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Modern aspects of drug treatment in children with epilepsy

M SILLANPÄÄ

Departments of Public Health and Paediatrics, University of Turku, Turku, Finland

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This review paper deals with the drug therapy of children with epilepsy with special reference to diagnosis and differential diagnosis of epilepsy, measures before and at the initiation, follow-up, and withdrawal of the therapy. The updated aspects on the medication of various seizure types are discussed in detail.

People who have developed epilepsy have had their first seizures before the age of twenty years in 75 to 90% of the cases [1, 83, 99]. This fact is associated with various determinants that differentiate childhood epilepsy from adult epilepsy. Development of epilepsy, clinical and electrical manifestations of seizures, and the type of seizure disorders are highly determined by age, growth, and developmental aspects of children [98, 113]. Age has also been recognized as an important determinant of the prognosis both within single epileptic syndromes [5] and in general [123, 135]. Later, more sophisticated statistical methods using multivariate analyses applied to the same patient series have shown that the age at onset of epilepsies is not any independent prognostic factor, but on statistical analysis, absorbed by brain damage and other associated factors [137].

The younger the child, the more are pharmacokinetic and pharmacodynamic aspects to be considered. There are several developing physiological variables conditioning absorption, distribution and plasma protein binding, metabolic degradation, and excretion of drugs [95]. The pharmacokinetics of antiepileptic and other drugs are slower during the first days and weeks of life. The drug kinetics may be strongly modified by other variables such as blood pH, contents of free fatty acids, bilirubin, and protein, and many typological neonatal conditions and disorders. Therefore the therapeutic drug monitoring and concomitant determination of certain other variables are imperative to avoid toxic effects of the drug.

After the first week of life, the kinetic events are substantially faster. Drugs are absorbed and disposed at a faster rate and blood levels will be lowered if the daily dosage is not increased.

The rationale of interfering in the occurrence of epileptic seizures lies on the conception that recurrent seizures may produce brain dysfunction and damage and be conducive to a persistent epileptic state [10, 122].

In the treatment of a childhood epilepsy, there are some basic principles to be considered. Firstly, the drug therapy is the overwhelmingly most important means of preventing seizures but it is not the only one. Secondly, psychosocial factors may far outweight the mere problem of preventing seizures. Thirdly, there must be a total care of the child and the family. Fourthly, each patient and his/her family circumstances must be evaluated individually.

Diagnosis of epilepsy in children

When facing a child suspected of epilepsy one should ascertain the following four points: (1) Is there an epilepsy or not; (2) What is the seizure type; (3) Are there any seizure-provoking factors; (4) What is the aetiology of epilepsy.

There are two main requisites for making a diagnosis of epilepsy: one is exclusion of nonepileptic attacks and conditions, and another is recognizing factors arguing for the diagnosis of epilepsy. The attacks to be differentiated from epilepsy may be divided into organic and non-organic conditions. Organic conditions include cardiovascular disorders (aortic stenosis, arrhythmias, vasogenic and cardiogenic syncopes), transient cerebral ischaemia, movement disorders, toxic or metabolic disorders (e.g. hypoglycaemia, hypocalcaemia, renal insufficiency, drug toxicity) and migraine accompagnée. The non-organic conditions comprise psychogenic (hysterical, conversion, functional, and pseudoseizures, breathholding spells), and other psychiatric disorders, sleep disorders and malingering [90, 92, 114]. It is also to be remembered that epileptic and nonepileptic attacks may occur concomitantly. The modern methods of intensive monitoring may give a clearcut diagnosis [39, 92, 115], have put forward major and minor criteria for making a differential diagnosis between epileptic and psychogenic seizures.

There are many proposed and applied classifications of epileptic seizures and epilepsies. Many of them are too sophisticated and impractical for everyday clinical use, e.g. the ILAE classification of epileptic seizures [51] and its revised versions [31]. However, to meet the needs for assessing the seizure type and, in addition, medication and prognostication, the exact diagnosis of epilepsy or an epileptic syndrome in individual cases must be stressed. It is important to realize, as Dreifuss [41] emphasizes, that in almost all diagnostic categories there are two subgroups, namely the primary generalized epilepsy and the secondary, lesional epilepsy.

