# :: Severe myoclonic epilepsy in infancy

- This document is a translation of the French recommendations drafted by Dr. M. Chipaux and Prof. O. Dulac, reviewed and published by Orphanet in 2008.
- Some of the procedures mentioned, particularly drug treatments, may not be validated in the country where you practice.

**Synonyms:**
Dravet syndrome

**Definition:**
The typical form of severe myoclonic epilepsy in infancy combines: **normal psychomotor development prior to epilepsy, convulsive crises** which are often febrile and long lasting at **about six months of age**, even earlier. These **can evolve to grand mal states and focal convulsions alternating from one side to the other,** frequently with a post-ictal unilateral motor deficiency. **Polymorphic non-febrile crises then follow** which are often associated with **myoclonia** and **secondary intellectual deficiency** predominantly affecting language, and **ataxia**. Neither EEG nor MRI shows any specific abnormalities. This syndrome is mostly associated with a mutation, usually *de novo*, of the *SCN1A* gene that encodes a sodium channel.

**Further information:**
See the Orphanet abstract

# Pre-hospital emergency care recommendations
# Call for a patient suffering from Dravet syndrome

## Synonyms

- severe myoclonic epilepsy of infancy

## Aetiology

- epileptic syndrome usually related to mutation of the *SCN1A* gene

## Special risks in an emergency

- convulsions that are often febrile and prolonged
- convulsive grand mal state
- sudden death

## Frequently used long term treatments

- valproate, clobazam, stiripentol in combination
- +/- clonazepam, topiramate, levetiracetam

## Complications

- be aware of the risk of convulsive crises evolving into grand mal states
- be aware of the risk of a prolonged myoclonic grand mal state with periods of unconciousness and erratic distal myoclonias
- be aware of intellectual deficiency

## Specific medical care prior to hospitalisation

- Treat convulsions with high doses of benzodiazepines intra-rectal or even IV
- If this treatment has already been started by the parents without success, send a paediatric resuscitation unit
- Avoid the use of aggravating drugs: high doses of barbiturates, carbamazepine, oxcarbazepine, vigabatrin, lamotrigine
- Concomitant treatment of any hyperthermia and its cause
- Precautions related to drug interactions with stiripentol. This drug extends the half-life of other drugs that are catabolised by cytochrome P450 (including phenobarbitone, phenytoin and clobazam): this has no effect until the second administration where there is a cumulative effect due to the prolonged half-life

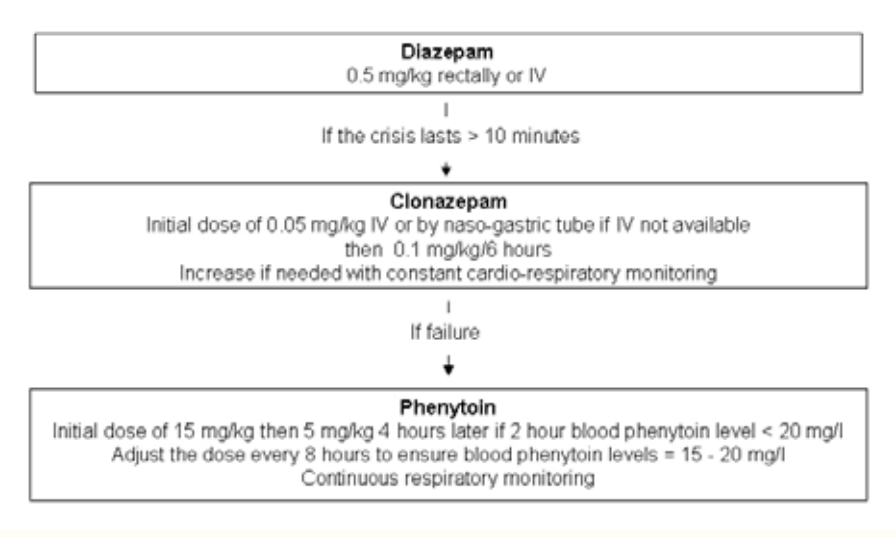
## Emergency issues and recommendations

### 1. Neurological complications: convulsions and grand mal states

**Febrile then non-febrile crises, generalised or unilateral switching from side to side.** These crises can start during the first months of life. They are sometimes **followed by a motor deficiency** lasting from a few minutes to several hours. They **can develop into a grand mal state** that is sometimes very prolonged.

