Bromides Were Effective in Intractable Epilepsy with Generalized Tonic-Clonic Seizures and Onset in Early Childhood

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Thirty-six children with epilepsy resistant to conventional treatment were treated with bromides in addition to the current therapy. Six out of 19 cases with prevailingly or exclusively generalized tonic-clonic seizures became seizure-free and in 9 cases a reduction in seizure frequency of more than 50% was achieved. Freedom from seizures could not be obtained in 13 cases, who had frequent minor seizures in addition to generalized tonic-clonic seizures. In some, minor seizures were even activated. Tonic and focal seizures showed no response. Side effects were observed in one-third of the cases (acne, loss of appetite, loss of weight, fatigue) but in no case they did become intolerable. Fifty to 80 mg potassium bromide per kg body weight seems to be an effective daily dose range. There is a preferential indication of bromides for patients suffering from early onset epilepsy with generalized tonic-clonic seizures and/or alternating hemi-grand mal, for whom other treatment is ineffective. This disorder is characterized by a high familial incidence of epileptic seizures, onset between 6 months and 3 years of age, normal development until the onset of seizures, generalized tonic-clonic seizures and often alternating hemi-grand mal, seizure precipitation by fever, and occasional combination with or transition to myoclonic-astatic and/or myoclonic seizures. EEG is often normal or shows slight slowing in the initial phase; later it shows theta rhythms and generalized spikes and waves. Especially, if the onset is during the first year of life, the course of the epilepsy is often unfavourable. **Key words: Epilepsy, generalized tonic-clonic seizures, therapy, bromides.**

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The anticonvulsant effectiveness of bromides was firstly reported by Locock in 1857 [1]. Until the introduction of phenobarbitone [2], bromides were the only effective anticonvulsant drugs. Later, when new antiepileptic substances were discovered, bromides fell into disuse and therapeutic experiences were reported only occasionally [3, 4]. Later Scheunemann [5] and Boenigk et al [6] reported positive results with bromide treatment in otherwise refractory epilepsies of early childhood with generalized tonic-clonic seizures (GTCS). Here, we report on our experiences with bromides in 36 children with severe epilepsies. We do not hesitate to state that our study is only of a retrospective nature. Our results, however, may show new aspects for the treatment of otherwise intractable epilepsies with GTCS. On the other hand, a controlled prospective study, although urgently desirable, will be a difficult task also in the future, because childhood epilepsies appropriate for bromide therapy are very rare.

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PATIENTS AND METHODS

During the last 15 years we treated 50 children with bromides. Thirty-six cases could be evaluated retrospectively. In the remaining 14 patients the information was insufficient due to external reasons, not related to the epilepsy or the effects of bromides: in some, the treatment was discontinued prior to sufficient steady state blood levels, but not on account of side effects. In no case, patients were excluded due to an unfavourable effect of treatment.

All patients suffered from severe epilepsies with GTCS which were insufficiently controlled by treatment with conventional anticonvulsants at the highest tolerable doses. At the onset of bromide medication, the patients

were between 1 and 22 years old, 9 years on average. The distribution of the age of onset of the epilepsy (Fig 1) shows a distinct maximum during the first year of life (27 out of 36 cases). The period between epilepsy onset and the introduction of bromides ranged between 3 months and 19 years, 8 years on average.

Group I: 19 cases, 11 male, 8 female; these patients suffered from exclusively or prevailingly GTCS.

Group II: 13 children, 6 male, 7 female, with GTCS and additional myoclonic, myoclonic-astatic seizures or absences (severe myoclonic, 9, or myoclonic-astatic epilepsy, 10).

Group III: Two boys with prevailingly nocturnal tonic seizures.

Group IV: Two boys with complex partial seizures and secondarily GTCS.

Practical therapeutic procedures

At first, bromides were prescribed as dibrophen® (potassium bromide, 400 mg; calcium bromide, 300 mg; phenobarbitone, 30 mg per tablet), which was later changed to Dibro-Be® (potassium bromide, 850 mg per tablet). Bromides were administered in addition to the current medication (phenobarbitone, primidone and/or valproic acid) and the dosage was increased to the intended level within a few days. As long as side effects remained tolerable, the current medication was left unchanged. Except in the first few years of our experience with bromide treatment, blood level analyses were carried out routinely at more or less regular intervals (x-ray fluorescence).

The therapeutic success of bromides was evaluated as follows: (1) freedom from GTCS for at least four average pretreatment seizure intervals, however, for at least 6 months; (2) reduction in GTCS frequency of at least 75%; (3) reduction of between 50 and 75%; and (4) no clear-cut effect or even deterioration.