Factors provoking single seizures should, if possible, be identified [9] because one of the nontreatment criteria is the exclusion of seizure precipitating factors. Fatigue, psychological factors and stress are likely to induce a high proportion of seizures. Sleep deprivation, alcohol withdrawal and irregular use or complete omittance of antiepileptic medication can be readily added to the seizure provoking factors. Furthermore, there is

a smaller group of people who may experience seizures at the occurrence of specific stimuli such as flickering light, somatosensory, auditory and many other external stimuli.

The aetiology of defined epilepsy should be ascertained as far as possible. Progressive processes such as neoplasms and neurodegenerations should be ruled out. The probability of the occurrence of brain damage varies from type to type of seizures. In cases with no suspicion of brain damage and no abnormality on neurological examination, investigations of the morphology of the brain are unnecessary and even undesirable. In childhood, pre- and perinatal factors, infections and postnatal trauma comprise the most part of the causative brain lesions. Intracranial tumours are seldom found as a cause of epilepsy in childhood, the occurrence being, after the first seizure, less than one percent [84, 105, 153]. Most of the brain tumours in children are, at the age of 4–11 years in particular, infratentorial ones. It is therefore understandable that partial seizures occur in less than 15% of the children with an intracranial lesion. In these few cases, however, the diagnosis should be made without delay. The duration of seizures for years does not rule out an intracranial haemispheral tumour [8, 78, 141].

Laboratory investigations in diagnosis

Epilepsy is a clinical diagnosis. Therefore, one cannot enough emphasize the value of detailed previous history concerning heredity, course of pregnancy and delivery, and the psychomotor development. Previous diseases of the central nervous system and any disease of the head may be of utmost importance when aetiology, development and prognosis of seizures are concerned.

An EEG examination in both waking and sleep states must be carried out in every child who shows clinically defined or suspected epileptic seizures. If normal, it does not entirely rule out the possibility of epilepsy. With the appropriate record setting, approximately 10% of the children with a clinically distinct epilepsy have a normal EEG [53]. The years of intensive polygraphic monitoring may increase the possibility of abnormal EEG in the form of ictal tracing [17, 104]. Although an important means of monitoring cerebral functions, EEG data play only a complementary role to clinical impression.

In cases of suspected morphological changes in brain tissue, ultra-sound investigation, computer-assisted tomography, nuclear magnetic resonance scan, positron emission tomography etc. can be selectively utilized. Cases with suspected metabolic progressive encephalopathy warrant neurochemical determinations of blood, cerebral spinal fluid and other body fluids, etc.

Measures preceding commencement of drug therapy

The doctor himself must first arrive at the conviction that a drug therapy

should be started. Before the decision, several aspects must be considered. Is there a defined diagnosis of epilepsy? Is the seizure type defined? Is there any causal therapy? Are there any identifiable and removable seizure-provoking factors? Are the seizures of self-limiting sort without any drug therapy? In cases with benign epilepsy of childhood with rolandic spikes, for example, a drug therapy is recommended, but as a monotherapy [5]. To be sure about a reasonable compliance, an informed consent from the parents of the child should be obtained. The data outflow from mass media concerning toxicity of drugs has frightened many parents, who are then reluctant to administer drugs to their children.

To ascertain as good a compliance as possible, the virtual state of affairs should be made clear to the parents in simple words. The doctor should also emphasize the necessity for a prolonged supervision. He should make the parents realize that the antiepileptic treatment is a reasonable compromise between beneficial effects on one hand, and unwanted side effects on the other hand. The parents should also be told in advance, that the purpose is to get a "tailor made" drug treatment for each patient. Therefore, several changes in drugs, drug combinations, doses and dosages may prove necessary in the near future before the purpose is achieved.

Avoidance of known seizure-inducing factors, regular rhythm of daily activities, regular administration of drugs, accurate record of the frequency of seizures and awareness of eventual side effects should be included in the information given to the parents in several successive sessions. Information to be given by the parents to day care personnel, teachers and relatives should be discussed. At the same time the avoidance of overprotection and seclusion of the child should be stressed.

The child's parents should be informed that the antiepileptic drug treatment is not a matter of weeks or months, but that of years. Therefore, the decision-making must be preceded by the doctor's careful risk-benefit analysis. He must balance the obtainable beneficial antiepileptic effects to several untoward circumstances such as daily administration trouble at home, risks of noncompliance, acute and chronic, idiosyncratic and dose-related unwanted effects, drug interactions, behavioral influences and social labelling.

Before the administration of the first drug dose, the baseline determination of the function of haematopoetic system, liver and kidney should be performed. These include urine analysis, CBC, differential, platelets, ASAT, bilirubin, and alcaline phosphatase plus amylase and fibrinogen in patients taking valproate [26].