- **Emergency diagnostic methods:**
  - If the crisis is febrile, seek the aetiology of the fever.
  - An EEG should not be done as an emergency unless there is a doubt in diagnosing a grand mal state.

- **Emergency therapeutic measures:**
  - **Diazepam** rectally or intravenously at 0.5 mg/kg as a 1st intention for a convulsive crisis.
  - **If the crisis lasts more than 10 minutes, do not use barbiturates** because of the risk of 'low flow' (several observations).
  - Inject **Clonazepam** at the following dose rates: 0.05 mg/kg as an initial dose preferably by IV or by naso-gastric tube when the veins are impossible to obtain, followed by 0.1 mg/kg/6 hours - renewed or increased depending on the evolution of the crisis, under cardio-respiratory monitoring.
  - Midazolam can also be used depending on the team's usual protocol.
  - **In the event of failure,** use **phenytoin**:
    - Initial dose of 15 mg/kg then 5 mg/kg four hours later if plasma phenytoin levels are less than 20 mg/l two hours after the initial dose.
    - **The interaction with stiripentol prevents any further use** except in a specialist service that can ensure that plasma levels are monitored.
    - **In practice,** try to adjust the dose every eight hours up to 36 hours based on the plasma phenytoin levels in order to avoid a phenytoin overdose which can cause the grand mal state to become resistant by a paradoxal effect. **The target plasma level is 15 to 20 mg/l.**
  - **Anticonvulsants to be avoided because they risk aggravating the convulsions:** barbiturates, lamotrigine, carbamazepine, oxcarbazepine, vigabatrin.
  - Take into account the **drug interactions** when treated with Stiripentol, see the drug interactions section in appendix
  - Managing grand mal state complications is as per normal protocols.
  - In every case, it is important **not to interrupt the patient's normal treatment** (including administering the product by naso-gastric tube if there is no injectable form) to avoid a sudden withdrawal effect.



- **Subsequent management:**
  - For short and 'normal' crises with a trigger factor (fever, drug withdrawal, photosensitivity, tiredness, toxicities...): non-urgent neurological or neuro-paediatric consultation. Hospitalisation is not needed every time.
  - For a series of crises or a grand mal state, the patient must be seen quickly by his/her usual neurologist or neuro-paediatrician to review his treatment.

### 2. Special case of a non-convulsive grand mal state

- **Prolonged obnubilation**, often associated with erratic myoclonias and occasionally other type of convulsive crises.
- These grand mal states are often poorly recognised.
- They are diagnosed by **EEG**.
- **IV benzodiazepines** are the treatment of choice. Phenytoin and phenobarbitone can have more of an aggravating effect.

### 3. Special case of SUDEP (sudden unexplained death during epilepsy)

- **Heightened risk of sudden unexplained death** (SUDEP).
- It is suggested, but not proven, that cardiac rhythm problems may be the cause possibly resulting from sodium channel pathology.
- Care is as for **normal cardio-respiratory arrest protocols.**

### 4. Traumatic complications

- Convulsive crises (generalised tonic-clonic crises, massive myoclonias) can cause **falls** because infants are incapable of anticipating them and protecting themselves.
- Risk of cranial trauma, haemorrhages, haematomas, fractures.
- Their management is as per the **normal protocols.**

## Drug interactions

- It is important to check that there is no drug interaction with the patient's long term therapy, especially when they are treated **with Stiripentol**. You can find a **list of drug interactions** in **appendix.**

## Anesthesia

- Possible drug interactions with long term treatment.
- Take account of moderate to severe intellectual deficiency

## Preventive measures

- **Closely monitor the temperature**, fever may induce a new crisis: treat quickly with antipyretics
- **Treat any new convulsive crisis quickly**

## Additional therapeutic measures and hospitalisation

- Patient with Dravet syndrome often present with a moderate to severe intellectual deficiency. The first convulsions occur in early infancy. These two reasons mean **that it is important to have the families present during an emergency admission or hospitalisation.**
- **The normal treatment**, especially for the epilepsy, **must not be interrupted**.
- It is important that the referring neuro-paediatrician's recommendations, **a copy has been provided to the parents, are taken into account by the emergency doctor who receives the infant.**
- Given the parents worry, **give adequate explanations** about the disease and the therapeutic and diagnostic measures that are being used.

## Organ donation

- There is *theoretically* no contra-indication for organ donation. The transplant service should be contacted.

