Convulex®50 mg/ml syrup for children

anticonvulsant

Composition

sodium valproate	50	mg
lycasin (sugar substitute)	800	mg
4-hydroxybenzoic acid methylester	1,0	mg
4-hydroxybenzoic acid propylester	0,4	mg
saccharin sodium	1,0	mg
sodium cyclamate	3,0	mg
	per	ml

Characteristics

Valproic acid is a saturated, single branched fatty acid thus differing from the circular structure of all other anticonvulsants. In animal studies valproic acid showed only small toxicity while exerting an effective anticonvulsive action.

The mood-elevating effect of valproic acid results in a better visomotor coordination and concentration ability.

Pharmacologically the effect of valproic acid is supposed to be due to the action it exerts on the metabolism of gamma-aminobutyric acid (GABA). The activation of glutamic acid decarboxylase and the inhibition of GABA-transaminase result in a strong increase of GABA-concentration in synaptosomes and the intersynaptic cleft. As an inhibitory neurotransmitter GABA impedes pre- and postsynaptic discharges and thus prevents the spread of convulsive activity.

The active substance is absorbed in the gastrointestinal tract. Plasma peak levels are reached 1–3 hours after the administration. Concurrent food intake has no influence on the quantity of the absorbed active substance. Steady state plasma levels are reached after 2–4 days depending on the dosage intervals. Their therapeutic range is situated between 50–100 mg/l (appr. 300–600 µmol/l). Valproic acid is bound to plasma proteins by 80–95 %. Liquor concentrations correlate well with the free part of the active substance.

Only 1–3 % of the administered dose are excreted via the kidneys in unchanged form. The major part is subject to glucuronisation and oxidation in the liver. The metabolites are excreted via the kidneys. Plasma half-life individually ranges between 9–16 hours.

As the intake is facilitated by the medication's good taste, Convulex syrup may be especially used for the treatment of infants.

Convulex syrup contains lycasin, a sugar substitute which is not reduced to saccharic acids by acid-forming bacteria and thus has no cariogenic effect.

Indications

* Primary generalized seizures

- Petit mal epilepsy
  - pyknoleptic absences
  - myoclonic-astatic seizures (Lennox'-syndrome)
  - impulsive Petit mal (myoclonic Petit mal seizures)
  - infantile spasms (West's-syndrome)
- Grand mal epilepsy (seizures on awakening, photosensitive forms)

partial (focal) seizures especially characterized by complex symptoms with secondary generalization.

Administration

To be taken during or after meals with some liquid.

Dosage

Starting with a daily dose of 15 mg/kg body weight the dosage should be slowly increased by 5–10 mg/kg body weight per week until the patient does no longer suffer from seizures.

general dosage guide-line: 30 mg/kg body weight per day

average daily dosage in children:

7,5–14 kg	3– 9 ml
14 –21 kg	6–12 ml
21 –32 kg	12–18 ml

Splitting the daily dose into several intakes is generally recommended. During monotherapy with valproic acid the total daily dose (up to a dose of 15 mg/kg body weight per day) may as well be administered once a day in the evening.

Regular blood level controls are indicated.

The previously applied anticonvulsive medication is to be gradually reduced in pretreated patients.

Contraindications

Hypersensitivity to valproic acid, disturbances of the hepatic or pancreatic functions.

Special caution is to be exercised with:

- anamnestic hepatic or pancreatic diseases or injuries of the bone marrow
- hemorrhagic diathesis
- disturbances of the renal function
- congenital enzymatic defects
- severe epileptic seizure forms
- mentally retarded children
- organic cerebral lesions
- children under the age of 2 years (as they are especially predisposed for hepatic damages).

Pregnancy and Lactation:

Teratogenic potential of valproic acid was proved by means of animal studies. During pregnancy valproic acid should consequently be administered in smallest effective doses only. If possible, a combination with other anticonvulsants should be avoided.

During the first three months of pregnancy therapy with valproic acid should not be initiated.

If the pregnant woman is actually treated with valproic acid, the medication should not be discontinued (risk of increase of seizure frequency or of causing a status epilepticus dangerous to the life of mother and fetus). Valproic acid levels in plasma (therapeutic range) should be controlled regularly.

Ablactation is recommended.

