA TL (μg/ml)	VPA FL (μg/ml)
Without side effects	77	33.9	2.8±1.4	44	1.12±0.56	10.2±6.5	56	3.68±1.10	6.1±4.5	0.4±0.3	36	9.76±4.65	5.3±1.5	1.4±0.5	20	11.45±5.01	40.4±21.6	2.7±1.9
Nervous system																		
Somnolence	76	33.5	3.5±1.1[c]	43	1.25±0.59	13.1±8.1	62	4.07±1.31	7.6±4.6	0.6±0.4[c]	49	12.20±4.27	6.7±2.2	1.6±0.7	15	18.80±7.76	44.4±23.9	3.6±2.4
Mental function impairment	42	18.5	3.4±1.1	24	1.09±0.66	7.9±6.5	38	4.27±1.42	7.6±4.8	0.6±0.4	25	12.00±3.81	6.2±1.9	1.3±0.6	10	17.72±7.54	40.7±23.8	3.4±2.3
Slowness of mentation	39	17.2	3.3±1.3	25	1.06±0.55	10.2±7.1	33	3.98±1.52	6.8±4.3	0.6±0.4	24	11.54±4.58	6.4±2.2	1.3±0.6	5	18.10±8.43	38.9±31.7	3.3±3.1
Headache	37	16.3	3.3±1.2	23	1.02±0.49	9.3±6.0	31	3.66±1.41	5.4±3.7	0.4±0.3	19	9.94±4.30	6.0±2.1	1.6±0.5	7	16.52±7.37	44.5±29.6	3.8±3.1
Vertigo	18	7.3	3.4±0.8	10	1.21±0.68	11.3±8.0	14	4.83±1.54	9.2±5.4	0.7±0.4	13	10.83±4.60	5.8±2.4	1.4±0.6	6	19.28±9.61	47.7±33.3	5.3±5.0
Diplopia and other ocular disorders	16	7.0	3.8±0.9	7	1.33±0.59	12.7±5.7	9	4.05±1.52	8.3±5.4	0.7±0.4	8	9.88±4.11	5.9±2.1	1.1±0.4	3	17.61±7.14	32.2±19.5	2.6±1.4
Tremor	7	3.1	4.4±1.3[c]	4	0.97±0.45	9.6±5.8	5	3.44±2.09	4.8±4.7	0.4±0.3	4	8.95±2.30	6.8±1.3	1.6±0.3	2	25.12	73.5	6.7
Ataxia	5	2.2	3.0±0.3	3	1.20±0.38	17.3±9.5	2	4.41	5.5	0.5	2	9.10	7.9	1.7	2	14.00	52.1	4.3
Skin and connectives																		
Gingival hyperplasia	23	10.1	3.3±1.3	15	1.20±0.52	9.9±6.1	21	3.90±1.17	7.5±4.1	0.7±0.2[c]	10	11.60±4.30	5.4±1.9	1.3±0.5	4	18.44±6.09	47.6±20.7	6.5±6.0
Rash	10	4.4	3.2±1.5	6	0.85±0.12	12.1±5.9	9	3.88±0.85	9.0±4.3	0.7±0.4	5	8.69±4.53	8.6±2.0[c]	1.8±0.6	2	26.11	57.0	4.7
Hypertrichosis	7	3.1	3.9±1.6	4	1.31±0.53	8.9±4.3	6	3.43±1.54	5.8±4.3	0.4±0.4	5	9.70±5.48	8.4±6.2	1.5±0.3	3	10.80±6.54	45.4±27.8	8.2±6.2
Digestive tract																		
Dry mouth	35	15.4	3.7±1.3[c]	22	1.28±0.51	12.6±8.7	29	3.87±1.69	7.2±4.4	0.5±0.3	24	10.49±3.93	6.3±2.0	1.4±0.5	11	15.91±8.46	41.3±25.2	4.5±4.1
Constipation	34	15.0	3.4±1.5	21	1.17±0.59	12.5±7.3	27	4.04±1.46	7.1±4.6	0.5±0.3	19	11.96±3.31	7.1±3.0	1.6±0.8	7	18.40±5.01	33.7±19.5	2.5±1.5
Anorexia	14	6.2	3.8±1.5	7	1.08±0.54	12.0±5.9	10	4.96±1.73	8.0±3.9	0.6±0.3	11	9.36±3.61	5.3±1.7	1.1±0.4	4	15.42±8.10	53.1±24.7	6.5±6.1
Nausea or vomiting	14	6.2	3.4±1.4	7	1.05±0.46	11.3±3.8	7	3.89±2.14	7.5±4.1	0.6±0.5	11	10.14±3.73	5.8±1.6	1.4±0.4	4	25.52±5.50[c]	44.8±19.4	3.2±1.8
Miscellaneous																		
General fatigue	47	20.7	3.3±1.2	30	1.27±0.57	11.6±5.4	37	4.02±1.57	5.7±4.1	0.5±0.3	22	10.39±4.84	5.6±1.7	1.3±0.4	10	16.82±7.45	51.6±24.1	4.7±4.5
Dysmenorrhea	17	7.5	3.3±1.8	10	1.28±0.73	12.1±7.8	11	4.80±1.78	5.5±3.4	0.4±0.3	8	10.82±5.19	4.6±3.3	0.8±0.7	4	22.44±5.56	37.4±23.3	2.9±1.5
Weakness	11	4.8	3.8±1.5	6	0.58±0.36	9.0±7.6	9	4.74±2.13	6.7±4.3	0.5±0.3	6	10.23±2.06	6.0±2.7	1.1±0.4	2	24.65	42.2	4.5