# Appendix

## 1. Drug interactions with Stiripentol

STIRIPENTOL acts mainly by inhibiting cytochrome P450 (CYP), principally CYP3A4 but also CYP1A2, 2C19 and 2D6. This inhibition results in an increase in plasma levels and half-life of drugs of which the hepatic metabolism depends on these same CYP:

- THEOPHYLLIN (use with STIRIPENTOL is not recommended)
- oral anticoagulants (use with STIRIPENTOL is not recommended)
- rye ergot derivatives
- MACROLIDES (ERYTHROMYCIN, JOSAMYCIN, ROXITHROMYCIN
- anti-arrhythmics
- beta-blockers
- hypnotics
- anti-depressants
- CYCLOSPORIN
- digitoxin
- testosterone
- LIDOCAIN parentally

- These interactions also concern other anti-epileptics especially CARBAMAZEPIN (contra-indicated in Dravet syndrome), PHENYTOIN and CLOBAZAM. But **the dose rate must not be changed without the advice of the infant's referring neuro-paediatrician:** indeed interaction with clobazam has a positive effect used in therapeutic protocols in combination with STIRIPENTOL.

In the event of combined treatment with VALPROATE, a lower dose of valproate is used due to a reduced clearance and the risk of reduced appetite at normal dose rates. Plasma levels of VALPROATE will therefore be lower than the usual levels. **The dose rate must not be changed without the advice of the infant's referring neuro-paediatrician.**

## 2. Products to be used with care

Prudence is recommended for all the following products (Precautions of use). Their use in conjunction requires heightened clinical monitoring when starting treatment with STIRIPENTOL and after it is stopped. Most of the time, the dose rate has to be adjusted, accompanied with monitoring of plasma concentrations.

*Therapeutic classes:*

- ANTI-HISTAMINES
- NSAIDS
- BENZODIAZEPINES
- BETA-BLOCKERS
- BIGUANIDES
- HORMONAL CONTRACEPTIVES
- HYPNOTICS
- HYPOGLYCAEMIA INDUCING SULPHAMIDES
- DIVERS

*Products:*

| | | |
|---|---|---|
| ACTRON | BRONCO-TULISAN | EUGLUCAN |
| ALEPSAL | BUTAZOLIOINE | GARASPIRINE |
| ALGISFIR | DIPHARMA | GLIBENESE |
| ALGOCRATINE | CEBUTID | GLUCINAN |
| ANTIGRIPPINE MIDI | CHYMALGYL | GYNOPHASE |
| APESMONE | CORGARD | HALGON |
| APTINE | DAONIL | HEMAGENE |
| ARTHROCINE | DEPAMIDE | HEMINEURINE |
| ASPEGIC | DETENSIEL | IMOVANE |
| ASSUR | DIABINESE | INSOMNYL |
| AZANTAC | DIAMICRON | JUVEPIRINE |
| BETAPRESSIN | DI-HYDAN | KERLONE |
| BI-PROFENID | EUCALYPTOSPIRINE | LIBRIUM |
| LOPRIL | PHENYLBUTAZONE | SUPPONIZINE |
| MANDRAX | PINIZONE | SUPPOPTANOX |
| MEDROCYL | PONSTYL | TAGAMET |
| MEPRONIZINE | PRENOXAN | TENORMINE |
| MIGLUCAN | PROFENID | TIMACOR |
| MILLIGYNON | RANGASIL | TRANDATE |
| MINIDIAB | RHONAL | TRANSICOR |
| MINIPHASE | ROHYPNOL | TRIELLA |
| MYSOLINE | SALIPRAN | TROMEXANE |
| NEURINASE | SECTRAL | VALIUM |
| NIFLURIL | SERESTA | VARNOLINE |
| NOCTRAN | SINTROM | VERATRAN |
| NORDAZ | SONUCIANE | VISKEN |
| NORISTERAT | SOTALEX | VOLTARENE |
| NOVACTOL | STEDRIL | ZARONTIN |
| NUCTALON | SUPPONERYL | |

## Documentary resources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*These guidelines have been prepared with the collaboration with Dr. M. Chipaux and Professor O. Dulac of the Centre de Référence des Epilepsies Rares, l'Association Française pour les Epilepsies (Réseau Aispace) and the Association Epilepsie-France, and Dr. Gilles Bagou SAMU-69 Lyon*

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