Drug compliance and seizure control in epileptic children

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Summary: The drug taking habits and compliance of 16 epileptic children were studied by means of a questionnaire, 'pill' count and serum antiepileptic drug levels (AEDL).

The questionnaire method overestimated patients' compliance while, because of the pharmacokinetics of antiepileptic drugs in children, single outpatients' drug levels may be misleading thereby not always reflecting the true degree of compliance.

Ten patients (62%) took more than 85% of their medication. Above this level of compliance there was a positive relationship to seizure control.

It would appear that drug compliance in epileptic children is as unsatisfactory as it is in adults on whom they largely depend for the administration of their medication.

Introduction

The compliance of adult patients with various medications has been extensively studied (Park & Lipman, 1964; Charney *et al.*, 1967; Stewart & Cluff, 1972). In the recent past, much attention has been focused on adult patients' compliance in the treatment of epilepsy. It has been found that poor compliance is a widespread and serious problem and affects control of seizures (Gibberd *et al.*, 1970; Wayne Marsey *et al.*, 1980). Furthermore, it is known that compliance can be improved by reducing the number and frequency of drugs taken with beneficial effect on seizure control.

In children many compliance studies have been done on short and long term medication but only a few of these relate to epilepsy (Dawson & Jamieson, 1971; Freiman & Buchanan, 1978). Since children rely on adults to administer their medication it is important to know whether the poor compliance of adults is reflected in the treatment of their children.

The aim of this survey is to study the drug taking habits of epileptic children, to see if compliance is a serious problem and to what extent it affects control of seizures.

Patients and methods

Patient selection

The study population was drawn from epileptic children attending the neurological out-patient department at Birmingham Children's Hospital for more than 6 months. The pattern and frequency of their attacks had been consistent during the 6 months immediately before the study period. Patients whose seizure patterns had altered significantly during that period were excluded as were children with petit mal epilepsy due to the difficulty in assessing accurately the frequency of their attacks.

The study period was between May and July, 1981 and in that time 16 patients were considered eligible for entry into the study. The age range was between 10 months and 14 y (mean 4 y). There were 9 females and 7 males. The clinical types of epilepsy are shown in Table I.

Table I Types of epilepsy in 16 children

	No. of children
Generalized tonic/clonic epilepsy	10
Partial epilepsy with elementary motor symptomatology	2
Partial epilepsy secondarily generalized	2
Complex partial epilepsy	1
Infantile spasm	1

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Table II Drugs used in 16 epileptic children

<i>Drugs</i>	<i>Number of children</i>
Sodium valproate	12
Carbamazepine	7
Phenytoin	2
Nitrazepam	2
Phenobarbitone	1
Acetazolamide	1
Diazepam	1
Total	26

Three patients were mentally subnormal, including one with cerebral palsy; three other patients, all mentally normal, had tuberous sclerosis (2) and hemiparesis (1). The 16 patients were either on single or multiple drugs as follows: 3 took three different drugs, 4 took two drugs and the rest (9) were on single medication. Table II shows the frequency and types of drugs used.

Patients were considered controlled if they had two or fewer seizures during the 7 months of known seizure frequency (i.e. 6 months before and 1 month during study) and uncontrolled if they had seven or more attacks during this period (i.e. more than once a month). So defined, there were seven controlled and nine uncontrolled patients. Of the seven controlled, five had no seizures and of the uncontrolled, eight had more than 12 attacks. Hence there was hardly any overlap between the two groups.

Method

Patients attended the clinic on their normal appointments. After being seen in the usual way, they were supplied with a special container or containers of known quantity of drugs prepared by the hospital pharmacy and told that the drugs were exactly the same as they had been on. They were then instructed that, as from the following morning, they should consume medication from the containers only and discard all previous drugs. They were then requested to return the containers and remaining drugs on their return visit in exactly 4 weeks time. The majority of parents did not question this sudden change in procedure, a point that had been noted by Park & Lipman (1964). The few who did were simply told that the pharmacy wanted to use up excess stock of medicines.

On their return visit the trial was explained and informed consent obtained for continuing the study. Parents were then taken through a questionnaire which enquired into various aspects of medication, including times of medication, doses missed, age of

commencement of self medication, seizure attacks during study period, size of family and occupation of parents. Blood was then withdrawn for anticonvulsant levels and finally the drug containers were retrieved for assessment of drugs consumed.

