Evolution of Cardio-Pulmonary Involvement in Friedreich’s Ataxia

M. Cote, M. Bureau, C. Leger, J. Martin, H. Gattiker, M. Cimon, A. Larose and B. Lemieux

SUMMARY: The evolution of 15 patients initially evaluated during Phase One of the Quebec Cooperative Study of Friedreich’s ataxia has been studied approximately three years later. It is concluded that the deterioration of cardio-pulmonary function in Friedreich’s ataxia is multifactorial. The neuropathy (or the underlying metabolic or cellular defect) appears to be the main contributing factor to the deterioration of cardio-pulmonary function, which is exacerbated by the scoliosis and varying severity of the cardiomyopathy.

INTRODUCTION

Cardio-pulmonary dysfunction is the primary cause of death in patients suffering from Friedreich’s ataxia. Death occurs at a young age, averaging twenty eight years (Thoren, 1964).

The cardiomyopathy is characterized by decreased ventricular compliance, with varying degrees of hypertrophy and, less frequently, obstruction to ventricular outflow. The electrocardiograms, which are almost always abnormal, frequently depict patterns compatible with right or left ventricular hypertrophy, ST-T wave changes and, less frequently, arrhythmias. Pulmonary function studies of patients with Friedreich’s ataxia showed that the pulmonary impairment in this neuropathy is a progressive pulmonary restrictive disease. (Thoren, 1964; Bureau, 1976). It has also been suggested that the universally encountered dorsal scoliosis plays a major role in the progression of the pulmonary disease (Geoffroy et al., 1976).

Fifteen patients suffering from classical Friedreich’s ataxia were followed prospectively to evaluate the rate of progression of the associated cardiomyopathy, pulmonary disease, and scoliosis, hoping to identify their relative importance in the clinical deterioration and possibly to construct a more rational base for therapeutic interventions.

CASE MATERIAL AND METHODS

Fifteen patients with Friedreich’s ataxia evaluated initially during phase One of the Quebec Cooperative study of Friedreich’s Ataxia (1976) were re-examined an average of 36 months later (range 24-48 months). There were 11 females and 4 males, and their median age at initial evaluation was 16 (range 7 to 28) and 19 at reevaluation (range 11 to 31). All were reexamined to determine the severity of their neurological impairment and signs of cardiopulmonary disease. A twelve-lead electrocardiogram (E.C.G.) was recorded for comparison with previous tracings. Chest X-Rays and scoliotic studies of their spines were compared by two different observers. Antero-posterior erect or supine views of the spine were obtained in all cases. The methods of Cobb (1948) or Ferguson (1945) were utilized to measure the degree of scoliosis.

Pulmonary function tests were performed in nine patients. Spirometric tests included total lung capacity (TLC), vital capacity (VC), residual volume (RV), maximal mid expiratory flow rate (MEFR), forced expiratory volume in one second (FEV₁), and peak flow (PF). All tests were performed as previously described (Bureau et al, 1976) with the same equipment and technician. Satisfactory echocardiographic records of ten patients were available for comparison with their initial evaluation tracings. The echocardiograms were obtained in the standard fashion using a Smith-French Ekoline 20 echocardiograph with a 2.25 MHZ transducer and a Honeywell 1856 strip chart recorder.

RESULTS — TABLE I

Age.

At reevaluation, eleven of the fifteen patients were between ten and nineteen years of age, four between twenty and thirty.

Neurological impairment. (Fig. 1)

The degree of neuro-muscular impairment was considered slight

From The Centre Hospitalier Universitaire de Sherbrooke.