Initiation of drug therapy

Starting the medical therapy with a single drug must today be regarded as self-evident. Acute and chronic unwanted effects of the chosen drug

must be explained and readily related to everyday risks of life. The daily dosage should be progressively increased to minimize acute dose-related side effects. The dosage should not be too rapidly increased as such a procedure hampers an adequate assessment of the effect. The daily dosage should be kept as low as possible to control the seizures. The so-called therapeutic levels are averages, which cannot be applied to individual cases. Every patient has his personal therapeutic level for each drug. Consequently, the clinical control may be complete, although the dosage is "subtherapeutic" [76]. The effect of the increase of dosage should be observed for one week to one month before further increases, although the full effect may be obtained only after two or three months of administration [96]. On the other hand, most recurrences will occur within three months from the previous seizure [118]. Then the period of three months is enough to show the efficiency of that drug dosage. At the same time, however, a careful monitoring of untoward effects should be carried out. Unwanted effects may develop at the early stage with a relatively low dosage. In such cases, a temporary lowering of the dosage is warranted.

Monitoring of certain laboratory values to control bone marrow, liver and renal function may be imperative on medical grounds and, in certain cases, due to the instructions of the National Medical Board. These measurements are particularly to avoid idiosyncratic side effects of the drug during the first three to six months of the therapy. However, although sometimes fatal, these haematological complications are very rare, and even frequent intensive monitoring may not provide any safety from this kind of catastrophe one week later [48].

If the first drug has failed to control the seizures when the blood level of the drug has reached the upper limit of the range, another drug may be combined with it in progressively increasing doses. An increasing risk of side effects and interactions must then be considered. If the new drug is successful, the dosage of the first drug should be gradually decreased and the drug then totally discontinued. On the other hand, a combination therapy may be continued, if its effect has been demonstrated as better than any single therapy [114, 124]. A monotherapy must, however, always be a therapeutic aim [42].

Follow-up and withdrawal of drug therapy

The doctor must see the patient with intervals of one to three months in the beginning of the drug therapy, and also as long as the condition is not stable. Otherwise, the clinical control with appropriate laboratory examinations may be needed once or twice a year.

There are still divided opinions about the length of the seizure free period sufficient to justify drug withdrawal. The range is in children from a few months to five or more years

[5, 63]. Recently, Peters et al [110] concluded that "there are no reliable predictive factors for withholding the benefits of stopping medication from any individual 'epileptic' child after two years of seizure freedom". Yet five or more years of seizure freedom before drug withdrawal is advocated e.g. in cases with Lennox syndrome, juvenile myoclonic epilepsy in adolescents, awakening generalized tonic-clonic seizures, and epileptic syndromes of proven or probable lesional origin in general [5, 54]. This is at least in part supported by the fact that relapses are substantially more frequent in these resistant cases even despite of five or more years' freedom from seizures [100–102]. The relapse rates varied from 5% in petit mal absences to 50% in secondary generalized partial seizures.

The practice we personally apply is to observe mainly clinically the patient to obtain for at least three years' freedom from seizures and then make an individual decision with consideration of various extraneous factors such as family situation, social events, desire of pregnancy, driver's licence, military service etc. In case of poor compliance, we are inclined to discontinue the therapy hoping that a possible relapse would make the compliance better.

To lower the frequency of recurrences, the drug withdrawal should be carried out over a time of six to twelve months [27, 84]. Single seizures recurring during the first two or three months elapsed from the discontinuation of the therapy, may be "withdrawal seizures" [142], but seizures occurring after that early period should be regarded as relapses [5].

Drug therapy of single seizure types

In the following, when the drug therapy of single types of seizures is concerned, a somewhat modified classification from that of the ILAE classification 1981 [31] with certain aspects from ILAE classification 1985 [31] will be applied. The primary grouping into partial and generalized seizures with subgroups of primary and secondary seizures is followed by stimulus-sensitive epilepsies, epilepsia partialis continua, neonatal convulsions, status epilepticus, and febrile convulsions. The various seizure types are defined in accordance with ILAE 1981 definitions. The following recommendations are based on personal experience, on data from the inquiry sent to Finnish doctors with full authorization in child neurology, and data in the literature based mostly on controlled studies. At present, many drugs, "major" anticonvulsants in particular, are quite comparable with each other in antiepileptic efficacy. Therefore, the choice between drugs appears to be more or less dictated by their potential toxicity [14, 136].

