BARBITURATE-REFRACTORY EPILEPSY

SAFE SCHEDULE FOR THERAPEUTIC SUBSTITUTION

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Barbiturates are the main line of antiepileptic drug therapy in many third world countries due to a traditional prescribing habit which survives to this day in relation to factors such as low cost and simplicity of use. An over-simplification of epilepsy as a uniform clinical entity allows usage of a single treatment at any age without regard to specific types of seizure disorders. There is also widespread belief that there are no side-effects of considerable importance associated with barbiturates, completing an illusory picture of a simple medical problem, epilepsy, which may be solved by a simple therapeutic manoeuvre, barbiturates. The frequency of barbiturate side-effects is high, but they may go unnoticed by physicians because they affect mood and intellect in a relatively subtle manner. In children the frequency of hyperkinetic behaviour varies from 8% to 42% in different studies [9,13]. The latter may be a more correct estimate related to increased awareness by more recent investigators. In adults there is evidence that barbiturates impair sustained attention [6] and memory function [7]. Some of these effects are related to serum concentrations and their severity decreases as the drug is withdrawn [6,10]. Sedation, psychomotor slowing and depression of mood are the most common observations during chronic therapy, although tolerance usually develops at least partially as time goes on [8]. Tolerance appears to develop to the therapeutic as well as to the side-effects of phenobarbitone [3]. Patients tolerate progressively higher doses which are needed to maintain seizure control [3,5]. Rebound increase in seizure frequency is the rule on withdrawal of barbiturates [4,5,10]. Varying rates of development of tolerance probably underlie the difficulty in establishing relationships between serum concentration and affect on central nervous system (CNS) function [11].

We have studied a population of epileptic patients who became refractory to barbiturates after varying amounts of time. Their types of seizures and the seizure frequency during replacement of barbiturates by therapy drugs with other drugs were evaluated in a prospective manner with the objectives of clarifying which patients tend to become refractory and what may be an appropriate schedule for withdrawal.

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PATIENTS AND METHODS

Approximately 600 epileptic patients were assessed in the Neurology out-patients clinic of the Hospital de Clínicas da Universidade Federal do Paraná between April 1982 and April 1984. They were included in a prospective study designed to obtain basic data on epilepsy in southern Brazil (1,2). The protocol established standard therapeutic procedures with the objective of achieving monotherapy. When patients were first seen on polytherapy with uncontrolled seizures, they were reduced to monotherapy with carbamazepine or phenytoin (partial seizures with or without generalization), sodium valproate (generalized seizures of the absence or myoclonic types) or any of these three drugs (primary generalized tonic-clonic seizures).

If patients presented with uncontrolled seizures while on pharmacological doses of barbiturate drugs these were withdrawn. The procedure for withdrawal was standardized. The new drug was adjusted until clinical toxicity or seizure control was achieved, after which the barbiturate was progressively withdrawn. For this purpose all barbiturates were changed to an equivalent dose of phenobarbitone. The rate of dose reduction depended on the frequency of seizures but usually it was reduced by 50% at intervals of one month.

RESULTS

Fifty-two patients agreed to enter the barbiturate withedrawal schedule. In 10 cases withdrawal could not be completed due to an increase in seizure frequency but none needed hospital admission. Four of these patients were male and 6 female. Their age was 24±8 (mean±standard deviation) years. All had primary educational level or were illiterate, two had neuro-psychiatric disturbances, two had a positive family history for epilepsy and two had a specific etiology for their epilepsy (infantile hemiplegia and meningo-encephalitis). Five patients had complex partial seizures, three had simple partial seizures with generalization and two had complex partial seizures with generalization. The electroencephalogram (EEG) was abnormal in 9 of the 10 patients. A focal temporal lobe abnormality was found in 5 patients, other focal abnormalities in two and generalized abnormalities in the remaining two cases. The 10 patients had had epilepsy for 12±6 (mean±standard deviation) years. Four patients were on barbiturate monotherapy. Five were also on phenytoin and one on sodium valproate. Taken together they had been on barbiturates for 7±6 (mean±standard deviation) years. Eight patients were on phenobarbitone at a dose of 125±20 mg daily (mean±standard deviation). Two were on primidone 750 and 1000 mg daily. The monthly seizure frequency of these 10 patients was 10. Seven patients developed increased seizure frequency when 50% of the barbiturate dose had been decreased, two when they did not follow the drug regimen correctly and one patient when the barbiturate dose had reached 25% of the initial dose. They settled after the dose of barbiturates was increased to the previous step. Due to their small number and to their characteristics which were similar to those patients in whom successful withdrawal was achieved, these patients wil not be considered any further (Table 1).