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### TABLE I

*Description and Evaluation of Patients*

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<td>M</td>
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<td>8°</td>
<td>42%</td>
<td>LVH</td>
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<td></td>
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<tr>
<td>6</td>
<td>26</td>
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<td>45°</td>
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<tr>
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<td>52°</td>
<td></td>
<td></td>
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<td>S</td>
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<td>Minor ST</td>
<td>13°</td>
<td>104%</td>
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<td>Major ST</td>
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<tr>
<td>9</td>
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<td>Normal</td>
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<tr>
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<td>RVH</td>
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<td>RVH — Major ST</td>
<td>75°</td>
<td>97%</td>
<td>LVH</td>
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<td>9</td>
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<td>LVH — Minor ST</td>
<td>15°</td>
<td>119%</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
<td>SL</td>
<td>No change — Asymptomatic</td>
<td>LVH — Minor ST</td>
<td>15°</td>
<td>100%</td>
<td>LVH</td>
</tr>
<tr>
<td>14</td>
<td>16</td>
<td>M</td>
<td>No change — Dyspnea 2/4</td>
<td>RVH — Major ST — APC</td>
<td>25°</td>
<td>146%</td>
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</tr>
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<td>19</td>
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<td>S</td>
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<td>RVH — Major ST — APC</td>
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<td>85%</td>
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<td>25°</td>
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<td>SAM</td>
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<td>S</td>
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<td>LVH</td>
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<td>77%</td>
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<td>RVH</td>
<td>65°</td>
<td>55%</td>
<td></td>
</tr>
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<td>Diabetes — Dyspnea 2/4</td>
<td>RVH</td>
<td>75°</td>
<td>76%</td>
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</tr>
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<td>18</td>
<td>28</td>
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<td>Diabetes — Congestive Heart Failure</td>
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<td>Diabetes — Congestive Heart Failure</td>
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incapacitated (able to walk with support) were now severely handicapped. Of the six patients initially severely incapacitated, two had died.

Clinical symptoms and signs.

Six patients, all aged less than the mean of the whole group, showed no clinical evidence of cardio-pulmonary involvement. Two patients died. Both complained of moderate to severe dyspnea before death. Seven patients initially complained of dyspnea during moderate exertion (Functional Class 2). Four remained stable while three others manifested dyspnea even during slight exertion (Functional class 3), including a 31 year old woman who presented with right and left heart failure improved by diuretics.

Six patients complained of palpitations, two of them with documented transient supraventricular tachyarrhythmias. None complained of chest pain or syncope and, surprisingly, only one suffered a respiratory infection requiring antibiotic treatment during the follow-up period. Atrial fibrillation developed in two patients, one died and the other is neurologically severely incapacitated. A third patient, also deceased, had had atrial fibrillation documented at the initial examination. Systolic heart murmurs were still audible in four of five patients and gallop rhythms in

Figure 2 — E.C.G. of a twelve year old, showing negative T waves from V1 to V4 compatible with ischemia.

Figure 3 — E.C.G. of a twenty year old showing prominent R wave in V1 compatible with right ventricular hypertrophy.

Figure 4 — E.C.G. of a twelve year old with voltage criteria compatible with left ventricular hypertrophy.

Figure 5 — E.C.G. of a twenty year old showing atrial flutter and right ventricular hypertrophy.
three of six, all of them symptomatic for some dyspnea.

**Electrocardiograms:**

The E.C.G. was normal in only one patient at the first evaluation, a twelve year old girl without symptoms of cardio-pulmonary involvement but now severely impaired neurologically. The second tracing, however, (Fig. 2) showed major ST-T wave changes (i.e. compatible with “ischemia”). As described previously, E.C.G. abnormalities compatible with ventricular hypertrophy were frequent. Six patients still had right ventricular hypertrophy patterns (Fig. 3) and RVH appeared during the course of this study in another patient. Two patients showing no significant changes had, respectively, left ventricular hypertrophy (fig. 4) and biventricular hypertrophy.

Isolated ST-T abnormalities, major or minor (flattened or diphasic T waves), were present on the E.C.G. of four patients. Arrhythmias were documented in nine patients, all supraventricular. Two patients transiently developed atrial flutter (fig. 5) or fibrillation. Atrial flutter or fibrillation was present during the terminal stage of the two deceased patients. Isolated atrial premature contractions were recorded in four patients and a short episode of paroxysmal atrial tachycardia in another.

**Chest X-Rays:**

The chest X-Ray was unchanged in twelve patients: eight remained normal, three had slight cardiomegaly, and one had a moderate degree of cardiac enlargement. Two patients with previously normal heart size showed a slightly enlarged heart on reevaluation. Only one patient with congestive heart failure had transient evidence of pulmonary hypertension. It should be noted, however, that evaluation of the heart size on antero-posterior recumbent views of patients with significant scoliosis is quite subjective and imprecise.

**Scoliosis:**

Scoliosis was defined as spinal curvature above 10°. All the patients now have a scoliosis (table 2). The degree of scoliosis increased in eleven since the initial evaluation: seven by less than 20° and four by more than 20°. The progression of the scoliosis is shown in figures 6 and 7, depicting a 45° progression of the scoliosis within three years in a seventeen year old girl who was previously slightly incapacitated but is now confined to a wheelchair. Only one patient showed a slight decrease, by 5°, but the first examination was done in an erect and the second in a recumbent position. The degree of scoliosis increased with age (fig. 8). During the observation period the mean degree of scoliosis (fig. 9) progressed from 42.1° (median age 16) to 55.6° (median age 19).