Side effect	PRM n	PRM Dose (mg/kg)	PRM TL (μg/ml)	CBZE/CBZ n	CBZE/CBZ Level ratio	5-HPPH/PHT n	5-HPPH/PHT Level ratio	NZP n	NZP Dose (mg/kg)	CZP n	CZP Dose (mg/kg)	DZP n	DZP Dose (mg/kg)	AZM n	AZM Dose (mg/kg)
Without side effects	11	8.66± 7.53	7.4± 6.2	36	0.26±0.12	56	0.54±0.29	2	0.11	9	0.05±0.04	3	0.14±0.12	8	2.34±1.25
Nervous system															
Somnolence	5	12.50± 8.44	15.3± 9.0	49	0.27±0.11	62	0.42±0.23	9	0.13±0.05	24	0.04±0.02	2	0.15	9	1.90±1.25
Mental function impairment	1	4.17	28.3	25	0.26±0.12	38	0.43±0.21	2	0.12	13	0.04±0.03	1	0.08	5	2.39±1.45
Slowness of mentation	3	12.94±11.77	17.7±15.0	24	0.23±0.10	33	0.44±0.21	1	0.17	11	0.04±0.02	1	0.25	7	1.64±1.15
Headache	2	16.13	28.3	19	0.23±0.12	31	0.56±0.26	2	0.17	13	0.05±0.03	1	0.25	5	2.58±1.43
Vertigo	2	15.24	28.3	13	0.27±0.14	14	0.40±0.26	0		3	0.04±0.02	0		4	1.99±1.43
Diplopia and other ocular disorders	3	13.03±12.06	13.7±13.3	8	0.21±0.05	9	0.27±0.15	3	0.06±0.01	6	0.06±0.04	1	0.08	4	1.93±1.31
Tremor	1	4.55	4.4	4	0.28±0.16	5	0.50±0.32	2	0.18	2	0.06	1	0.25	2	1.72
Ataxia	1	2.63	28.3	2	0.43	2	0.79	0		3	0.05±0.01	0		1	0.88
Skin and connectives															
Gingival hyperplasia	1	5.95	2.1	10	0.33±0.15	21	0.48±0.40	0		9	0.04±0.03	2	0.16	4	1.96±1.90
Rash	1	13.80	28.3	5	0.29±0.09	9	0.40±0.23	1	0.06	3	0.06±0.02	0		1	1.56
Hypertrichosis	1	5.95	2.4	5	0.31±0.19	6	0.48±0.34	0		3	0.05±0.02	0		3	3.85±2.90
Digestive tract															
Dry mouth	4	4.70± 2.17	5.4± 2.3	24	0.26±0.12	29	0.43±0.24	6	0.11±0.04	7	0.04±0.03	1	0.25	9	2.27±1.45
Constipation	2	5.25	3.3	19	0.24±0.10	27	0.50±0.2	3	0.13±0.05	11	0.05±0.03	0		4	2.20±1.21
Anorexia	2	4.29	4.4	11	0.27±0.14	10	0.60±0.24	3	0.16±0.03	3	0.03±0.01	1	0.25	2	4.40
Nausea or vomiting	1	4.54	4.4	11	0.23±0.11	7	0.45±0.32	4	0.14±0.04	3	0.03±0.02	1	0.25	3	1.52±0.62
Miscellaneous															
General fatigue	5	8.37± 7.22	14.4±11.3	22	0.27±0.13	37	0.49±0.24	5	0.15±0.04	10	0.06±0.04	2	0.26	7	2.51±1.63
Dysmenorrhea	0			8	0.22±0.01	10	0.59±0.31	1	0.12	2	0.03	1	0.27	1	1.33
Weakness	0			6	0.22±0.13	9	0.50±0.30	1	0.16	3	0.06±0.02	1	0.25	2	1.53

Dose and serum concentration are mean±S.D. *a*) Total concentration in serum. *b*) Free concentration in serum. *c*) $p<0.05$ with respect to patients without side effects (ANOVA).

