Value of Blood Phenytoin Estimation in Management of Childhood Epilepsy

Phenytoin has been invaluable in the management of epilepsy for over 30 years. It has many side effects, but serious adverse reactions are very unusual. Optimum control of therapy is difficult, however, because of a low toxic/therapeutic ratio and because of variations between patients in the rate of metabolic destruction of phenytoin (Kutt and McDowell, 1968). Many drugs, including several anticonvulsants, alter phenytoin metabolism and may lead to intoxication with the drug (Taylor, 1970).

In an attempt to obtain optimum control of therapy in epileptic children receiving phenytoin we have been estimating blood phenytoin levels.

Method

A modification of the method described by Dill et al. (1956) was employed. Phenytoin is extracted from blood into an organic solvent, evaporated, and the residue nitrated. The nitro compound is reduced to form an aromatic amine, is diazotized, and finally coupled with N-1-naphthylendiamine dihydrochloride to give a coloured solution, the optical density of which is then read at 550 nm. Standard preparations were prepared from sequestrated blood. Citrated whole blood obtained from blood transfusion gave low optical densities, and was not used for this purpose.

A 2·5 ml specimen of sequestrated blood was required from the patient for each estimation.

The first 30 children who attended as outpatients or were admitted to the ward and were at that time receiving phenytoin alone, or in a combination with phenobarbitone, were included in the study. They were observed in detail for six months. The age range of the group was 6 months to 12 years. At the beginning of the study period the length of time the patients had previously received phenytoin ranged between 1 month and 5 years.

Each patient was seen at fortnightly intervals until the blood levels had neared therapeutic range, and then at monthly intervals. At the end of the six-month observation period each patient has serum folic acid, blood sugar, liver function tests, and a full blood count performed.

Results

The striking finding on initial investigation was the fact that only 25% of the children had therapeutic blood levels. Fig. 1 and 2 show the blood levels of the first 20 patients at the beginning and the end of the survey. At the end of the survey, 80% of the children had therapeutic levels.

Within the group, no blood abnormalities or folic

Discussion

From these results it seems that the presence of triangular hairs is one characteristic that contributes to a palpable coarseness of normal human hair. Triangular hairs are frequently seen in patients over the age of 2 years who have Hurler's syndrome or Sanfilippo syndrome.

This finding is not claimed to have any diagnostic value. Should further studies reveal that triangular hairs are a universal feature of the Sanfilippo syndrome, the absence of this feature could help in exclusion of the diagnosis in retarded children with coarse features. Clinical recognition of this syndrome is not always easy, even in children 5 to 10 years of age.

Summary

A simple method of cutting transverse sections of hair is described. Triangular-shaped hairs were found in patients with the Hurler and Sanfilippo syndromes and may account for the coarse feeling of the hair in these patients. Triangular hairs were also found in normal persons with coarse feeling hair.

TABLE

Frequency of Triangular Hairs in Patients with Hurler and Sanfilippo Syndromes

<table>
<thead>
<tr>
<th>Patient (Sex)</th>
<th>Age (yr)</th>
<th>Total No. of Hairs</th>
<th>% Triangular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hurler syndrome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S.A. (F)</td>
<td>9½</td>
<td>49</td>
<td>26·5</td>
</tr>
<tr>
<td>10</td>
<td>56</td>
<td></td>
<td>16·1</td>
</tr>
<tr>
<td>S.C. (M)</td>
<td>1</td>
<td>80</td>
<td>0·0</td>
</tr>
<tr>
<td>2</td>
<td>100</td>
<td></td>
<td>6·0</td>
</tr>
<tr>
<td>Sanfilippo syndrome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D.W. (M)</td>
<td>12</td>
<td>48</td>
<td>29·2</td>
</tr>
<tr>
<td>14</td>
<td>60</td>
<td></td>
<td>13·3</td>
</tr>
<tr>
<td>M.L. (F)</td>
<td>6</td>
<td>60</td>
<td>26·7</td>
</tr>
<tr>
<td>7</td>
<td>83</td>
<td></td>
<td>12·0</td>
</tr>
<tr>
<td>G.S. (F)</td>
<td>9½</td>
<td>73</td>
<td>19·2</td>
</tr>
<tr>
<td>10</td>
<td>38</td>
<td></td>
<td>26·3</td>
</tr>
<tr>
<td>W.T. (M)</td>
<td>4</td>
<td>26</td>
<td>15·4</td>
</tr>
<tr>
<td>5</td>
<td>30</td>
<td></td>
<td>26·7</td>
</tr>
<tr>
<td>P.T.</td>
<td>2</td>
<td>32</td>
<td>0·0</td>
</tr>
<tr>
<td>3</td>
<td>44</td>
<td></td>
<td>4·5</td>
</tr>
</tbody>
</table>

REFERENCE


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acid deficiency occurred. Random blood sugars appeared lower than in a control group, but the difference was not statistically significant.

Three patients, aged 4 years, 11 years, and 9 years had moderate gum hyperplasia. They had been receiving the drug for 3, 3, and 1 year, respectively. Five patients developed neurological signs due to phenytoin. On each occasion the dosage prescribed had been excessive and blood levels were above 25 µg/ml. The neurological signs were transient in all patients and disappeared on reduction of the dosage. Two of these children had in addition a concurrent bacterial infection.

Seven patients had therapeutic blood levels of the drug throughout the assessment period. Only one of these patients continued to have periodic convulsions, despite phenobarbitone and phenytoin.

This boy experienced three grand mal fits within the six-month period. 10 of the remaining 23 patients were free from convulsions at the onset of the study, despite low blood levels. One patient in this group had a subsequent convolution when her blood phenytoin level was within therapeutic range. 4 of this group of patients failed to attain therapeutic levels after six months.