**Pulmonary function.**

The changes in pulmonary function tests are shown in table 3 for individual patients and the mean for the group in figure 10. All results are expressed in percentage of predicted value (100 percent) for their size and age. There is a decrease in lung volume including total lung capacity (TLC), vital capacity (VC), residual volume (RV), and functional residual capacity. There are no significant changes in maximum mid-expiratory flow rate (MMEF) and forced expiratory volume in one second (FEV1), but peak flow (PF) decreased significantly.

**Echocardiogram**

Sequential echocardiograms of ten patients were analysed. (Table 1, Fig. 11). The echocardiograms of two patients had been and were still normal: one, of a 17 year old girl who died during the course of this study,
had a vectocardiogram showing a RVH pattern, the other of a 12 year old girl who had only ST-T abnormalities on her E.C.G. Eight patients had mild to moderate left ventricular hypertrophy on Echo which progressed in only one patient. Only one patient showed persistent asymmetrical septal hypertrophy (ASH) with a ratio of septal to left ventricular free wall thickness exceeding 1.3. Five patients had mild ASH (ratio less than 1.3) and two had concentric hypertrophy. Only one patient, a 14 year old with a previously documented 60 mmHg left intra-ventricular systolic pressure gradient, depicted persistent systolic anterior movement of the mitral valve (SAM) and also ASH. A 17 year old girl developed intermittent SAM. Her previous hemodynamic study at rest revealed increased right and left end diastolic pressures but no significant right or left out-flow tract obstruction. The echocardiographic left ventricular internal diameter in diastole was below normal and remained unchanged in six patients, reflecting a decreased left ventricular volume.

**DISCUSSION**

Friedreich's ataxia is a relentlessly progressive degenerative neuromuscular disorder. The prospective observation of modification of cardiopulmonary function in fifteen patients during three years of evolution revealed a rapid progression of the neuromuscular involvement during adolescence. Twelve of the fifteen are now confined to a wheelchair or bedridden. Clinical symptoms or radiological evidence of cardiac failure appeared in only one patient, a thirty one year old diabetic patient.

The terminal deterioration of two deceased patients was compatible with a low cardiac output, but without clinical evidence of severe congestive heart failure or severe respiratory insufficiency. Clinically, there were few signs of progression of the cardiomyopathy in the remainder of the patients. The progression of scoliosis, however, was remarkable, in some cases exceeding 40° in three years. It seemed to coincide with neurological deterioration, principally when the patient stopped walking. Scoliosis alone does not modify the vital prognosis and is not the principal cause of deterioration in pulmonary or cardiac function. One patient with a 120-130° scoliosis present for nine years is still living, while a 17 year old who died had only a 50° curve of the spine. All primary curves are thoracic or thoraco-lumbar and remain relatively well balanced without pelvic obliquity, permitting easier displacement in a wheel-chair and prevention of skin ulceration. Six of our patients were treated with a brace during their evolution. A brace is considered useful in reducing the progression of the scoliosis, but it increases the pulmonary restriction.
and is uncomfortable for a wheel-chair dependant paralytic patient. All patients eventually discontinued the use of the brace. Three patients were operated upon: one spinal fusion and two Harrington procedures. The follow-up period is too short to assess results, but the expected benefits from surgery must be weighed against the progression of muscle weakness due to prolonged post-operative immobilisation (Hensinger, 1976). The accepted indications for spinal fusion in idiopathic scoliosis and in non-progressive paralytic scoliosis associated with cerebral palsy, for example, should be reevaluated when applied to patients with Friedrich’s ataxia because of the inevitable progression of the neuro-myopathy.

Serial pulmonary function tests also demonstrated a progressive deterioration. The most striking change was the decrease in residual volume (RV) and functional residual capacity. The changes cannot be entirely attributed to progression of the scoliosis, since RV has been shown to be independent of the degree of scoliosis (Weng, 1969). Thus, the fall in RV, as well as lung volume in three years is mainly attributable to the severity and progression of the neuro-muscular disease. Although the deterioration of pulmonary function appears rapid in these patients, there was a surprisingly low incidence of pulmonary infections. Therapeutic interventions to alter the progression of the pulmonary disease have yet to be fully evaluated. Intensive respiratory training and prevention or correction of the thoracic deformity are presently worthwhile working hypotheses.