Partial epilepsies

Primary partial epilepsies. Primary partial epilepsies, a modification from the ILAE classification 1981 by Gastaut [52] comprises benign childhood epilepsies with centromidtem-

TABLE 1

Drug choice in primary and secondary partial epilepsies in children

Choice	Drug	Responders* Quota	%
Primary			
1st	Carbamazepine	13/15	87
2nd	Phenytoin	5/10	50
	Valproate	4/10	40
3rd	Phenytoin	3/8	38
	Valproate	3/8	38
Secondary			
1st	Carbamazepine	15/15	100
2nd	Valproate	7/14	50
	Phenytoin	5/14	36
3rd	Phenytoin	5/15	33
	Valproate	3/15	20

* Quotas and percentages in the tables refer to the results of the questionnaire mentioned in the text

poral, midtemporal, or parietal spikes or occipital spike-waves [5, 52].

Carbamazepine monotherapy is almost unanimously recommended as the treatment of choice in benign partial epilepsies [5, 36] because of its few side effects and low toxicity. Some authors prefer phenytoin [50, 80]. Valproate may be recommended as the second or third choice [36, 86], although some [80] consider it as inefficient in these cases.

Secondary partial epilepsies. What has been said about primary partial seizures, can also be applied to secondary partial epilepsies with or without secondary generalization [50]. Although the preference is in the monotherapy, secondary partial seizures with generalization may prove rather drug-resistant. In such cases a combination of carbamazepine with other drugs such as phenytoin, valproate, or primidone may be efficient [57, 136].

Generalized epilepsies

Petit mal absence epilepsy (pure petit mal). The greatest consensus has been obtained in the treatment of cases with petit mal absence epilepsy, although a certain confusion in the terminology still prevails [5]. However, the drug treatment is largely the same in various petit mal absence epilepsies and syndromes. Ethosuximide is the first choice in young children without generalized tonic-clonic convulsions or irritative discharges in EEG other than typical bilateral, bisynchronous 3-Hz spike-and-wave epileptic discharges [23, 98, 133]. Sato [128] regards it as the first

choice even in cases with atonic or myoclonic seizures.

Many authors prefer valproate to ethosuximide particularly in cases with ethosuximide-resistance or in children with both petit mal absence and generalized tonic-clonic convulsions [35, 36]. No distinct difference in antiepileptic effect between ethosuximide and valproate has been demonstrated [25, 129]. A combination of valproate and ethosuximide has proved useful in refractory cases [124, 126]. If this combination does not work, benzodiazepines should be tried [5].

Petit mal myoclonic epilepsy (myoclonic petit mal). There is a marked consensus on valproate being the drug of first choice also in the late childhood myoclonic type of petit mal epilepsy [39, 67, 69]. In these cases, too, ethosuximide or a combination of valproate and ethosuximide may be tried for low toxicity reasons, if the valproate monotherapy has failed [5, 128]. The second choice is benzodiazepines, notably clonazepam in the first place [99]. Also the combination of valproate and clonazepam may be efficient, although severe side effects such as stuporous condition, profound sedation and petit mal absence status [5] may occur. In many cases clonazepam may be substituted for by nitrazepam or clobazam, because clonazepam has frequent and severe side effects [28, 93, 128] and develops

TABLE 2

Drug choice in generalized epilepsies in children

Choice	Drug	Responders	
		Quota	%
PM absence			
1st	Ethosuximide	14/15	93
2nd	Valproate	14/15	93
3rd	Ethosuximide + valproate	14/15	93
PM myoclonic			
1st	Valproate	11/14	79
	Ethosuximide	2/14	14
2nd	Clonazepam	5/11	45
	Valproate	2/11	18
3rd	Valproate + ethosuximide	4/10	40
Tonic-clonic			
1st	Carbamazepine	12/14	86
	Valproate	2/14	14
2nd	Valproate	8/13	62
	Phenytoin	3/13	23
3rd	Phenytoin	7/13	54
	Phenobarbitone	2/13	15

tolerance within some few weeks or months [22, 131].

