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Pharmacology, Efficacy, and Tolerability of Potassium Bromide in Childhood Epilepsy

Rudolf Korinthenberg, MD, Peter Burkart, MD, Christiane Woelfle, MD, Jürgen Schulte Moenting, PhD, and Jan Peter Ernst, MD

This study investigated the efficacy and tolerability of potassium bromide in 113 patients (aged, 1-20 years) with severe epilepsy and generalized tonic-clonic seizures. Potassium bromide was started at 45 mg/kg and raised to 70 mg/kg (median). Steady-state blood level was reached after a median of 28 days (range, 5-95 days). The number of patients who had suffered generalized tonic-clonic seizures during the last month dropped from 82 to 41, and the median frequency, dropped from 4.5 to 0 per month. Of the patients with generalized tonic-clonic seizures during baseline, 49% showed none in the last 4 weeks of the study, and another 31% showed a reduction by more than 50%. Potassium bromide should have a place as a drug of tertiary choice in the treatment of children with epilepsy. Experience with the drug and close clinical and pharmacologic monitoring are necessary to achieve the greatest possible benefit and avoid side effects.

Keywords: epilepsy; potassium bromide; tonic-clonic seizures

The scientific history of bromides as antiepileptic agents began in 1857 when C. Locock reported his positive experience in catamenial epilepsy.[1,2] Until the introduction of phenobarbitone in 1912, bromides were the only remedy in epilepsy, and a growing number of reports about their effectiveness appeared. However, the negative effects on the nervous system, skin, and gastrointestinal tract were soon recognized as well. These adverse effects were abundant at a time when the dosage had to be determined without pharmacologic monitoring, and some regarded the appearance of side effects as a measure of effectiveness.

The use of bromides as a routine drug for epilepsy declined sharply, due mainly to these side effects and the advent of modern drugs, which were readily available and easier to administer. However, bromides continued to be used in refractory cases in specialized epileptologic institutions.[3,4] In the 1980s, a renaissance of potassium bromide occurred, mainly in Germany and Japan. This was furthered by the observation that it had clear activity, with responder rates between 30% and 70%, including the severe epileptic syndromes of childhood with otherwise treatment-resistant generalized tonic–clonic seizures.[5-13] In addition to those original reports, several review articles summarizing clinical experiences and pharmacologic data appeared.[14-18]

Although these publications illustrate broad experience with potassium bromide in specialized centers, the number of studies on its pharmacology, efficacy, and tolerability under modern monitoring conditions is small compared with other antiepileptic drugs. It was the aim of this study to retrospectively review these aspects in a rather large cohort of children and adolescents treated in a single epilepsy center in Germany.

Methods

This retrospective study collected data from children and adolescents who were treated with potassium bromide for a minimum of 12 weeks. All were in-patients or outpatients of the Pediatric Department of the Epilepsy Center Kehl-Kork, Germany. The indication for treatment was pharmacoresistant epilepsy, usually with generalized tonic-clonic convulsions. Many patients also presented with focal or minor seizures.

Data were collected in a structured manner from the patient files. The last 4 weeks before the start of bromide therapy were defined as the baseline period. The first,

From the Department of Pediatrics and Adolescent Medicine, Division of Neuropediatrics and Muscular Disorders, University Hospital Freiburg, Freiburg, Germany (RK, CW); Epilepsy Center Kehl-Kork, Kehl-Kork, Germany (PB, JPE); and the Institute of Medical Biometry and Informatics, University Hospital Freiburg, Freiburg, Germany (JSM).

Address correspondence to: Prof Dr Rudolf Korinthenberg, Division of Neuropediatrics and Muscular Disorders, Department of Pediatrics and Adolescent Medicine, University Hospital Freiburg, Mathildenstr 1, D-79106 Freiburg, Germany; e-mail: rudolf.korinthenberg@uniklinik-freiburg.de.

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Table 1. Epileptic Syndromes

Syndrome	Patients (n)
Localization-related, symptomatic epilepsies	5
Generalized, idiopathic epilepsies	31
Generalized, cryptogenic epilepsies	13
Generalized, symptomatic epilepsies	19
Not determined, whether generalized or localization-related	45

second, and third months after start of treatment were defined as treatment periods, with data collected at the end of each of these periods.