The cardio-myopathy did not appear to progress rapidly as assessed either by clinical or paraclinical evaluation. However, as with all cardio-myopathies with thickened non-compliant ventricles, the onset of supraventricular tachy-arrhythmias and loss of synchronised atrial contraction were frequently associated with increased symptoms and signs of heart failure and probably contributed to the terminal deterioration of the two deceased patients. The E.C.G. abnormalities showed little change, with persisting frequent RVH patterns and ST-T changes reflecting, in our view, an abnormal depolarisation and repolarisation of the myocardium due to extensive myocardial fibrosis rather than true RVH. Echocardiography revealed persistent mild to moderate left ventricular hypertrophy (LVH) in

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<th>T.L.C.</th>
<th>R.V.</th>
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### FIGURE 11

*Echocardiograms: Left Ventricular Hypertrophy*

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ASH — Asymmetric septal hypertrophy.
SAM — Systolic anterior movement of mitral valve.

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*Figure 12 — Multiple pathophysiological factors contributing to cardio-pulmonary failure.*

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eight of ten patients. Only one patient showed a persistent pattern compatible with asymmetrical septal hypertrophy (ASH).

Therapeutic interventions aimed at altering the progression of the cardiomyopathy have been tentative at best. Symptoms and signs of congestive heart failure in one patient were easily controlled by diuretics. Still controversial is the possible accelerated development of arteriosclerosis, particularly of small and medium size coronary arterioles, in Friedrich's ataxia which may contribute to the diffuse myocardial degenerative process. Overt diabetes mellitus was present in two patients. The severity of the myocardial fibrosis visualised at necropsy (Sanchez-Casis, 1976) seems, however, disproportionate to the degree of arteriosclerosis. The etiology of the primary hypertrophic cardiomyopathies remains unknown. In Friedrich's ataxia, a membrane defect has been implicated (Barbeau, 1976). The medical treatment of the cardiomyopathy ideally should be directed at correcting a specific metabolic abnormality when identified. The use of beta-blockers in idiopathic hypertrophic cardiomyopathies frequently provides symptomatic improvement, but may not alter the mortality of the disease (Goodwin, 1974). In Friedrich's ataxia our limited experience suggests that therapeutic doses of beta-blockers is often poorly tolerated. Should a prospective clinical trial of beta-blockers in this disease be attempted, therapy should be instituted early in view of the already extensive myocardial fibrosis found even in patients in their middle-teens.

In conclusion, the deterioration of cardio-pulmonary function in Friedrich's ataxia is multi-factorial (fig. 12). The neuromyopathy (or the underlying metabolic or cellular defect) appears to be the main contributing factor to the deterioration of cardio-pulmonary function which is exacerbated by the scoliosis and varying severity of the cardiomyopathy. Rational therapeutic interventions to decrease morbidity, and possibly mortality, should be individualized with a low risk to benefit ratio.

REFERENCES


Depakene Valproic acid better control for more epileptic patients
Depakene
valproic acid

A major advance in anticonvulsant therapy that could bring more epileptic patients closer to normal as sole and adjunctive treatment of simple or complex absence seizures, including petit mal as adjunctive therapy of multiple seizures that include absence attacks.

a unique chemical structure

DEPAKENE is a simple fatty acid, chemically unrelated to other anticonvulsants.

a physiological mode of action

DEPAKENE appears to increase GABA (γ-aminobutyric acid) levels in the brain and cerebellum. GABA is known to inhibit neuronal excitability.1

Depakene extends the range
"remarkably free of side effects in the general context of antiepileptics"³

Patients taking DEPAKENE have been reported to be more lively and alert and better able to carry out their daily tasks.³

DEPAKENE has not been associated with cosmetically undesirable side effects such as hirsutism, acne and gum hyperplasia. Although inhibition of platelet aggregation and leukopenia have been occasionally reported, it has not been associated with aplastic anemia or agranulocytosis. And DEPAKENE has no record of tolerance in long-term use.²

world-wide documentation of effectiveness

Numerous publications and clinical trials involving more than 4000 patients whose ages ranged from 5 months to 71 years, have demonstrated the antiepileptic efficacy of DEPAKENE.

An overview of clinical studies² involving valproic acid in 1020 patients demonstrates an excellent (75-100%) reduction in seizure frequency in 45.7% of patients, and satisfactory results (33-74% reduction of seizures) in 25.4% more.
Prescribing Information

Dekapene (valproic acid) has anticonvulsant properties. Although its mechanism of action has not been established, it has been suggested that its activity is related to increased plasma levels of gamma-aminobutyric acid (GABA).