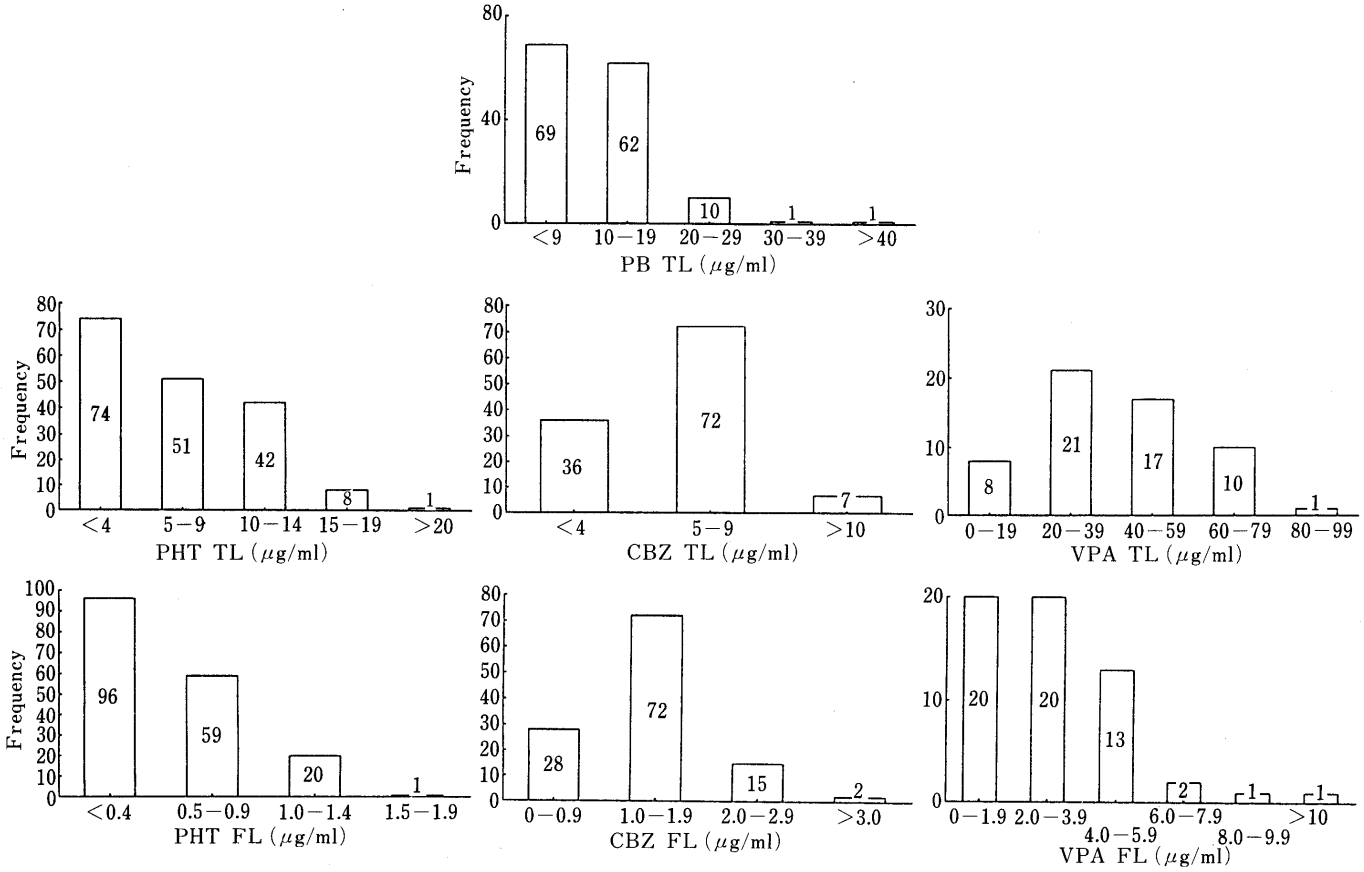

Fig. 1. Distribution Histograms of Serum AED Concentrations for 227 Epileptic Patients

were somnolence (SL), followed by mental function impairment (MI), slowness of mentation (SM) and headache (HA). No significant differences in PHT total concentration were observed between the patients with nervous system disorders and the patients without SEs. However, PHT free concentration was significantly higher in patients with SL. On the other hand, the 5-HPPH/PHT level ratio was lower in patients with SL or MI or vertigo (VT) or diplopia (DP) compared with patients without SEs.

The digestive tract disorders most frequently observed were dry mouth (DM) and constipation (CP). The incidence of anorexia was similar to that observed with nausea or vomiting (NV). With the exception of VPA in NV, the daily dose showed no significant difference between patients with digestive tract disorders and patients without SEs. In addition, no significant differences in the serum concentrations—either total or free—were recognized.

The average free concentration of PHT in patients with gingival hyperplasia (GH) was significantly higher than in patients without SEs. On the other hand, no significant differences in PHT serum concentrations, either total or free, were found between patients with or without hypertrichosis (HT). Patients with skin rash indicated a significantly higher CBZ total concentration than patients without SEs.

When the numbers of patients in the lower therapeutic, therapeutic and higher therapeutic range were compared, most patients with SEs were in the therapeutic or below therapeutic range [*i.e.*, PHT 10—20, CBZ 4—10, VPA 50—100, and PB 10—40 μg/ml].[15] Consequently, no clear relation could be established between the incidence of SEs and serum concentrations, even in free concentration (Fig. 1).