Results

Patient co-operation in the study was excellent. Thirteen patients returned their containers on their next visit and two had to go home to get them. One patient did not attend on the required day and was immediately contacted and encouraged to attend a few days later. All 16 patients assured us that only medication from the containers supplied was consumed during the study period and their dose regime was reconfirmed. The relevant data are presented in Table III.

Questionnaire

Thirteen patients denied missing any dose of their drugs. Three patients admitted to missing the occasional dose which on estimation was less than 5% of the total medication for the month. Another 13 patients declared that their drugs were taken within an hour of a specific time or times each day. Two patients took theirs within 2 h of a given time and one was erratic. Four children administered their own medication, the earliest age of commencement of self medication being 7 y. All morning drugs were taken between 06.30 and 08.00 h, but, as expected, there was greater variation in the time evening doses were taken, being between 17.30 and 21.30 h. One patient took her first daily dose at 15.30 h and the second at 20.30 h. None of the school-going children were on a midday dose.

'Pill' count

The percentage of drugs consumed was calculated from the quantity returned knowing the frequency and dose of medication and the amount supplied. For patients on multiple therapy the mean compliance was calculated. Patients who took more than 85% of their medication were considered as good compliers. On this criterion, 10 out of 16 patients (62%) were good compliers. Of the 7 controlled patients, 6 were good compliers compared to 4 of the 9 uncontrolled ($P < 0.005$). Two patients achieved 100% compliance. No patient consumed more of the drugs than was required.

There was no relationship between pill count and questionnaire. Of the 3 patients who admitted missing therapy, one was a good complier on pill count. Four of the 13 patients who said they took all their medication were poor compliers on pill count. The number of patients on more than one drug was too

Table III Clinical details of 16 patients

Patient	Age	Sex	Degree of control	Drugs	Serum level† µg/ml	% 'pill count' compliance	Mean % compliance
1	5	F	Uncontrolled (> 12)*	Carbamazepine	5.6	94	91
2	3	M	Controlled (< 2)	Valproate	46	88	60
3	10 months	F	Controlled (0)	Valproate	18	60	60
4	7	F	Uncontrolled (> 12)	Nitrazepam	—	94	94
5	9	F	Controlled (0)	Carbamazepine	7.3	78	78
6	3	M	Uncontrolled (> 12)	Valproate	76	‡	97
7	3	M	Uncontrolled (> 12)	Valproate	75	97	97
8	4	F	Uncontrolled (> 12)	Valproate	77	83	83
9	3	M	Controlled (0)	Valproate	68	100	92
10	1½	M	Uncontrolled (7)	Carbamazepine	9.5	83	93
11	7	F	Uncontrolled (> 12)	Diazepam	—	98	93
12	11	F	Controlled (0)	Valproate	53	80	100
13	13	M	Controlled (2)	Carbamazepine	10.7	100	100
14	12	M	Uncontrolled (> 12)	Valproate	77	100	100
15	8	F	Uncontrolled (> 12)	Carbamazepine	2.7	100	80
16	14	F	Controlled (0)	Phenobarbitone	15	60	85
				Carbamazepine	8.0	92	85
				Valproate	64	69	85
				Acetazolamide	—	93	85
				Phenytoin	27	100	100
				Valproate	66	95	95
				Phenytoin	2.0	90	81
				Carbamazepine	7.0	90	81
				Nitrozepam	—	63	79
				Valproate	110	79	79
				Valproate	52	91	91

*Numbers in bracket signify number of fits in 7 months period.

†Therapeutic ranges for the laboratory: valproate, 40–120 µg/ml; carbamazepine, 2–10 µg/ml; phenytoin, 7–17 µg/ml; phenobarbitone, 5–50 µg/ml.

‡Had to change from tablets to syrup during trial because of vomiting.

small to assess the effect of polypharmacy on compliance. These patients, however, showed variable compliance with their individual drugs which could indicate drug preference. No definite conclusions could be drawn between compliance and size of family or occupation of parents.

Drug levels

Only single blood samples were taken for drug level estimation. It was considered unjustified to do multiple levels during the study period because of the age group of patients investigated and also one would

have had to discuss the nature of the study from the onset which might have affected the compliance of patients.

The 16 patients took 26 drugs (Table II). Of these, 4 could not be measured. These were acetazolamide (one), nitrazepam (two) and diazepam (one). Therefore there were 22 estimations. All but two were within the therapeutic range for the laboratory (see Table III). Of these two, one was from a patient with the lowest compliance on 'pill' count, i.e. 60%, and the other was a patient on multiple therapy although the pill count compliance for the drug in question was 90%.