Primary generalized (grand mal) epilepsy. In the treatment of primary generalized grand mal seizures, the spectrum of the antiepileptic is similar to that of partial seizures. Here again, carbamazepine is the drug of choice as equally efficient but less toxic than phenytoin, phenobarbital or primidone [40, 117, 130, 134, 144]. In addition, carbamazepine may have desirable psychotropic effects [136]. Valproate is to be preferred to phenytoin due to efficacy of the same order but with fewer side effects [24, 138, 150]. Phenobarbitone may be utilized as an add-on drug in certain cases [40]. Various combinations of these drugs may be tried if monotherapy fails.

Infantile spasms. Any evaluation of the pharmacological treatments of infantile spasms appears rather difficult and complicated because of the heterogeneous background of clinical studies [5, 77]. There is still a lack of double-blind controlled studies [73].

Corticotropin (ACTH) and steroids have occupied the first place in the treatment of infantile spasms since 1958. The daily dosage has varied in a range from 5 to 240 units [49, 143], but nowadays mostly 20–40 units are given as a single intramuscular injection in the morning. The high doses of 120–160 units generally employed previously, give no better results than 20–40 units [119]. The mean daily secretion of cortisol from the adrenals, when ACTH was administered to infants with infantile spasms was approximately 100 mg, whether the daily dose was 20 or 40 units of ACTH [6, 29]. With the use of this dose, the maximum blood levels of cortisol are obviously obtained [73].

20–40 units of ACTH seems to correspond to approximately 15 mg/kg/day of hydrocortisone [6], or 2 mg/kg/day of prednisone [65]. Also prednisolone (2–10 mg/kg/day), and dexamethasone (0.3–0.5 mg/kg/day) have been recommended [75, 140, 152]. No significant difference in efficacy between ACTH and corticosteroids has been found [61, 121, 152]. Some authors prefer ACTH therapy [81, 87, 139], with a consideration that ACTH has an antiepileptic effect at least partly independent of cortisol stimulation [40, 46]. Few existing studies [109, 151], however, show that ACTH fragments devoid of corticotropic effect do not give any favourable results.

The duration of the ACTH treatment is recommended to be from three weeks to six months in the literature. Relatively short periods of four to eight weeks may be preferred [7, 119].

The best results given in the literature have been based on selected patient series of cryptogenic infantile spasms [81]. A favourable short-term effect [3, 73] is followed by a much less dramatic success in the long run with a high frequency of relapses [71, 119] and of lowering mental level [78, 113]. Obviously, the steroid treatment has nothing to do with the psychomotor outcome, because no differences in psychomotor performance have been found between treated and nontreated cases [15, 68].

There are good reasons for treating cases of cryptogenic infantile spasms with ACTH and corticosteroids. On the other hand, symptomatic cases have no use of it in the long run and they should not be treated with ACTH or corticosteroids [4, 19, 61, 70, 98, 143, 152]. Contrary results have also been reported [73]. In cases of cryptogenic infantile spasms, at least the first relapse is adviced to be retreated, because the rate of secondary remission may be as high as 74% [120].

In infants with a symptomatic infantile spasm syndrome, and in ACTH-resistant cryptogenic cases, benzodiazepines, notably nitrazepam, are advocated [58, 66, 87, 148]. Clonazepam is less effective than nitrazepam [73, 87, 91], although some investigators have found clonazepam as effective as nitrazepam [98, 146]. In resistant cases, valproate may be tried [11, 107].

Akinetic-myoclonic (Lennox) epilepsy. The drug of first choice is valproate [13, 24, 59, 62]. If valproate fails for some reason, benzodiazepines are the second choice. Many investigators prefer nitrazepam to clonazepam, because clonazepam has frequent untoward side effects and it readily develops intolerance [5].

TABLE 3

Drug choice in infantile spasms, Lennox syndrome and progressive myoclonus epilepsy in children

Choice	Drug	Responders	
		Quota	%
Infantile spasms			
1st	ACTH	15/15	100
2nd	Nitrazepam	9/15	60
	Other benzodiazepines	6/15	40
3rd	Valproate	9/14	64
Lennox syndrome			
1st	Valproate	10/15	67
2nd	Nitrazepam	4/15	27
	Clonazepam	4/15	27
3rd	ACTH	5/14	36
	Clonazepam	3/14	21
Myoclonus syndrome			
1st	Valproate	13/15	87
2nd	Clonazepam	4/13	31
3rd	Valproate + clonazepam	4/10	40
4th	Valproate + clonazepam + phenobarbitone	2/10	20

A combination of valproate and clonazepam may be effective but may produce an absence stupor [16, 125, 132]. Clobazam is reported to be very effective in the Lennox syndrome [55]. In cryptogenic cases of akinetic-astatic epilepsy, a combination of valproate and ethosuximide may be tried. Reports on the efficacy of ACTH or corticosteroids in Lennox syndrome have been primarily anecdotal [5, 37]. However, in cases with a "primary" or cryptogenic akinetic-astatic epilepsy a steroid therapy has been proposed on the basis of possible immunodeficiency state [45]. If primary or secondary generalized tonic-clonic seizures are associated, carbamazepine may be added to the therapy.