TABLE III. Stepwise Discriminant Function Analysis Results of Risk Factors for Incidence of Side Effects

Side effect	Variables	Coefficients	χ^2	p
Somnolence	NZP	+6.053		
	CZP	+1.857		
	CBZE/CBZ		10.52	0.001
	Level ratio	+7.634		
	(Intercept)	−6.653		
Gingival hyperplasia	PHT	+3.630		
	5-HPPH/PHT		11.65	0.0006
	Level ratio	−2.397		
	(Intercept)	−4.256		
General fatigue	PB	+3.074		
	VPA	+4.287		
	NZP	+11.517	21.72	0.0001
	Sex (male)	−1.163		
	(Intercept)	−28.951		
Dysmenorrhea	VPA	+11.629		
	(Intercept)	−13.168	8.26	0.004

The percentages of patients treated with each AED, and who had each type of SE, are compared in Fig. 2. General fatigue (GF) was most common with AZM (26.9%) or BZN (27.2%), DM with AZM (34.6%) and SL with CBZ (41.9%) or BZN (49.2%).

Risk Factors for Side Effects; the Stepwise Discriminant Function Analysis (DFA) From 14 variables (Table I), the factors related to the occurrence of each SE were explored by the DFA (Table III). Their associated weights

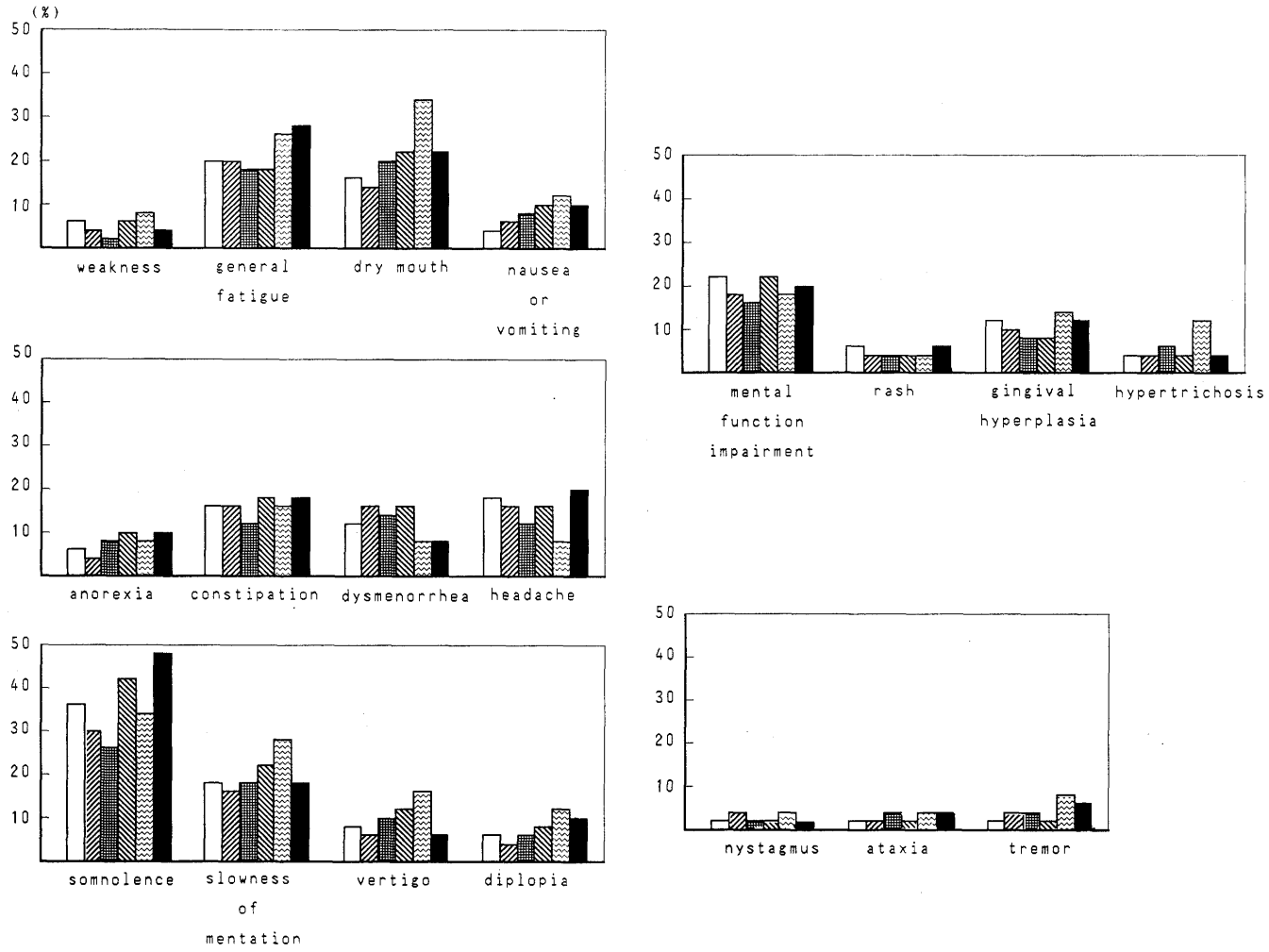

Fig. 2. Percentage of Patients Treated with PHT ($n=176$), PB ($n=143$), CBZ ($n=117$), VPA ($n=57$), AZM ($n=26$) or BZN ($n=82$) with Each Side Effect

□, PHT; ▨, PB; ■, VPA; ▧, CBZ; ▩, AZM; ■, BZN.