Discussion

The level of patient compliance that is acceptable in medical practice varies from different reports and also according to the disease treated. Ideally it should be regarded as that degree of departure from the doctor's instructions known to be associated with a clinically important deterioration in the patient's condition (Anonymous, 1979). No universally acceptable level has been found for epileptic patients though it is believed that improved compliance leads to better seizure control (Wayne Marsey *et al.*, 1980). A level of 85% intake of tablets prescribed has been chosen because at and above this level there was a definite relationship to improved control of seizures.

It would seem that compliance in epileptic children is as poor as in adult patients. Between 42% (Gibberd *et al.*, 1970) and 60% (Dawson & Jamieson, 1971) of adult epileptics have been found not to comply with treatment. In a group of 'reliable' adult patients, 31% took less than 70% of their medication (Moulding *et al.*, 1970). Compliance studies in children have been much fewer than in adults and those relating to epilepsy fewer still. In Shope's (1981) review of long term oral medication compliance in children between 1960 and 1980, sixteen publications were cited of which only five related to epilepsy. In these, compliance ranged from 25% to 75%. Serum drug level was used to determine compliance in each case and inadequate prescribing was found to be an important factor in some studies. Prescription errors were eliminated by the design of this study.

The information obtained from the 'pill' count method is taken as an adequate assessment of drug intake. Previous studies (Roth *et al.*, 1970) have found a good correlation between pill count and more reliable methods such as tracer substances in the blood. Questionnaires on this subject are known to overestimate patient compliance as it did in our study. We feel that the accuracy of the 'pill' count was further enhanced by failing to disclose to the patients that a survey was being undertaken until after the drugs were returned. An earlier disclosure may have prejudiced the outcome.

The relationship between antiepileptic drug levels (AEDL), seizure control and patient compliance is inconsistent (Livingstone *et al.*, 1979). In a study of epileptic children in South Africa (Frieman & Buchanan, 1978) seizure control was poor (38%) in patients having therapeutic levels of phenobarbitone whilst it was good in those with subtherapeutic levels and even those showing no detectable drug in their serum. Lund (1974) found that by increasing phenytoin levels from 11.7 µg/ml to 15 µg/ml annual seizure frequency was reduced from 4.1 to 1.6. This positive relationship between increasing AEDL and reduced seizure frequency is established (Kutt & Penry, 1974;

Reynolds, 1978). Nevertheless, the converse is not true – namely, improving control may not be associated with improved AEDL. Wannamaker *et al.* (1980) noted that reducing clinic intervals from a mean of 3.4 months to 1.1 months results in improvement in seizure control. Of the 9 patients so improved only one also improved his AEDL. Indeed, 4 patients actually had a reduction in their AEDL. The improved control was thought to be due to better compliance but this was not reflected in drug levels. These authors concluded that it was difficult to utilize AEDL as sole analysis for compliance or non-compliance.

The usefulness of AEDL in children must be taken in its full pharmacokinetic context. Single out-patient levels as were done in this study serve little, if any, useful purpose as a guide to therapy or compliance unless the latter is gross, as it was in one of our cases. Drug half lives in children are much shorter than adults and hourly variations greater, particularly for carbamazepine and valproate, when it may be considerable (Livingstone *et al.*, 1979; Redenbaugh *et al.*, 1980). Although most of our patients took their drugs about the same time in the morning and blood samples were taken between 14.30 h and 16.30 h, individual variation in rates of metabolism is such that meaningful conclusions cannot be drawn on their AEDL. This point is emphasized as many physicians looking after epileptic children still base therapeutic judgement on single out-patient AEDL. One should note that the antiepileptic activity of sodium valproate is not thought to be directly related to its serum level. We would suggest therefore that the finding of a therapeutic AEDL on a single out-patient estimation does not imply that the patient is fully compliant with treatment and, if such a patient is uncontrolled, the temptation to increase the dose or add another drug must be resisted until his degree of compliance is ascertained either by hospital admission or more frequent clinic visits.

It is noteworthy that all the controlled patients were on single medication thus confirming the views of Shorvon *et al.* (1978) that the majority of epileptic patients can be controlled on monotherapy. In addition, compliance may be further enhanced by a single dose regimen. Unfortunately because of the shorter half lives of antiepileptic drugs in children this may not be possible with many preparations. A possible exception to this rule is sodium valproate which has been shown by Covanis & Jeavons (1980) to be effective in single doses in children.

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