Valproic acid is rapidly absorbed after oral administration. Peak serum levels occur approximately one to four hours after a single oral dose. The serum half-life (t1/2) is approximately 8 to 12 hours. Valproic acid is rapidly distributed throughout the body and the drug is strongly bound (90%) to human plasma proteins. The therapeutic plasma concentration range is believed to be from 43 to 86 µg/mL.

Excretion of valproic acid and its metabolites occurs principally in the urine, with minor amounts in the feces and expired air. Very little unmetabolized parent drug is excreted in the urine. The principal metabolite formed in the liver is the glucuronide conjugate.

INDICATIONS AND CLINICAL USE

Dekapene (valproic acid) is indicated for use as sole and/or adjunctive therapy in the treatment of absence seizure and complex absence seizures, including petit mal. Valproic acid may also be used adjunctively in patients with multiple seizure types which include absence.

In accordance with the International Classification of Seizures, simple absence is defined as a very brief clonic or tonic-clonic movement of the head or body (lasting 2-15 seconds) accompanied by certain generalized epileptic discharges without other detectable clinical signs. Complex absence is the term used when other signs are also present.

CONTRAINDICATIONS

Dekapene (valproic acid) is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS

Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in a few patients receiving Dekapene (valproic acid). Anticonvulsant drugs. These events have occurred during the first six months of therapy. Although a causal relationship has not been established, caution should be observed when administering Dekapene to patients with pre-existing liver disease. Liver function tests should be performed prior to therapy and every two months thereafter.

Use in pregnancy

The safety of Dekapene (valproic acid) during pregnancy has not been established. However, animal studies have demonstrated teratogenicity. Therefore, the physician should weigh the potential benefits against the possible risks of anticonvulsant treatment of the woman of childbearing age who may become pregnant.

Recent reports indicate an association between the use of anticonvulsant drugs and the incidence of birth defects in children born to epileptic women taking such medication during pregnancy. The incidence of congenital malformation in the general population is regarded to be approximately 2%, in children of treated epileptic women this incidence may be increased two to threefold. The increase is largely due to specific defects, e.g. congenital malformations of the heart, and cleft lip and/or palate. Nevertheless, the great majority of mothers receiving anticonvulsant medications deliver normal infants.

Data are more extensive with respect to diphenhydantoin and phenobarbital, but these drugs are also the most commonly prescribed anticonvulsants. Some reports indicate a possible similar association with the use of other anticonvulsants, including ethosuximide and parahemodone. However, the possibility also exists that other factors, e.g. a genetic predisposition or the epileptic condition itself may contribute or be mainly responsible for the higher incidence of birth defects.

Anticonvulsant drugs should not be discontinued in patients in whom the drug has been administered to prevent major seizures, because of the high possibility of precipitating status epilepticus with attendant hypoxia and risk to both the mother and the unborn child. With regard to drugs given for minor seizures, the risks of discontinuing or during pregnancy should be weighed against the risks of congenital defects in each particular case and with the particular family history.

Epileptic women of childbearing age should be encouraged to consult the counsel of their physician and should be reported on the absence of the drug not to exceed 50 mg/kg/day. Where the necessity for continued use of antiepileptic medication is in doubt, appropriate consultation might be indicated.

Nursing Mothers

Dekapene is secreted in breast milk. As a general rule, nursing should not be undertaken while a patient is receiving Dekapene.

Fertility

Chronic toxicity studies in juvenile and adult rats and dogs demonstrated no teratogenicity and testicular atrophy of doses greater than 350 mg/kg/day to testes at 90 mg/kg/day. The effect of Dekapene (valproic acid) on the development of the testes and sperm production and fertility in humans is unknown.

PRECAUTIONS

General

Because of the rare reports of platelet aggregation dysfunction, thrombocytopenia, and elevated liver enzymes, it is recommended that liver function tests, platelet counts and bleeding time determinations be performed before initiation of therapy and at periodic intervals.

Because valproic acid may interact with other anticonvulsant drugs, periodic serum level determinations of such other anticonvulsants are recommended during the early part of therapy (see Drug Interactions). Valproic acid is partially eliminated in the urine as a ketone-containing metabolite, which may lead to a false interpretation of the urine ketone test.