(coefficients) were also tabulated, and are provided to allow evaluation of the relative importance of the value to each other.

In patients with SL, the most important discriminant factor was the CBZE/CBZ level ratio, followed by NZP and CZP. Consequently, SL is more frequently observed in patients indicating a high CBZE/CBZ level ratio.

Similarly, in the analysis of GH, the discrimination could be explained by two variables, such as PHT and 5-HPPH/PHT level ratio. However, they show a contrary effect on the incidence of GH. It is suspected that GH is more frequently observed in patients with PHT and in those who exhibit a lower 5-HPPH/PHT level ratio.

A comparison of the coefficients suggested that NZP was the most significant discriminant factor in patients with GF, followed by VPA, PB and sex (male). Similarly to SL, NZP intake was a significant contributing factor. VPA monotherapy or PB monotherapy was not significantly responsible for the incidence, however, NZP polytherapy with AEDs was an enhancement factor in the incidence of GF.

In patients with dysmenorrhea, only one variable but a very strong discriminant factor, VPA therapy, could be detected.

In the aggregate, it may be concluded that the BZN with AEDs polytherapy was the most important factor responsible for the increased incidence of these SEs.

The Effects of Drug Combination Patterns on the Incidence of Side Effects Table IV shows the association between various drug combination patterns and the incidence rate of each SE. Significant relations were observed for SL, MI, DM, and CP.

The incidence of SL was significantly higher in patients with PHT plus CBZ (±other AEDs) and in patients with BZN in combination with either PHT, PB or CBZ (±other AEDs) than those on PHT, PB or CBZ therapy (±other AEDs), respectively.

The drug combination pattern responsible for MI and CP were PHT plus VPA therapy and CBZ plus BZN therapy, respectively. MI was more frequently observed in patients with PHT plus VPA therapy (±other AEDs) than in patients with PHT therapy (±other AEDs).

The incidence of DM was significantly different in patients exposed to combinations of PB with or without AZM (±other AEDs) and PHT with or without AZM (±other AEDs). The incidence was significantly higher in patients taking AZM polytherapy compared with those on PB or PHT therapy (±other AEDs).

TABLE IV. Association of Incidence of Side Effects with Drug Combination Patterns

Side effects	Drug combination		Total No. of patients	Patients with each side effect		χ^2 ($d.f.=1$)	p
				No.	%		
Somnolence	PHT	(±others[a])	83	24	28.9		
	PHT+CBZ	(±others)	73	34	45.2	5.19	0.023
	PHT	(±others[b])	109	30	27.5		
	PHT+BZN	(±others)	45	26	57.8	12.6	0.0004
	PB	(±others[b])	90	25	27.8		
	PB+BZN	(±others)	32	16	50.0	5.22	0.022
	CBZ	(±others[b])	65	23	35.4		
	CBZ+BZN	(±others)	32	20	62.5	6.39	0.011
Mental function impairment	PHT	(±others[c])	139	27	19.4		
	PHT+VPA	(±others)	16	7	43.8	4.96	0.026
Dry mouth	PB	(±others[d])	112	14	12.5		
	PB+AZM	(±others)	12	6	50.0	11.3	0.0008
	PHT	(±others[d])	141	20	14.2		
	PHT+AZM	(±others)	13	5	38.5	5.16	0.023
Constipation	CBZ	(±others[b])	66	7	10.6		
	CBZ+BZN	(±others)	31	9	29.0	5.20	0.023

Combination patterns include antiepileptic drugs (AEDs) specified with or without other AEDs. *a*) Except CBZ therapy. *b*) Except BZN therapy. *c*) Except VPA therapy. *d*) Except AZM therapy.

The Limit (Stratifying Point) for Occurrence of SEs and Additional Responsible Risk Factors The stratifying points in variables related to drug therapy and additional risk factors for patients staying below these limits but have clinical SEs, are shown in Table V.

(1) Nervous System Disorders When the limit was set at $\geqq 4$ drugs for the number of prescribed drugs, the incidence of SL significantly increased ($\chi^2=5.85$, $p<0.05$). So SL was more frequently observed in patients taking more than 4 drugs, including BZN. The stratifying point of the CBZ daily dose was 10.0 mg/kg/d ($\chi^2=5.44$, $p<0.05$). Physiological and drug factors in patients whose CBZ daily dose stayed below the limit were compared with patients with and without SL. The age was significantly lower in patients with SL (36.1 ± 12.1 years *vs.* 46.1 ± 14.2 years, $p<0.05$). From a similar analysis for PB daily dose, the limit was 1.25 mg/kg/d ($\chi^2=4.78$, $p<0.05$), indicating that the incidence rate of SL was significantly enhanced above this limit. However, the CBZ total serum concentration was also a risk factor for SL, even in patients whose PB daily dose stayed below this limit. The stratifying points of PB total level and CBZ total level were 11.0 μg/ml ($\chi^2=5.47$, $p<0.05$) and 5.0 μg/ml ($\chi^2=4.32$, $p<0.05$), respectively, and the additional risk factors for patients staying below the limit were also tabulated. In addition, the effect of a combination pattern on the stratifying point was evaluated. The limit of 10.0 μg/ml for the PB total level and 8.0 μg/ml for the PHT total level ($\chi^2=4.48$, $p<0.05$) was obtained. Consequently, the limit in the PB total serum concentration shifted slightly downward from 11.0 to 10.0 μg/ml, indicating that with the administration of PB and PHT, equivalent toxicity levels were produced with lower PB levels.