Epilepsia myoclonica progressiva. In the treatment of progressive myoclonus epilepsy, the same antiepileptic drugs are employed as in other myoclonic epilepsies. Valproate is definitely the first choice, not least in cases with associated generalized tonic-clonic convulsions. Valproate as a single drug or combined with clonazepam may produce a successful outcome [5].

In more resistant cases, phenobarbitone may be needed as an additional drug. The efficacy of steroids in these cases remains to be evaluated.

Specific metabolic encephalopathies. Diseases which are here regarded as belonging to specific metabolic encephalopathies are e.g. different types of neuronal ceroid lipofuscinosis, phenylketonuria, and a number of other, very rare neurometabolic diseases. In these cases, valproate is recommended as the first drug—provided that there is no existing liver damage—in part due to the fact that the seizures may occur as infantile spasms or akinetic-myoclonic epilepsy [19, 34, 98]. In some cases, these metabolic diseases present with secondary or complex partial seizures [40, 103]. Carbamazepine may be preferred to valproate in these cases. In case of failing monotherapy, various combinations of carbamazepine, valproate, diazepam or even phenobarbitone may be tried.

Other epilepsies

Stimulus-sensitive epilepsies. Stimulus-sensitive epilepsies, including reflex epilepsies induced by specific sensory stimuli, "are precipitated by known or unknown factors acting on a CNS that is predisposed to the production of epileptic discharges by the presence of an organic lesion, a genetic constitution, or both" [5]. There are tens of known seizure-precipitating mechanisms [9] which should be avoided to prevent seizures. Because some of the known and any of the unknown factors cannot be avoided, a drug therapy must be tried. The choice of drug depends on the type of stimulus and that of seizures.

In photosensitive epilepsy, the most common stimulus-sensitive epilepsy, occurs in 80–90 per cent of the cases as primary generalized tonic-clonic convulsions [72]. In fewer cases, there may be seen (myoclonic) absence seizures and secondary generalized sei-

zures. Primary and secondary generalized seizures have in common a good response to valproate [43], which is then the first choice [44, 98].

Another larger group is startle-induced seizures which occur in children with focal brain laesions mostly originating from the pre- or perinatal period. The seizures are manifested as complex partial seizures. The drug of choice is carbamazepine [127]. Clonazepam or clobazam alone or combined with carbamazepine or valproate may be the second choice.

Epilepsia partialis continua. Two types of epilepsia partialis continua may be recognized: the non-progressive type, which is a particular form of rolandic partial epilepsy with a lesion in the motor cortex, and the progressive type with a progressive mental and motor deterioration and originally unilateral structural changes spreading bilaterally [12]. Carbamazepine, phenytoin, clonazepam and phenobarbitone may respond in patients with a non-progressive type. The progressive type may defy any drug therapy.

Neonatal convulsions

Benign neonatal convulsions. Two types of benign neonatal convulsions can be differentiated: a non-familial (fifth day fits), and familial convulsions. The syndrome of the fifth day fits is characterized by repeated clonic focal or multi-focal convulsions, which occur between the third and seventh day of life in full-term neonates without any neurological abnormality in the perinatal or neonatal period. These seizures are repeated frequently leading to a status epilepticus with the main duration of about twenty hours. Bursts of alternating theta rhythms particularly after a status epilepticus are suggestive but not characteristic of the syndrome.

Benign familial neonatal convulsions have their onset at the age of two to three (up to fifteen) days. Seizures are frequently repeated, of clonic type, and occur in full-term infants with a normal birth weight and usually a normal neurological state. There are some differences to fifth day fits. A positive family history

TABLE 4

Drug choice in epilepsia partialis continua in children

Choice	Drug	Responders	
		Quota	%
Partialis continua			
1st	Carbamazepine	6/15	40
	Valproate	3/15	20
2nd	Phenytoin	3/11	27
	Clonazepam	3/11	27
3rd	Phenobarbitone	3/8	38

of epilepsy, earlier age at onset, longer duration of convulsions, and more frequent occurrence of secondary epilepsy are more characteristic of familiar neonatal convulsions than of fifth day fits [111].