At the beginning of the baseline, the following data were recorded: age, gender, body weight and height, etiology, and epileptic syndrome and seizure type(s) according to the respective International League Against Epilepsy classification from 1981 and 1989. At the end of baseline and each treatment period, the following data were recorded: antiepileptic comedication, seizure types and their frequency per month, the longest duration of generalized tonic–clonic seizures, the longest seizure-free interval during the last 4 weeks, electroencephalogram (EEG) findings scored for background activity, focal and generalized epilepsy typical activity, and adverse reactions.

The dosage of potassium bromide and bromide serum level were recorded more frequently at roughly weekly intervals. The serum level was determined using the photometric method.[9] A steady state was assumed when, after reaching a constant dosage, the coefficient of variation (standard deviation/mean × 100) for at least 3 successive blood-level measurements was less than 15%.

Statistical analysis was performed using SAS (SAS Institute, Cary, NC) and SPSS (SPSS Inc, Chicago, Ill) statistical software. A $P < .05$ was considered significant.

No informed consent from the patients and their families was required because this was a retrospective data collection without active intervention. Data were recorded without name and birthday, and the local ethics committee was not involved.

Patients

Data from 113 patients (66 boys, 47 girls) were evaluated. They were between 1 and 20 years old, with a peak between 2 and 7 years, and had been treated between 1981 and 1999. Generalized tonic-clonic seizures occurred in 105 patients: 28 from tonic, 25 from myoclonic, 15 from atonic, and 14 from complex-partial seizures alone or in combination. The respective epileptic syndromes are listed in Table 1. The etiologies were symptomatic in 50 of the epilepsies (35 prenatal, 6 perinatal, 8 postnatal, 1 undetermined timing), cryptogenic in 32, and idiopathic in 31.

Results

Pharmacologic Data

During the baseline period, the patients had been treated with a median of 2 antiepileptic drugs (range, 1-4 drugs; 42% each with 1 and 2 drugs), and their blood levels were usually in the therapeutic range. Ranked according to frequency (% of patients), these drugs were valproate (52%), phenobarbitone (33%), carbamazepine (20%), ethosuximide (16%), and phenytoin (13%). Other drugs given in less than 10% of patients were primidone, mesuximide, vitamin B_6, clobazam, vigabatrin, clonazepam, lamotrigine, sulthiame, oxcarbazepine, and adrenocorticotropic hormone.

During treatment with potassium bromide, the comedication was not kept constant. Thirteen patients were converted to monotherapy. Phenobarbitone was tapered and finished in 30, phenytoin in 6, primidone in 9, clonazepam in 14, and clobazam in 4 patients. Valproate and ethosuximide were not usually reduced. Overall, the blood levels of those drugs not tapered remained unchanged.

Potassium bromide was administered as DIBRO-BE mono (850-mg tablets, Dibropharm GmbH, Baden-Baden, Germany). Treatment was started with a median dosage of 45 mg/kg body weight (range, 7.5-99 mg/kg). After 4 weeks, the median dosage was 72 mg/kg (range, 32-150 mg/kg), which remained nearly unchanged until the end of the study at a median of 75 mg/kg (range, 22-140 mg/kg). After 4 weeks of treatment, the median bromide blood level was 145 mg/dL (range, 75-248 mg/dL). It rose to a median of 168 mg/dL after 8 weeks (range, 90-332 mg/dL) and to a median of 164 mg/dL after 12 weeks (range, 83-330 mg/dL).

We were able to calculate the time to reach steady state in 74 patients. The median time to reach steady bromide levels was 28 days (range, 5-95 days; interquartile range, 20-43 days). By Cox regression, the time to reach the steady state in our patients was not correlated to gender and age. A moderate linear correlation was found between the dosage (mg/kg) and the blood level (Spearman's $\rho = 0.35$, $P = .029$). After 2 months of treatment, the median blood level/dosage ratio was 2.2 (95% confidence interval [CI], 1.2-6.4). Regression analysis showed that age was another significant factor influencing the blood level. There was a significant positive correlation between the blood level/dosage ratio after 3 months of treatment and age ($n = 44$, Spearman's ρ, 0.52; 2-sided $P < .001$, Figure 1). Apparently, as with other drugs, the necessary dosage to reach a given blood level is higher in younger than in older individuals.