MI occurred significantly more often in patients taking more than three prescribed drugs ($\chi^2=12.4$, $p<0.001$). On the other hand, in patients treated with PHT or CBZ in a high daily dose, the rate of MI tended to be enhanced even when the VPA free fraction stayed at <0.08.

TABLE V. The Limit (Stratifying Point) in Various Drug Factors for Incidence of Side Effects and Their Responsible Additional Risk Factors

Side effect	Variable	Limit[a]	Additional risk factor[b]		
			Variables	With each SE	Without each SE
Nervous system					
Somnolence	No. drugs[c,r]	4	N.D.[d]		
Male ; 36	CBZ dose[e,r]	10.0	Age[r]	36.1	46.1
Female; 40	PB dose[r]	1.25	CBZ TL[f,r]	7.7	5.4
	PB TL[r]	11.0	5-HPPH/PHT[g,r]	0.49	0.67
	CBZ TL[r]	5.0	Age[r]	38.0	47.0
			PHT dose[r]	5.7	4.0
	PB TL[r]	10.0	5-HPPH/PHT[r]	0.56	0.77
	PHT TL	8.0			
	CBZ TL[r]	7.0	N.D.		
	PHT TL	7.5			
	CBZ FL[h,r]	1.6	N.D.		
	PHT FL	0.7			
Mental function impairment	No. drugs[o]	3	N.D.		
	VPA FF[i,r]	0.08	PHT dose[r]	5.2	3.5
Male ; 22			CBZ dose[r]	14.2	7.5
Female; 22	PHT FF[r]	0.085	No. drugs[r]	3.4	2.8
			T.P[i,r]	6.8	7.4
Slowness of mentation	No. drugs[r]	5	N.D.		
	CBZ dose[r]	16.0	Alb[k,r]	3.8	4.4
Male ; 22	VPA dose[r]	24.0	N.D.		
Female; 17					
Headache	PHT FF[r]	0.085	CBZE/CBZ[l,r]	0.51	0.36
Male ; 17	VPA dose[p]	19.0	N.D.		
Female; 20	CBZ dose[r]	10.0	N.D.		
	VPA dose	15.0			
Vertigo	PHT dose[p]	5.5	No. drugs[r]	3.8	2.9
Male ; 6			PHT TL[r]	9.3	6.1
Female; 12			PHT FL[r]	0.7	0.4
	PHT FL[q]	1.0	CBZE/CBZ[p]	0.62	0.46
Skin and connectives					
Gingival hyperplasia					
Male ; 12	PB TL[r]	15.0	PHT FL[r]	0.41	0.20
Female; 11	PHT TL	8.0			
Digestive tract	No. drugs[p]	4	CBZ therapy[m,r]	1.7	24.8
Dry mouth	PB TL[r]	16.0	No. drugs[o]	3.9	2.8
Male ; 20			PHT FL[r]	0.52	0.30
Female; 15			5-HPPH/PHT[r]	0.44	0.65
	PB TL[r]	10.0	γ-GTP[n,r]	112.8	54.9
	PHT TL	8.0			
Constipation					
Male ; 11	No. drugs[r]	4	N.D.		
Female; 23					
Nausea or vomiting	VPA dose[r]	15.0	N.D.		
Male ; 6					
Female; 8					
Miscellaneous					
General fatigue	PB dose[r]	1.25	5-HPPH/PHT[r]	0.43	0.57
Male ; 18			VPA dose[r]	1050.0	700.0
Female; 29					
Weakness					
Male ; 5	No. drugs[p]	5	N.D.		
Female; 6					

a) The significance was tested using a χ^2 with 1 degree of freedom on the basis of observed frequencies across groups. *b*) The additional risk factor showing comparisons between patients with each side effect and patients without side effects, and all patients stayed below each limit. *c*) Number of prescribed drugs. *d*) Not detected significant responsible factors. *e*) Dose, daily dose (mg/kg/d). *f*) TL, total serum concentration (μg/ml). *g*) 5-HPPH/PHT, serum concentration ratio. *h*) FL, free serum concentration (μg/ml). *i*) FF, free fraction-FL/TL. *j*) T. P, total protein concentration in serum (mg/dl). Normal range, 6.3—8.4. *k*) Alb, albumin concentration in serum (mg/dl). Normal range, 4.0—5.0. *l*) CBZE/CBZ serum concentration ratio. *m*) Duration of each drug therapy (month). *n*) γ-GTP, γ-glutamyl transpeptidase (IU/l). Normal range, 5—55. *o*) $p<0.001$, *p*) $p<0.005$, *q*) $p<0.01$, *r*) $p<0.05$.