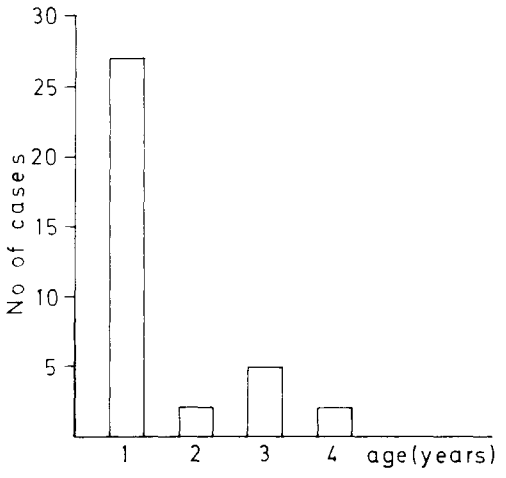

Fig 1 *Age at onset of the epilepsy in 36 children treated with bromides.*

RESULTS

Seizures (Table 1)

Group I: Six out of 19 cases became free of GTCS, 9 cases improved, while GTCS in the other 4 children showed no response. In one of these cases, the frequency of nocturnal tonic seizures increased.

Group II: Freedom from GTCS could not be achieved in these 13 cases with GTCS and additional minor attacks. Eight cases, however, improved for GTCS. In 2 cases, tonic and minor seizures, however, increased remarkably.

Group III: In these 2 cases, nocturnal tonic seizures did not respond positively.

Group IV: These two cases with complex partial seizures and secondarily GTCS did not respond positively.

EEG findings

In 90% of the cases EEG showed a rhythmic slowing of the background activity, and it showed in 40% hypersynchronous activity, prevailingly irregular spikes and waves. EEG was not influenced by the bromide treatment. Only in a few cases did the rhythmic slowing of the background activity tend to become less pronounced.

Bromide blood levels

In 34 patients for whom blood samples were taken at least 3 weeks after the last change in dosage, bromide blood levels were determined and evaluated conditionally as to total daily dose and body weight. In this group, the average dosage, body weight and blood level (1 SD) were 1,520.2 (674.7) mg/day, 33.1 (19.2) kg and 75.8 (23.5) mg/l, respectively. Taking the blood level as the dependent variable, the data yielded the following multiple linear regression equation:

$$y = 50.0 + 0.05*d - 1.30*w,$$

where d and w are the dosage in mg/d and the body weight in kg, respectively. The pertinent partial correlation coefficients were $r_{dy} = 0.88$ and $r_{wy} = -0.83$, and the coefficient of multiple correlation was $r_{mult} = 0.88$. Although the partial correlation coefficients were formally significant with respect to the sign at the 0.00000-level, these data should be interpreted descriptively because the distributions of both body weight and dosage significantly deviated from normal.

These results as well as practical experience of our cases led to the following therapeutical scheme: Bromide treatment should be started with approximately 60 mg/kg/day to obtain blood levels of between 80 and 120 mg/dl (x-ray fluorescence). For serum, corresponding levels are 20% higher (96-144 mg%). Blood level determinations should not be perfomed before 3 weeks after the last

change in dosage. It has to be stressed, however, that the laboratory results critically depend on the analytical method used.

Side effects

Side effects were observed in 13 patients, specifically, eruption of preexisting acne (4 cases), loss of appetite and loss of weight (5 cases), and ataxia and impaired vigilance (4 cases). All side effects were reversible when the dosage was reduced.

DISCUSSION

This retrospective evaluation demonstrates that bromide treatment may lead to decisive improvement in otherwise intractable epilepsies. In agreement with Scheunemann [5] and Boenigk et al [6], the relatively best results could be obtained in epilepsies with GTCS and an onset during the first 3 years of life. Freedom from GTCS could be achieved in 6 out of 19 cases, while another 9 children improved considerably. In the group of 18 cases suffering additionally from frequent minor seizures, GTCS could not be controlled completely, however, half of the patients improved. Minor seizures were even evoked in 2 cases. Nocturnal tonic seizures (2 patients) and complex partial seizures (2 cases) were not influenced by the bromide treatment. Except for slight acceleration of the background activity, EEG was not influenced by bromides.

Definite clues concerning the optimal blood level range cannot be obtained from our data. In some cases positive effects were observed at blood levels of 50 to 60 mg/dl, but others showed no response until 120 to 140 mg/dl full blood. Generally, full blood levels of 80 to 120 mg/dl seemed to be optimal (x-ray fluorescence). The daily dose ranged between 50 and 80 mg/kg. It has to be stressed again that the results of blood level evaluations vary greatly with the laboratory method used.