Clinical Efficacy

Under treatment with potassium bromide and with increasing blood levels, the number of patients presenting

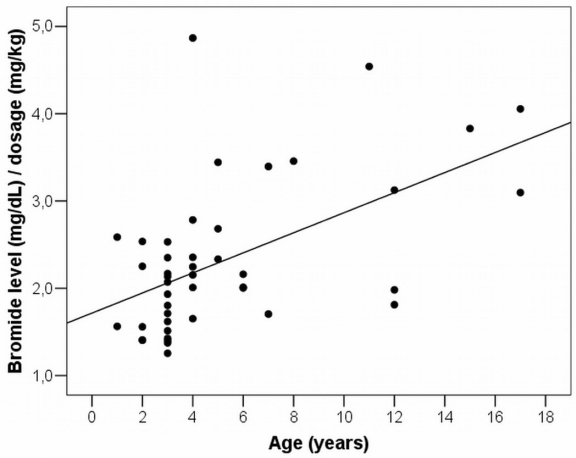

Figure 1. Ratio of bromide blood level (mg/dL) over dosage (mg/kg), according to age.

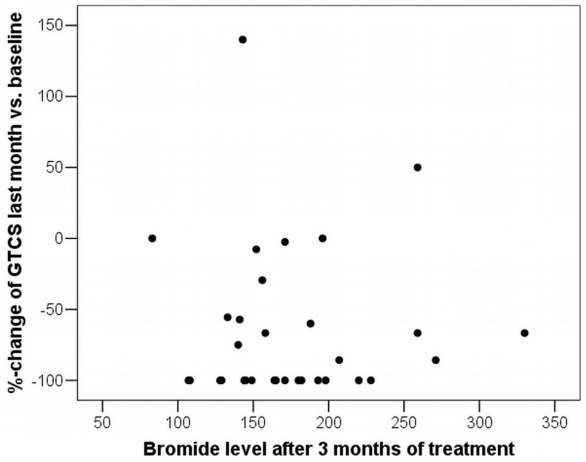

Figure 2. Percentage change of generalized tonic-clonic convulsions (GTCS) during the third month of treatment with potassium bromide compared with baseline, according to blood level at the end of the third month of treatment.

with generalized tonic-clonic seizures during the last 4 weeks dropped from 82 (weeks -4 to 0) to 70 (weeks 0 to 4), 57 (weeks 4 to 8), and 41 (weeks 8 to 12). The frequency of generalized tonic-clonic seizures dropped from a median of 4.5 per month (range, 0-78) to a median of 0 per month (range, 0-78) (Friedman test $P < .001$). At the end of the study period, 49% of the patients who had presented with generalized tonic-clonic seizures during the baseline period were free from these during the last 4 weeks. A further 31% showed a reduction of more than 50%, 8% were unchanged, and 7% showed an increase of more than 25%.

The number of patients with tonic seizures fell from 20 (weeks –4 to 0) and 22 (weeks 0 to 4) to 15 (weeks 4 to 8) and 6 (weeks 8 to 12). Also, the median frequency of tonic seizures decreased from 3 per month (range, 0-56 seizures) to 0 per month (range, 0-11 seizures; $P = .009$). Focal (simple and complex) seizures didn't change significantly.

As a further measure of treatment efficacy, we recorded the longest seizure-free period between 2 successive seizures. At baseline, this parameter amounted to a median 7 days (95% CI, 0.1-30.9). During the first month of treatment with potassium bromide, it rose to a median 12 days (95% CI, 0.0-31.0), during the second month to a median 14 days (95% CI, 0.0-31.0), and during the third month to a median 28 days (95% CI, 0.9-31.0; Friedman test χ^2, 44.4; $P < .001$).

We did not find a significant correlation between blood level and efficacy during the last month of the study (Kruskal-Wallis test). Patients with a 100% reduction in generalized tonic–clonic seizures compared with baseline showed median blood levels of 141 mg/dL (range, 94-216 mg/dL). In patients with a decrease between –50% and –99% and in those without a clear effect (≤50%), these values were 157 mg/dL (range, 102-248 mg/dL) and 153 mg/dL (range, 110-221 mg/dL), respectively (Figure 2).