In the treatment of benign neonatal convulsions, the aetiology must self-evidently be considered both in the differential diagnosis and therapeutic measures. As to the medical therapy, phenobarbitone is mostly preferred [5, 48, 88, 98, 147]. In addition, phenytoin [5, 88] and in fewer cases primidone [107] or diazepam, paraldehyde, chloral hydrate, clomethiazole, or clonazepam can be used [111]. Obviously, most convulsions are self-limited in these cases.

Secondary neonatal convulsions. Secondary neonatal convulsions have an early onset at the age of two or three days. Two types can be recognized [5]: early-onset seizures with marked neurological involvement or those occurring in neurologically well babies. In cases with a marked neurological involvement, the seizures occur during the first three days of life in long series or as episodes of status epilepticus. The neurological state often presents with general muscular hypotonia, sucking disorder, defective reactivity and other serious abnormalities [18]. A hypoxic-ischaemic encephalopathy with secondary metabolic disturbances may often be diagnosed as the cause of the seizures. The early-onset seizures in neurologically well babies are characteristically associated with primary subarachnoid haemorrhage and localized intracerebral bleeding with partial seizures and a usually normal interictal neurological state.

The drug therapy of secondary neonatal convulsions is in principle the same as in benign neonatal convulsions. The discontinuation of seizures with diazepam followed by an intravenous infusion of phenytoin under cardiac monitoring can be helpful. In our experience carbamazepine in low daily doses may also be successful in these cases.

TABLE 5

Drug choice in neonatal convulsions in children

Choice	Drug	Responders	
		Quota	%
Primary			
1st	Phenobarbitone	10/12	83
2nd	Chloral hydrate	3/6	50
3rd	Clonazepam	2/5	40
Secondary			
1st	Phenobarbitone	12/12	100
2nd	Chloral hydrate	5/10	50
	Nitrazepam	2/10	20
3rd	Clonazepam	5/10	50
	Phenytoin	2/10	20

Pyridoxine deficiency should always be considered in resistant cases of newborn period or any time up to late infancy. Biotin should also be given a trial in failure of drug treatment of infantile seizures.

Status epilepticus

Status epilepticus, either a life-threatening convulsive state or a non-convulsive one, means an immediate intervention to prevent a fatal outcome or permanent sequelae in the brain. The intensive care unit facilities should always be available if the status epilepticus cannot be stopped within half an hour.

Diazepam is the drug of first choice for several reasons. It can be given both intravenously and rectally [22, 64, 116]. It has very rapid entry into the brain [85, 131]. It is highly effective in discontinuating the statuses of most kinds [5, 22, 40]. However, it is very short-acting and often warrants a readministration within 15 to 20 minutes. It may cause a respiratory arrest given alone or particularly in combination with phenobarbitone. The diazepam dose may be repeated no more than twice to avoid a dangerous accumulation of diazepam and its metabolites and potential toxicity. Diazepam must also be given cautiously to patients who have previously received a loading dose of long-acting anticonvulsant, phenobarbitone in particular [20]. Contrary to expectations, clonazepam, although may be effective in solitary patients after diazepam failure, has not proved better than diazepam [33,108], but has more side effects such as bronchial and salivary hypersecretion.

To avoid reappearance of status epilepticus after the bolus of diazepam or clonazepam, a loading dose of a second long-acting antiepileptic drug should be given [108]. This would be preferably phenytoin [5, 40, 85] to phenobarbitone, because the brain is more readily reached by phenytoin than phenobarbitone and because phenytoin is not a CNS depressant. A slow intravenous administration (0.5 to 1.0 mg/kg/min) is advisable as a first loading dose of 15–20 mg/kg b.w. and the following doses should be double the daily maintenance dose for at least three days.

The brain uptake of paraldehyde is rapid and, given 0.3 ml/kg rectally or

TABLE 6

Drug choice in status epilepticus in children

Choice	Drug	Responders Quota	Responders %
Status epilepticus			
1st	Diazepam	14/15	93
2nd	Clonazepam	6/14	43
	Paraldehyde	5/14	36
3rd	Phenobarbitone	7/15	47
	Phenytoin	3/15	20

0.1–0.3 ml/kg intramuscularly, it may effectively control convulsive status epilepticus. The intramuscular dosage should not exceed 5 ml. It may be repeated after an hour. It can also be given as an intravenous infusion at doses of about 0.15 ml/kg when diluted in saline.