A significantly increased risk of SM with the increasing number of prescribed drugs, especially with more than 5 drugs, was also observed ($\chi^2=4.14$, $p<0.05$). The stratifying points for CBZ daily dose and VPA daily dose were

16.0 mg/kg/d ($\chi^2=4.38$, $p<0.05$) and 24.0 mg/kg/d ($\chi^2=5.05$, $p<0.05$), respectively. However, in patients indicating a lower serum albumin level (mean; 3.8 mg/dl), SM was more frequently observed even when the CBZ daily dose stayed at <16.0 mg/kg/d.

When the limit was set at 0.085 for the PHT free fraction, the incidence of HA was significantly enhanced in patients indicating levels over this limit ($\chi^2=6.35$, $p<0.05$). On stratification by PHT free fraction, patients with a high CBZE/CBZ level ratio demonstrated more frequent HA than those with a low level. As shown in Table V, the limit of the VPA daily dose shifted down from 19.0 mg/kg/d ($\chi^2=8.18$, $p<0.005$) to 15.0 mg/kg/d ($\chi^2=4.65$, $p<0.05$) in patients treated both VPA and CBZ. Consequently, in such cases, a reduction in VPA daily dose was necessary to avoid HA.

From a similar analysis of the daily dose and free level of PHT, the limits of VT were 5.5 mg/kg/d ($\chi^2=8.71$, $p<0.005$) and 1.0 μg/ml ($\chi^2=6.92$, $p<0.01$), respectively. Additional risk factors such as the number of prescribed drugs, total and free levels of PHT, and the CBZE/CBZ level ratio, were also detected.

(2) Skin and Connective Tissue Disorders When the limit was set at $\geqq 15.0$ μg/ml for the PB total level and at $\geqq 8.0$ μg/ml for the PHT total level, the incidence rate of GH was significantly increased ($\chi^2=5.64$, $p<0.05$).

(3) Digestive Tract Disorders When the limit was set at $\geqq 4$ drugs for the number of prescribed drugs, the incidence rate of DM was significantly increased ($\chi^2=7.52$, $p<0.01$). This value was the same as for SL. The stratifying point of PB total level was 16.0 μg/ml in patients with DM ($\chi^2=5.34$, $p<0.05$); however, this limit shifted down to 10.0 μg/ml in patients taking both PB and PHT ($\chi^2=4.69$, $p<0.05$). In patients treated with PB, number of prescribed drugs, the PHT free level and the 5-HPPH/PHT level ratio were additional risk factors for the incidence of DM.

From a similar analysis for the number of prescribed drugs, the limit was 4 drugs ($\chi^2=5.27$, $p<0.05$), indicating that CP occurred significantly more often in patients taking more than four prescribed drugs, including BZN.

When the limit was set at $\geqq 15.0$ mg/kg/d for a VPA daily dose, the incidence of NV was significantly increased ($\chi^2=4.76$, $p<0.05$). However, an additional risk factor could not be observed.

(4) Miscellaneous When the limit was set at $\geqq 1.25$ mg/kg/d for the PB daily dose, the incidence of GF significantly increased ($\chi^2=4.07$, $p<0.05$). This value was the same as for SL. Drug factors in patients whose PB daily dose stayed below the limit were compared between patients with and without GF. The 5-HPPH/PHT level ratio (0.43 ± 0.16 *vs.* 0.57 ± 0.21, $p<0.05$) was significantly lower, and the VPA daily dose (1050.0 ± 475.1 *vs.* 700.0 ± 358.1, $p<0.05$) was significantly higher in patients with GF. Consequently, in patients indicating a lower 5-HPPH/PHT ratio or treated with VPA in a high daily dose, GF was more frequently observed even when the PB daily dose stayed at <1.25 mg/kg/d.

Weakness occurred significantly more often in patients taking more than five drugs ($\chi^2=4.29$, $p<0.05$).

Discussion

Side effects were present in 150 patients (66.1%), indicating that AEDs gave rise to SEs in 1 of every 2 patients. A collaborative group[16] described SEs in 31% of patients of all ages and in 22% with monotherapy, but there was a very wide range (6—79%) among the various centers.

Examination of the individual AEDs showed that SEs of PB occurred in 5—30% of our patients (Fig. 1). Mattson *et al.*[3] reported neurologic SEs in 24% and digestive disorders in 11% of patients receiving PB as compared to 15—30% and 5—15% in our experience.