Twenty-four female and 18 male patients (81%) of the initial group achieved successful barbiturate withdrawal. Their age was 29±13 years (mean±standard deviation), with a range of 15 to 64 years. Eighty-eight per cent of the patients had a primary educational level or were illiterate, 17% had neuro-psychiatric associated

Characteristics	Not withdrawn	Withdrawn
Number	10	42
Age	24 ± 8	29 ± 13 years
Primary education	100 %	80 %
N-P features	20 %	17 %
Partial epilepsy	80 %	71 %
Duration of epilepsy	12 ± 6	15 ± 9 years
On polytherapy	60 %	50 %
Time on barbiturates	7 ± 6	6 ± 6 years
Phenobarbitone dose	125 ± 20	113 ± 39 mg/day
Monthly seizure frequency	10	7

Table 1 — Characteristics of patients in whom barbiturate drugs were or not successfuly withdrawn and replaced by carbamazepine, phenytoin and sodium valproate. (NP = neuropsychiatric).

features and 24% had a positive history for epilepsy. A specific etiology for epilepsy was found in 17 patients (40.4%). Six patients had history of severe head injury, 6 of severe hypoxia around the time of their birth, two had had infantile hemiplegia, one had a history of meningitis, one was hemophiliac and his epilepsy started after severe head injury, and one patient had sustained an infarct on the territory of the right middle cerebral artery. The frequency of seizures types is shown (Table 2). Routine EEG records showed epileptogenic features in 52% of the patients. A focal temporal lobe abnormality was demonstrated in 54.6% of the EEGs. In 18.2% focal abnormalities were found in other areas. In 18.2% focal or generalized slowing and in 9% generalized spike-wave discharges were found. Combining clinical evidence of the presence of a focal brain lesion (partial seizures) with EEG evidence of a focal disturbance (focal spikes or slowing) 30 of the 42 patients had partial epilepsy with or without generalization (71.4%).

Seizure Type		Patients Number
Partial	Simple	1
	Complex	12
Partial with Generalization	Simple	8
	Complex	13
Generalized	Tonic-clonic	13
	During sleep	5
	Absence or mioclonic	1

Table 2 — Seizures types in 42 patients who had barbiturates withdrawn and replaced by carbamazepine sodium valproate or phenytoin. Thirty-two patients had 1 seizure type, 9 had 2 and 1 had 3 types of seizures.

The 42 patients had had epilepsy for 15±9 years and had been on barbiturates por 6±6 years (mean±standard deviation). Fifty per cent of the patients were on monotherapy with a barbiturate and the other 50% were on polytherapy. Of the latter 57% took phenytoin as a second drug, 19% took carbamazepine and 15% took carbamazepine and phenytoin. The daily dose of barbiturates used before withdrawal was 113±39 (mean±standard deviation) mg of phenobarbitone in 40 patients. Two patients took primidone at the dose of 750 and 1000 mg daily. The 42 patients had been on barbiturates for 6±6 years. The time necessary for withdrawal was 5±3 months and subsequent follow-up was 13±7 months. The frequency of seizures per patient per month before the drug changes were started was 7.1. The frequency of seizures after complete barbiturate withdrawal became 1.7 per patient per month (Table 3). Forty patients were changed over to monotherapy with carbamazepine (67.5%) or phenytoin (22.5%), respectively at dosages of 752±245 mg and 333±39 mg daily (means±standard deviations). Four of the patients were changed to polytherapy with carbamazepine and/or phenytoin and/or sodium valproate.

Month	Number of patients with					
	0 sm	1 sm	2 sm	3 sm	4 + sm	Total
1	24 (57%)	6	4	3	5	42
2	26 (61%)	9	2	0	5	42
3	23 (56%)	7	5	1	5	41
4	22 (61%)	5	3	0	6	36
5	22 (66%)	4	2	0	5	33

Table 3 — Number of patients with 0, 1, 2, 3, 4 or more seizures monthly (sm) during change over from barbiturates to carbamazepine, phenytoin or sodium valproate. Time of barbiturate withdrawal varied.

COMMENTS

The results demonstrate that withdrawal of barbiturate with concomitant replacement by efficient antiepileptic drug therapy is possible in 4 out of 5 patients with uncontrolled epilepsy. The absence of complications such as status epilepticus was possibly due to the progressive nature of the drug change. Besides making possible the withdrawal of medication which was not efficient any longer, this manoeuvre improved seizure control in 42 of 52 patients. Few similar studies have been published. Theodore and Porter reported the results of withdrawal of benzodiazepine and barbiturate drugs in 78 patients with intractable epilepsy [12]. In 48 cases this was accomplished while patients were admitted to a specialized epilepsy unit and in the 30 remaining cases the change-over was carried out on and out-patient basis. Seizure frequency, signs of central nervous system toxicity and in some cases performance at school improved in subjective criteria used by the investigatores. Our results suggest that hospitalization is not generally necessary for withdrawal of barbiturates.