In monitoring bromide treatment, the following facts have to be considered (for literature, see Woodbury [7]). Bromides are rapidly and completely absorbed from the intestinal tract. Since they are not excreted in the feces, all of an administered dose is transported into the blood stream. The bromide ion rapidly becomes distributed throughout the extra- and intracellular spaces. After initiation of therapy, the bromide level increases in a short time in the body at the expense of chloride, which is more readily excreted by the kidneys than bromide. The plasma half-life of bromide was found to be 12 days. Therefore, the blood level should not be estimated before 3 weeks after the last change in dosage. There is no evidence that bromide induces or inhibits the activities of drug-metabolizing enzymes in the liver, leading to metabolic interactions with other anticonvulsant drugs (for literature, see Woodbury [7]). Since bromide, however, is a central depressant, it is expected to enhance the depressant effects of other antiepileptic drugs. So, the side effects observed in our series may be at least in part a consequence of the combined treatment with primidone and/or phenobarbitone, although there were no indications that bromides affected the blood levels of these drugs.

To date, we have no experince with bromide monotherapy. According to Kruse [8], this too may be successful in comparable cases.

According to our results, conventionally intractable epilepsies with GTCS and onset in early childhood are the preferential indication for bromides. In an unselected sample of epileptic children this type of severe epilepsy is very rare (probably less than 2% of all types of epilepsy). Therefore it has to be characterized in more detail as follows. The disorder usually affects children between 6 months and 3 years of age, until then showing normal development. The presenting symptomatology is febrile or afebrile GTCS. Especially if the onset is during the first year of life, the epilepsy tends to run an unfavourable course, leading to frequent and prolonged attacks. In many cases, although constant focal symptoms are absent, definite but mostly alternating lateralisation can be observed ("alternating hemigrand mal"). Postictal pareses and even irreversible neurological deficits are not unusual. In epochs of high seizure frequency, erratic myoclonias (not related to epileptic EEG discharges) can be observed, resembling a myoclonic syndrome of neurometabolic origin. The motor and mental development is often secondarily retarded in these severe cases. Some children have myoclonic or myoclonic-astatic seizures. These cases can be classified as having severe myoclonic epilepsy [9]

Table 1 *Results of bromide therapy in 36 children. *Definition of groups, see text.*

*Group**	*No*	*Male*	*Female*	*Controlled for GTCS*	*Improved by 75%*	*Improved by 50–75%*	*Failure*
I	19	11	8	6 (32%)	4 (21%)	5 (26%)	4 (21%)
II	13	6	7	0	2 (15%)	6 (46%)	5 (39%)
III	2	2	–	0	0	0	2
IV	2	–	2	0	0	0	2

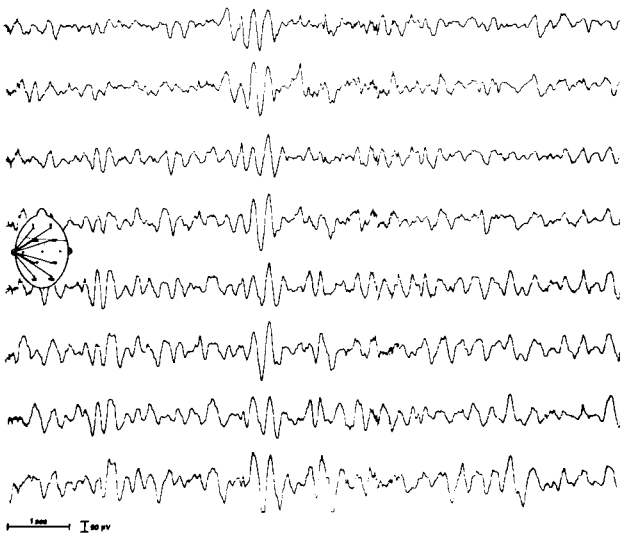

Fig 2 *EEG of a 10-year-old boy with generalized tonic-clonic seizures since the age of 11 months. The EEG shows diffuse rhythmic slowing but no hypersynchronous activity.*

or myoclonic-astatic epilepsy [10]. The later course may be complicated by nocturnal tonic seizures. Initially, the EEG can be totally normal or is characterized by a rhythmic slowing of the background activity. Usually, generalized spikes and waves occur some months later, at first during sleep. The rhythmic slowing, however, is the prevailing finding during the later course (Fig 2). For a differential diagnosis one has to consider secondarily generalized or focal seizures, which might erroneously be diagnosed because of the (mostly alternating!) lateralisation and because of postictal paralysis. Diagnostic pitfalls may then lead to invasive diagnostic procedures and to inappropriate treatment. According to the histories of our cases, it has to be stressed that phenytoin and carbamazepine are not only ineffective but can even worsen the clinical course. According to our experience, phenobarbitone constitutes the treatment of first choice and valproic acid that of second choice. In those cases who do not respond to this medication, bromide therapy should be initiated without delay.

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