Of the 13 patients who were having convulsions and were outside therapeutic levels, 11 were free from convulsions six months later. The 2 patients who continued to have fits failed to attain therapeutic levels.

Discussion

Therapeutic levels of phenytoin have been established at 10–20 µg/ml by several workers. Kutt and McDowell (1968) have shown maximum seizure control and least side effects at these levels.

Svensmark and Buchthal (1963) showed a return towards normal in the EEG at levels of 10–20 µg/ml.

We have found the estimation of blood phenytoin an easy and useful estimation. No specialized equipment is required. Specimens can be stored for 2 to 3 weeks, preferably refrigerated, but not necessarily so. Batches of 10 to 20 specimens can be estimated simultaneously. Blood phenytoin has now been included among the routine estimations offered by the Biochemistry Department of this hospital. The small amount of blood required makes frequent testing possible. Blood estimations, however, at intervals of less than two weeks when a dosage increase or decrease has been prescribed appear to add little. Blood level changes do not appear to reflect dosage alterations for several days.

The correct dosage of the drug for each child is a difficult problem. Our findings suggest that the younger and lighter children tolerate an initial dosage regimen of 10 mg/kg per day. The older children above 25 kg would tolerate an initial regimen of 5 mg/kg per day. Variation occurred at each weight level and blood estimations were required for stabilization.

Of our 30 patients, 11 were receiving phenobarbitone during the period of assessment. No increase or decrease in phenytoin requirements was noted in these children.

Our children were receiving a very low dosage of phenobarbitone, less than 3 mg/kg, during the study. The dosage was not altered nor was the drug withdrawn from any patient. The combination of youth, low phenobarbitone dosage, and the absence of other drugs, probably accounts for the
lack of influence of phenobarbitone during the study.

Blood phenytoin affords a check on patients with regard to their intake of prescribed drugs. The addition of blood tests and frequent supervision was reflected in the mother's increased interest in the supervision of the child's therapy. In retrospect, the poor initial levels in our series were due to inadequate dosage being prescribed and to patient failure.

Summary

Estimation of blood phenytoin has proved to be a valuable addition in the management of childhood epilepsy. 75% of children on initial testing were found to have inadequate blood levels. Closer supervision by the use of blood phenytoin levels reduced this figure to 20%.

REFERENCES


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Nephronophthisis (Medullary Cystic Disease)

Renal medullary cystic disease, first described by Smith and Graham in 1945, is characterized by progressive renal insufficiency, hypotonic polyuria, negative or sparse urinary findings, and normal blood pressure. The kidneys are uniformly contracted and show cystic changes in the medulla as well as in the cortex. Renal histology shows interstitial nephritis with marked periglomerular and peritubular fibrosis and thickening of tubular basement membrane. A closely related nephropathy has been reported and termed 'familial juvenile nephronophthisis'. Recently several authors (Strauss and Sommers, 1967; Herdman, Good, and Vernier, 1967; Mongeau and Worthen, 1967; Axelsson and Ödlund, 1968) have suggested that these two disorders might indeed be identical. An example of nephronophthisis, previously unreported in British or Indian literature, is described.

Case Report

A 4½-year-old boy was admitted for the investigation of renal rickets. He was the product of a term normal pregnancy. Excessive thirst and frequent passage of large amounts of urine were reported to have been 'always' present. Shaking of his eyes was noticed in early infancy. Weakness and bowing of his legs appeared at about the age of 2 years and gradually progressed. At 2½ years rickets with anaemia was diagnosed by a local doctor who prescribed vitamin D and iron. Despite therapy, his disability continued to increase till at 4 years he could not walk unaided. The finding of a raised blood urea level prompted his referral to this hospital.

A history of urinary tract infection or haematuria was denied. Examination revealed a pale, poorly developed child. His weight was 15 kg and height 97.5 cm. The blood pressure was 100/70 mm Hg. A fine horizontal nystagmus was present. The optic fundi were normal. Extremities showed severe rachitic deformities with a marked genu valgum.

Hb 7.5 g/100 ml, blood urea 120 mg/100 ml, serum creatinine 3.8 mg/100 ml, creatinine clearance 9.5 ml/min, serum calcium 8.6 mg/100 ml, serum phosphorus 5·3 mg/100 ml, alkaline phosphatase 67 KAU units, blood pH 7·35, and bicarbonate 17·5 mEq/l. The serum values of proteins and cholesterol were within the normal range. ECG and audiogram were normal. Multiple urinalyses showed a maximum specific gravity of 1006. Proteinuria and glycosuria were absent and no casts were seen in the sediment. Several urine cultures were sterile. The urinary amino acid chromatogram was normal. X-rays of the long bones showed advanced rachitic changes. An intravenous pyelogram faintly visualized the kidneys which were small with regular outlines. The chromosomal pattern was normal.

On a daily sodium intake of 35 mEq/l, his urinary sodium excretion averaged 42 mEq/24 hours. A 12-hour overnight water deprivation preceded by an intramuscular injection of 2·5 units of vasopressin tannate in oil resulted in a maximum urine osmolality of 158 mOsm/kg.

Renal histology. A percutaneous renal biopsy specimen, representing only cortical tissue, revealed varying degree of glomerular hyalinization. An occasional glomerulus appeared normal. Hypercellularity, crescent formation, and capillary basement membrane thickening were absent. Dilatation and atrophy of the tubules with thickening and wrinkling of the tubular basement membrane, periglomerular, peritubular, and
Value of blood phenytoin estimation in management of childhood epilepsy.

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