Electroencephalogram Changes

At baseline, only 3 EEGs showed normal background activity, and 54 were slightly, 46 moderately, and 1 severely slow. Generalized epilepsy-typical potentials were found in 42, multifocal epilepsy-typical potentials in 19, and focal epilepsy-typical potentials in 6 patients. The EEG background activity did not change significantly from baseline to the end of the study. The focal and multifocal epilepsy-typical activity showed no significant changes either. However, the number of patients without generalized epilepsy-typical potentials rose from 59% to 70%, and the severity of those changes was reduced in many patients ($P = .03$).

Tolerability

During baseline, 83 (76%) of 109 patients were free of recorded side effects. At the end of the study and 3 months of therapy with potassium bromide, this rate had declined to 46 (58%) of 80. Central nervous system side effects increased from 15% at baseline to 22% to 28% after 1 to 3 months of treatment. This included tiredness, somnolence, and concentration deficits, whereas psychic slowing improved and ataxia remained unchanged. Further side effects attributable to potassium bromide included acne, perioral dermatitis, and swollen eyelids (2% at baseline; 12.7% after months of treatment). The number of gastrointestinal complaints (2%-8%) and mood

changes (12%-19%) did not vary significantly during the study period. Aside from the observation that during the last month of the study all 3 children with blood levels exceeding 250 mg/dL reported side effects, and all 3 with levels below 100 mg/dL reported none, there was no clear statistical correlation between the blood level and the occurrence of side effects: patients without side effects had a median level of 152 mg/dL (range, 83-235 mg/dL) and those with side effects had a median level of 157 mg/dL (range, 107-330 mg/dL).

Discussion

Prospective, randomized trials are the methodologic gold standard of studies investigating the efficacy and tolerability of drugs. They are difficult to conduct for rare diseases, however, especially in children. In their phase IV study on potassium bromide, Stephani et al[12] could only include 9 patients prospectively from the start of treatment, whereas 84 had already been treated for a mean of 4 years. A strength of our retrospective study is that all patients were treated at 1 experienced center and that the recording of seizures and side effects was made quasi-prospectively.

We were only able to compare the number of seizures during a baseline period of 4 weeks before start of treatment with potassium bromide with a 3-month period under treatment. We are fully aware that neither the duration of the baseline nor the follow-up is long enough to yield data that could represent the long-term efficacy. With this reservation in mind, we could show that potassium bromide demonstrated significant activity against generalized tonic-clonic seizures and to a lesser degree against tonic seizures, whereas focal seizures were not influenced. This finding is in accordance with published experience:

- Boenigk et al[5] reported a seizure reduction by more than 50% in 5 of 11 patients; 2 became free of seizures. The results in children with pure generalized tonic-clonic seizures were better than in those with mixed seizure types.
- Ernst et al[6] reported the treatment effects in 36 children with generalized epilepsy. Six of 19 with pure or prevailing generalized tonic-clonic seizures became seizure-free, and another 9 showed a more than 50% reduction. None of 13 patients with frequent minor seizures became seizure-free.
- In a mixed group of epileptic syndromes reported by Woody et al,[7] 2 of 11 patients became seizure-free, and 4 showed significant and sustained improvement.
- In the study of Steinhoff et al,[9] 16 of 60 patients became free of generalized tonic-clonic seizures, and a further 19 showed a significant amelioration of more than 50% for a mean observation period of 28 months. Compared with a parallel group treated with phenobarbitone or phenytoin, the potassium bromide effect was slightly better, but to a statistically insignificant degree.
- Tanaka et al[8] reported that 9 of 20 patients with mixed seizures showed a clear benefit from bromide therapy.
- Oguni et al[10] reported their experience in 22 children with Dravet syndrome or its borderline variant with predominant generalized tonic-clonic seizures.[10] After 3 months of treatment, 77% showed a clear benefit: 8 had a reduction in generalized tonic-clonic seizures by more than 75% and in 9 by 50% to 75%. However, the positive effect had been maintained in only 8 children after 12 months. Myoclonic and focal seizures responded only exceptionally. Patients with focal seizures as their only symptoms were infrequently reported to respond to potassium bromide.[11,13]
- Stephani et al[12] reported a mainly retrospective, multicenter phase IV study that included 93 patients with various types of epilepsy. The effectiveness of potassium bromide was judged as good and very good by 75% of physicians and parents, and tolerability by 75% to 90%. During the prospective observation period, the frequency and duration of generalized tonic-clonic seizures decreased in 37 patients and increased in 16.