Driving and Hazardous Occupations

Valproic acid may produce CNS depression, especially when combined with other CNS depressants, such as alcohol. Therefore, patients should be advised not to engage in hazardous occupations such as driving a car or operating dangerous machinery, until it is known that they do not become drowsy from the drug.

Drug Interactions

Dekapene (valproic acid) may potentiate the CNS depressant action of alcohol.

There is evidence that valproic acid may cause an increase in serum phenobarbital levels, although the mechanism is unknown. Patients receiving concomitant barbiturate therapy should be closely monitored for neurological toxicity. Serum barbiturate drug levels should be obtained, if possible, and the barbiturate dosage decreased, if indicated.

There is conflicting evidence regarding the interaction of valproic acid with phenytoin. It is not known if there is a change in unbound (free) phenytoin serum levels. The dose of phenytoin should be adjusted as required by the clinical situation.

The concomitant use of valproic acid and clozapine may produce abnormal blood counts. Caution is recommended when valproic acid is administered with drugs affecting coagulation, e.g. warfarin, warfarin-like and warfarin (see Adverse Reactions).

ADVERSE REACTIONS

The most commonly reported adverse reactions are nausea, vomiting and diarrhea. Since Dekapene (valproic acid) has usually been used with other anticonvulsants, it is not possible in most cases to determine whether the adverse reactions mentioned in this section are due to valproic acid alone or to the combination of drug.

Gastrointestinal

Nausea, vomiting and indigestion are the most commonly reported side effects at the initiation of therapy. These effects are usually transient and rarely require discontinuation of therapy. Diarrhoea, abdominal pain, constipation and diarrhoea have also been reported. Anorexia with some weight loss and increased appetite with some weight gain have also been seen.

CNS Effects

Sedative effects have been noted in patients receiving valproic acid alone but are often found in patients on combination therapy. Sedation usually disappears upon reduction of other anticonvulsant medication. Ataxia, headache, paresthesias, dizziness, "feeling of being drunk" tremors, drowsiness and dizziness, incoordination have rarely been noted. Rare cases of coma have been reported in patients who were also on phenytoin.

Dermatologic

Transient increases in hair loss have been observed. Skin rash and petechiae have rarely been noted.

Psychiatric

Emotional upset, depression, psychosis, aggression, hyperactivity and behavioral deterioration have been reported.

Musculoskeletal

Weakness has been reported.

Hematopoietic

Valproic acid inhibits the secondary phase of platelet aggregation. This may be reflected in altered bleeding time. Relative lymphocytosis and mild thrombocytopenia have also been noted in isolated cases. Leucopenia has been reported.

Hepatic

Increases in serum alkaline phosphatase and serum glutamic oxaloacetic transaminase have been noted isolated, as have been reported (see Warnings).

SYMPTOMS AND TREATMENT OF OVERDOSE

In a reported case of overdose with Dekapene (valproic acid) after ingesting 36 g in combination with phenobarbital and phenytoin, the patient presented in deep coma. An EEG recorded diffuse slowing, compatible with the state of consciousness. The patient made an untoward recovery.

As valproic acid is absorbed very rapidly, gastric lavage may be of limited value. General supportive measures should be applied with particular attention to the prevention of hypotension and the maintenance of adequate urinary output.

DOSAGE AND ADMINISTRATION

Dekapene (valproic acid) is administered orally. The recommended initial dose is 15 mg/kg/day, increasing at one week intervals by 5 to 10 mg/kg/day until additional side effects are controlled or side effects predominate increase further. The maximum recommended dose is 30 mg/kg/day. When the total daily dose exceeds 250 mg/day, it is given in a divided regimen.

<table>
<thead>
<tr>
<th>Weight</th>
<th>Total Daily Dose (mg)</th>
<th>Number of Capsules or Teaspoonfuls of Syrup</th>
<th>Dose 1</th>
<th>Dose 2</th>
<th>Dose 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>kg</td>
<td>lb</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2</td>
<td>5-8</td>
<td>250</td>
<td>0</td>
<td>1</td>
<td>1</td>
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<td>8-12</td>
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<td>1</td>
<td>2</td>
</tr>
<tr>
<td>5-9</td>
<td>12-16</td>
<td>1000</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

As the dosage of valproic acid is raised, blood levels of phenobarbital and/or phenytoin may be affected (see Precautions).

Further information on experience G. initiation may benefit from administration of the drug with food or by a concomitant increase of the dose from an initial low level. The capsules should be chewed to avoid local irritation of the mouth and throat.