Chlormethiazole, given as an intravenous infusion of 20–60 mg/min and followed by a maintenance infusion of 4–8 mg/min (0.8% solution) may be effective in some cases after failure of other agents [21]. There is a certain risk of respiratory and circulatory depression. Lidocaine, given as an initial intravenous bolus of 2–3 mg/kg and followed by slow infusion of lidocaine at 4–6 mg/kg/hr may give a rapid but transient effect and produce convulsions in high doses [20, 49]. Valproate may be useful given by nasogastric tube or even rectally [145]. If the status epilepticus defies any drug treatment, a lumbar puncture and/or general anaesthesia is required to control the condition.

Febrile convulsions

There are three determinants in the aetiology of febrile convulsions: fever, age dependency and genetic disposition [5]. Livingston [83] differentiated two subgroups within the category of febrile convulsions: simple and atypical febrile convulsions, also called complex febrile seizures. This differentiation is of practical significance in terms of prognosis but there is no clear difference of nature between the two types.

The treatment of febrile convulsions is a very controversial matter. Some kind of consensus might prevail on one goal of the drug therapy: to prevent recurrences of febrile convulsions. Recurrences occur in 30 to 35% of the cases and the long-term prophylactic anticonvulsant therapy may prevent about two thirds of them [5]. The Consensus Development Panel [33] on management of children with febrile seizures arrived at the decision that "anticonvulsant prophylaxis in therapeutic levels may be considered under any of the following conditions: (a) in the presence of abnormal neurological development (e.g. cerebral palsy syndromes, mental retardation, microcephaly); (b) when a febrile seizure is 1) longer than 15 minutes, or 2) focal or 3) followed by transient or persistent neurological abnormalities; or (c) history of non-febrile seizures of genetic origin in a parent or sibling." Other risk factors have been presented. These are the age of 12 to 18 months at the first febrile convulsion [79, 97], occurrence of a complex seizure or an abnormal status before the first febrile convulsion [97] or a pathological EEG.

A prophylactic anticonvulsant therapy may prevent recurrent febrile seizures [89] but there is no evidence that such kind of treatment might prevent later epilepsy [96]. The risk for recurrent seizures in the future is relatively low but may not be omitted in individual patients. Furthermore, the prevention of recurrences is desirable because they are frightening events for the children and their family [4, 5].

Two drugs, phenobarbitone and valproate are the overwhelmingly most effective drugs in a continuous prophylaxis. Their effectiveness is of the same order [149]. Phenobarbitone has frequent and valproate relatively few but more serious side effects. Reports are still very controversial and preferences are based on personal likings.

In continuous daily prophylaxis, there may be problems of compliance, not least because of side effects of the drug. In such cases intermittent prophylaxis may be advocated. Rectal solution of diazepam twice a day at the first signs of febrile illness has given successful results. As a drawback, there may be difficulties in recognizing the onset of illness so that medication can be given early enough to be effective. However, the third alternative in treating febrile convulsions is to stop a manifested febrile seizure as soon as possible by giving diazepam solution rectally. This method is preferable to other drug treatments in cases of simple febrile convulsions. If there is a young child, 18 months of age or less, with prolonged (more than 15 minutes) seizures and an abnormal neurological state, we use to discuss with the family about all possible items concerning whether or not to start a therapy and if so, which kind of drug would then be preferable in regard to side effects, number of daily doses etc. This is very important, because a good compliance can only be obtained in cooperation with the family.

Intractable epilepsy

There are several known reasons for intractable epilepsy. There may be an incorrect diagnosis of epilepsy or that of seizure types; a faulty drug or inappropriate dosing; poor compliance; or a serious associated brain disease. It is estimated, that 15–20% of the children with epilepsy have persistent seizures in spite of any drug therapy [137]. These patients may have a progressive neurological disease, infantile spasms, akinetic-myoclonic epilepsy, epilepsia partialis continua or an undiagnosed, very slowly expanding brain tumour.

In these cases massive efforts must be made to diagnose any underlying process. These patients often receive a combination of many drugs. Returning to fewer drugs or monotherapy may decrease the frequency of seizures and unwanted side effects.

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Matti SILLANPÄÄ, MD, professor
University of Turku
Departments of Public Health and Paediatrics
Lemminkäisenkatu 1
20520 TURKU
Finland