The 42 patients in whom successful withdrawal was achieved had a history of brain injury due to trauma, hypoxia, infection or other causes in 40% of the

cases, as compared to similar etiology in 30% of the general epileptic population of Curitiba [1]. The frequency of patients with partial seizures is higher in the barbiturate refractory group (74.4%) than in the general epileptic population 60%[1], using similar definitions. The frequency of abnormal EEGs was higher in the present group (52% as compared to 40%). There was a high frequency of temporal lobe epileptogenic abnormalities (55% of abnormal EEGs).

The group of barbiturate refractory patients is characterized by long-standing epilepsy, the diagnosis having been made approximately 15 years before they entered the study. They had been on barbiturates for approximately 6 years but the study did not show how long after beginning barbiturates patients became refractory. Evidence from earlier studies [4,5,10] as well as from these results indicate that the antiepileptic effect of barbiturate drugs may decrease during chronic therapy, specially in cases of partial epilepsy with or without generalization when a temporal lobe abnormality is found in the EEG. The amount of time necessary for development of tolerance is not clear, but is under 6 years in average. The difficult situation then achieved may be improved significantly by a progressive decrease of barbiturates drugs over a period of in average 5 months on an out-patient basis, in the majority of cases. As most patients which become refractory suffer from partial epilepsy, carbamazepine and phenytoin seem the most appropriate drugs to be instituted.

Serum concentrations were not measured in this study because they are not available routinely in most third world countries. As demonstrated previously (Bittencourt et al. 1983)[2] tailoring the dosage through close clinical observation of seizure frequency and signs of CNS toxicity appears to suffice in the majority of cases, if pharmacokinetic principles are kept in mind. Although formal assessment of neuro-psychological function was not carried out, there was a generalized feeling among patients and physicians that irritability, slowness of thought, depressed mood and generalized viscosity of behaviour improved significantly as patients became free of barbiturate drugs. These uncontrolled observations are in agreement with similar observations of Theodore and Porter [12] and with a number of previous studies showing impairment of various aspects of higher brain functions by barbiturate drugs [6,7,9,10].

Taken together, the development of tolerance and the resulting reapperance of seizures with the impairment of brain functions seem to contra-indicate barbiturates as first-line antiepileptic drugs, contrary to widespread and traditional practices in third world countries.

SUMMARY

Barbiturates are considered first line antiepileptic drugs in third world countries due to traditional and economic reasons. This prospective uncontrolled study of 52 patients aged 15 to 64 years (mean 24) demonstrates that patients who become refractory to barbiturates are mainly those with partial seizures with or without generalization or with a focal EEG abnormality (71%). Seizures tend to become refractory approximately 6 years after barbiturates were started. Progressive barbiturate withdrawal over a period of two to 8

months (mean 5) with institution of treatment with carbamazepine, phenytoin or sodium valproate allowed complete barbiturate withdrawal in 42 of the 52 patients (81%). Furthermore monthly seizure frequency in those in whom barbiturates were withdrawn decreased from 7.1 to 1.7 per patient. An improvement in mental status was observed but not measured. These results show that barbiturates should not be first-choice drugs in patients who have a chronic disease such as epilepsy, and indicate a schedule for barbiturate withdrawal which is safe and independent of hospitalization or monitoring of antiepileptic drug serum concentrations.

RESUMO

Epilepsia refratária a barbitúricos: esquema seguro para substituição de terapêutica.

Barbitúricos são considerados tratamento anti-epiléptico de primeira escolha em países do terceiro mundo devido a razões econômicas e tradicionais. Este estudo prospectivo e não-controlado de 52 pacientes com idades entre 15 e 64 anos (média de 24) demonstra que pacientes que se tornam refratários a barbitúricos são principalmente aqueles com crises parciais com ou sem generalização secundária ou com uma anormalidade focal no eletrencefalograma (71%). As crises parecem se tornar refratárias aproximadamente 6 anos após o início do tratamento com barbitúricos. Retirada progressiva em um período de dois a 8 meses (média de 5) com início de tratamento com carbamazepina, difenil-hidantoína ou valproato de sódio permitiu retirada completa dos barbitúricos em 42 dos 52 pacientes (81%). Além disso a frequência mensal de crises naqueles de quem barbitúricos foram retirados diminuiu de 7,1 para 1,7 por paciente. Melhora no estado mental foi observada, porém não medida. Estes resultados indicam que barbitúricos não deveriam ser drogas de primeira escolha em pacientes com doença crônica tal como epilepsia, e indicam uma forma de retirada de barbitúricos que é segura e independente de hospitalização ou de monitorização de níveis séricos de drogas anti-epilépticas.

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