All children in our study had severe epilepsy and were treated with a combination of drugs. Thus, it was not surprising that at baseline, 24% already had reported side effects. To avoid additional side effects, sedating agents such as phenobarbitone and phenytoin were tapered with the start of potassium bromide in a large number of patients. The blood levels of the comedication maintained did not change, as was to be expected owing to the metabolic inertia of bromide. At the end of the study period, however, the number of patients with reported side effects had risen to 58%.

The unwanted effects involved the central nervous system, gastrointestinal tract, and skin in a frequency and manner that is familiar from earlier reports and reviews.[5,9,15,19,20] Steinhoff et al[9] reported 30% of patients with mainly mild side effects, including acne, loss of appetite and weight, and fatigue. In the large observational study including 93 patients reported by Stephani et al,[12] side effects occurred in a significant number of children. Their severity was rated as low in 16 patients and moderate in 27, among them 14 with sedation and 13 with ataxia. Only in 3 was it rated as severe, who presented with anorexia in bromide intoxication, apathy, and developmental regression.

Potassium bromide is a water-soluble salt that is rapidly and nearly completely absorbed in the upper intestine and distributed in the extracellular space. Different from chloride, the concentration of bromide in cerebrospinal fluid is lower than in serum. Meierkord et al[21] demonstrated potassium bromide's anticonvulsive action in 2 experimental epilepsy models. They found signs that it acts by increased γ-aminobutyric acidergic inhibition rather than by an altered acid-base status.

Potassium bromide is excreted nearly exclusively by the kidneys and has a very long half-life, which has been estimated at 8 to 14 days in adults and 6 to 8 days in children.[22] The half-life depends on several external and internal factors, including the dietary intake of fluids and chloride, as well as age, gender, and nutritional state. The

mismatch of rapid absorption and slow excretion explains the marked tendency to accumulate, one of the main problems that must be considered in treatment. The time required to reach steady state has been reported to be 30 to 40 days in adults and 3 to 4 weeks in children.[23]

In our study, the potassium bromide dosage was chosen according to conventional recommendations, starting with a median of 45 mg/kg and increasing to 70 to 75 mg/kg.[15] This range corresponds to the young age of most of our patients, whereas the recommended dosage for adults is 30 to 50 mg/kg. Median blood levels of 140 to 150 mg/dL were achieved in the steady state. We could confirm that with increasing age, higher blood levels resulted from a given dosage than was the case in younger children.

Because only few patients in our study exceeded the therapeutic range of 100 to 250 mg/dL, we are not in a position to comment on the efficacy and tolerability outside these limits. It was of interest that we did not see a correlation between the blood level and efficacy and tolerability within these limits. Some children became free of seizures at relatively low bromide levels (Figure 2), and others showed early side effects.

The long half-life and resulting very long time to reach steady state are well known. In addition, our data show that the time to reach steady state was extremely variable, 5 to 95 days. In 25% of patients, the steady state was reached within 20 days, but in another 25% it had not been reached even after 43 days. One must consider that at least some of this variability could depend on the amount of sodium chloride intake, which could not be controlled or evaluated in our study. As a practical consequence, during potassium bromide treatment, the sodium chloride intake should be kept as constant as is feasible. Once the bromide dosage is changed, the patient should be monitored both clinically and with blood level determinations for at least 2 to 3 months, as has been proposed by Boenigk et al.[5]

Conclusion

Because of its repeatedly verified efficacy against generalized tonic-clonic seizures that are otherwise difficult to control, potassium bromide should have a place as a drug of tertiary choice in treating children with epilepsy. The therapeutic window is not wide, however, and the specific pharmacokinetics imply the danger of accumulation over many weeks after reaching a fixed dosage. Experience with the drug and close clinical and pharmacologic monitoring are necessary to achieve the greatest possible benefit and avoid intolerable side effects.

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