Gingival hyperplasia occurred in 13% of patients with PHT, in agreement with some literature (12% by Millichap and Aymat[17]; 15% by Buchanan and Allen[18]). The relationship between gingival hyperplasia and high free serum levels of PHT was observed in our study, in contrast to the findings of Herranz *et al.*[19]

CBZ produced SEs in 5—40% of our patients, in agreement with the previous report.[19] Like Troupin *et al.*,[20] no significant differences were found in CBZ dosages or serum levels between patients who did and did not experience any SEs except rash. Digestive disorders occurred in 10—20% of our patients during CBZ treatment. This rate is similar to that reported in patients of all ages during monotherapy[21] or polytherapy.[22]

SEs were observed in 5—25% of patients during treatment with VPA in our study. When VPA was given alone, SEs were described in 30—35% of patients of all ages.[23] The commonly observed VPA SEs in our patients were digestive disorders, in agreement with the literature. Nausea and/or vomiting occurred in 10% of the patients, with no relation to serum levels, as also reported by Froscher *et al.*[24] Nervous system disorders occurred in 15—20% of patients with VPA, however, nearly all publications mention these SEs attributed to the start of polytherapy.[25,26]

AEDs is often given in combination with other AEDs in the hopes of improving the control of epilepsy.[27] In our study, the incidence of SEs (*e.g.* SL, MI, SM, DM, CP, weakness) significantly increased when three AEDs were co-medicated with BZN or AZM. The mean number of the prescribed drugs was 3.1, which decreased from 4.1 to 3.1 during the last decade[28] in our hospital, and this value is similar to that surveyed in four European countries by Guelen *et al.*[29] The reasons for the widespread use of polytherapy have been reviewed by Reynolds *et al.*,[30] who have also discussed the many serious problems related to prolonged polytherapy. In addition, the negative effects induced by polytherapy, such as chronic toxicity, drug interactions and failure to evaluate individual AEDs, were also reported.[31,32] A collaborative group[16] showed that the proportion of patients with SEs increases with the number of AEDs taken, such that nearly half of the patients taking three or more drugs will have significant complaints. Thus, it is emphasized that one or at most two AEDs should be given to minimize the risk of SEs.

The findings indicate that it may be important to consider the drug combination patterns before inferring serum concentration related SEs. Indeed, the majority of patients had clinical SEs in or below the "therapeutic range," even in free concentration. A relationship between the drug combination patterns and the incidence of SEs (*e.g.*, SL, MI, DM, CP) was clearly observed. The occurrence limits of SEs in AEDs serum levels and daily dosage were also recognized. Interestingly, these limits changed with the

co-medication of other AEDs. Furthermore, BZN polytherapy with AEDs was observed as a risk factor for SEs in this study. There are various reports of BZN being associated with the deterioration of cognitive function.[33] Sommerbeck *et al.*[34] showed that concurrent treatment with clonazepam was associated with greater decrements in cognitive function. Consequently, the commonly accepted "therapeutic range" or "usual daily dose" may be shifted down in patients taking more than two AEDs with BZN or AZM, especially BZN.

The combination of two AEDs may alter the pharmacokinetic and metabolism of either or both. For example, the addition of PHT or VPA to CBZ caused an increased level of CBZ epoxide by different mechanisms,[35,36] and this pharmacologically active metabolite may contribute to CBZ's efficacy and toxicity.[37] There is little information on how to interpret simultaneous serum concentrations of AEDs and its metabolite in clinical situations. However, the contributory role of metabolites in the occurrence of SEs can be speculated in this study. As shown in Tables III or V, positive associations between the CBZE/CBZ ratio and the incidence of SL or HA or VT, and the 5-HPPH/PHT ratio and SL or DM or GF or GH, are suggested. The SL or HA or VT could have been due to a combination of CBZ and its epoxide. In spite of CBZ, the metabolites of PHT have so far not been shown to possess significant pharmacological activity.[38] The 5-HPPH/PHT level ratio was significantly lower in patients with SL or DM or GF (Table V). Drug interactions reducing PHT metabolite may contribute more strongly. However, there is no firm evidence in the literature to support this hypothesis. Recently, the relationship between the incidence of GH and HT and the index of stereoselective metabolism, the (*R*)-HPPH/(*S*)-HPPH ratio, was speculated.[39]

The hypothesis of synchronization between a variation in serum AEDs concentrations (both total and free) or daily dose and SEs was not confirmed. The negative finding was consistent with those reported by Thompson *et al.*[40] This confirms that in some patients, factors additional to the serum concentrations of the AEDs determine the development of SEs. Reynolds also failed to find a relationship between toxic plasma levels and neurotoxic SEs.[41] Individual susceptibility to SEs is different interindividually and is probably multifactorially determined. The observed limits of SEs in serum concentrations and daily dosages are also within the normal ranges, indicating that an additional factor may be a more important risk factor for the incidence of SEs. In this study, the additional risk factors are more closely related to drug factors than patient's characteristics. Patients in this study were all ambulatory patients who did not have severe hepatic and renal dysfunctions, which would have altered AEDs pharmacokinetics.[42,43] It seems likely that these patients' condition reflects this result. Although it is not clear that all SEs relate to the prescription of AEDs, the drugs themselves have been shown to have an additional, important impact. Larkin *et al.*[44] suggested that the therapeutic range had a smaller influence on decision-making than might be expected; however, the AED concentration measurement affected management decisions for the patient's treatment in >20% of patient visits. The incidence of SEs, which are commonly observed but more easily ignored in ambulatory patient treatments, could be greatly reduced by careful monitoring of single-drug therapy.

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