Side-Effects

Convulex syrup is well tolerated. Rarely occurring side-effects manifest mostly with plasma levels above 100 mg/l and during combination therapy. Gastrointestinal disturbances count among the most frequent side-effects. Nausea, vomiting and anorexia mostly occur at the onset of therapy and disappear with adaption of the dose or intake during or after meals. Increased appetite, weight gain, gastralgia, gastrospasms, diarrhea and constipation were observed as well. Sedation, vertigo, headaches, depressive deterioration, aggression, involuntary movements, hyperactivity, tonic cramps, ataxia, coordination disturbances, tremor, asterixis, dysarthria, nystagmus, diplopia are to be characterized as rarely occurring side-effects. In isolated cases states of confusion, stupor and coma - leading to the tentative diagnosis of a paradoxical effect in psychologically predisposed patients - were observed some days after reaching therapeutic plasma levels. Thrombocytopenia, inhibition of platelet aggregation, neutropenia, lymphocytosis, hypofibrinogenemia and very rarely anemia and bone-marrow depression were observed as hematologic disturbances. Hyperammonemia, increase of the plasma glycerol level or decrease of the carnitine level were observed as well. Allergic skin reactions occur only very rarely. Petechial bleedings, tendency to hematomas and transitory loss of hair were observed in isolated cases. Manifestation of severe hepatic damage, being independent of the administered doses, and occurring during the first six months of treatment was mentioned very rarely. The occurrence of a Reye-like syndrome was described as well. Impaired parameters of the hepatic function (increase of GOT, GPT, LAP, gamma-GT, alkaline phosphatase, bilirubin) occur frequently during the therapy but usually normalize after dosage adaption. The treatment is to be discontinued immediately after the occurrence of clinical symptoms pointing to a hepatic damage (recurrent epigastric complaints, vomiting, anorexia, fatigue,weakness, jaundice, ascites, hepatic encephalopathy). Affections of the pancreas (acute pancreatitis) accompanied by high plasma levels of amylase and lipase and a similar picture of symptoms was observed in very rare cases. Edema as well as rare dysmenorrhea and galactorrhea are possible.

Drug Interactions

By displacing phenytoin, phenobarbital and diazepam from plasma protein binding, valproic acid increases the free level of these active substances. The metabolism of diazepam is inhibited. Primidone levels are increased as well. The effect of ethosuximide is potentiated. Phenytoin, phenobarbital and primidone increase the clearance and thereby reduce the plasma concentration of valproic acid. Concomitant administration of carbamazepine may enhance or decrease the blood levels of valproic acid. In rare cases a combination with clonazepam may induce absence status. During combination therapy with several anticonvulsants exact determination of blood levels (drug monitoring) is therefore required. The centrally depressive effect of pharmaceutical preparations (like e. g. neuroleptics and antidepressants) and alcoholic beverages is potentiated by valproic acid. The effect of platelet aggregation inhibitors (acetyl salicylic acid), anticoagulants of the coumarin series and heparin is potentiated. Some studies demonstrated that salicylates displace valproic acid from plasma albumin binding and impair the metabolism of valproic acid thus causing toxic blood level values of valproic acid (clinical relevance especially in children).

A concomitant administration of hepatotoxic medication may potentiate the adverse effects valproic acid may have on the liver.

Drug interactions with oral contraceptives are not known.

Interactions in laboratory tests:

As valproic acid is partially degraded to ketone-like metabolites, a urine test for ketones may show falsely positive results in diabetics.

Depending on its plasma concentration valproic acid leads to a displacement of thyroid hormones from protein binding and a more rapid metabolism, thus creating a false interpretation of hypothyreosis in thyroid function tests.

Cautionary Advice

Liver function tests, determination of coagulation state (bleeding time, Quick's test, plasma fibrinogen, thrombocyte count, control of platelet aggregation, thrombelastogram) and control of serum amylase and lipase are to be performed prior to the treatment, on the occasion of a dosage increase and afterwards at intervals of 2 months. The treatment should be stopped immediately after the manifestation of hypofibrinogenemia or a coagulation disturbance, an increase of transaminases to their triple value as well as an increase of alkaline phosphatase and bilirubin or first symptoms of toxic hepatitis (pathologic laboratory tests in connection with clinical symptoms). If only transaminases are slightly increased, a dose reduction should be made while concomitantly controlling liver function and coagulation values. Controls of the pancreatic function (amylase, lipase) should take place prior to and repeatedly during the treatment with valproic acid, especially on the occurrence of epigastric distress of unknown etiology, symptoms of organic lesion or haemorrhagic anomaly. The treatment is to be stopped immediately after the first symptoms of a pancreatitis (pathologic laboratory values in connection with clinical symptoms).

Regular controls of renal function and determination of the plasma ammonia level are recommended as well.

Sudden discontinuance of valproic acid may lead to more frequent seizure activity.

Information for the Patient

The intake of Convulex is neither to be started nor to be discontinued without medical control.

The physician should be consulted immediately after the occurrence of first symptoms of side-effects (especially on the part of liver and pancreas;epigastric distress of unknown etiology, vomiting, anorexia, high fever, fatigue, general weakness, disorientation, abulia, cramps, unconsciousness, transitory cutaneous eruptions, enlargement of the liver, jaundice, ascites, deepened respiration, impairment of the central nervous system, coagulation disturbances). The physician is to be informed without delay of any pregnancy.

During a treatment with Convulex the physician is to be consulted prior to the application of any other medication.

The physician is to be informed of the intake of Convulex prior to any surgical or dental intervention.

In combination with alcohol or at the onset of therapy, especially, reactivity may be changed to an extent causing difficulties when driving or operating machines. The consumption of alcoholic beverages should be avoided.

Caution in diabetics! When stabilizing a diabetic patient the contents of 600 mg carbohydrates/ml syrup will have to be taken into consideration.

Overdosage

Acute overdosage causes coma accompanied by areflexia and central respiratory depression. Gastric lavage, administration of activated charcoal as well as hemoperfusion should be tried as a therapy.

A treatment with assisted respiration requires intensive medical care. A successful administration of naloxone as an antidote was reported as well.

Pack Size: 100 ml

Storage Advice

Store at room temperature not exceeding 25°C. Protect from light. Keep out of the reach of children!

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Producer:

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