Paediatric Drug-Resistant Epilepsy: Nitrazepam 1mg/ml solutions to avoid Clinical-Therapeutic Error

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#nitrazepam #galeniccompounding #epilepsy ( NON RICORDO gli #)

Background and Importance
The management of pediatric patient with drug-resistant epilepsy (EDR) is complicated and often requires therapy and dosages adjustment. Clinical Pharmacist and Child Neuropsychiatry cooperate to prevent the clinical-therapeutic error, common in prescription of drugs with reduced and personalized dosages. Benzodiazepine Nitrazepam (NTR) in children is recommended in: epileptic spasms, in Dravet, West and Lennox-Gastaut syndromes.

A risk of dosage administration error due to (Fig. n 1):
the low prescribed dosage (125micrograms/Kg)(1) and the need to crush the commercial tablets.

Aim and Objectives
Set up a liquid formulation with a standard concentration, easily adaptable to pediatric needs as:
weight changes, palatability, suitability, simple to use during the patient hospitalization and even at home.

Materials and Methods

Multi-phase study
Phase I: Data Collection.
Retrospective study examine medical records of children born 2008-2019 with certain diagnosis of EDR: patients number, sex, age, Epilepsy-Classification according to International League Against Epilepsy (ILAE) Guidelines criteria(2), antiepileptic therapy and dosage drugs.

Phase II: Subject study Nitrazepam. Paediatric dosage research and formulation three galenic compoundings possible to use.

Phase III: Chemical-physico-microbiological stability analysis of Nitrazepam1mg/ml. Samples stored 30 days 2-8°C and/or ambient 25°C. Chemical-physic stability by qualitative determination of molecular ions NitrazepamC282.1/C236, in High Pressure Liquid Chromatography(HPLC), equipped with a UV detector, interfaced with a triple quadrupole mass detector (Mass Spectrometer, MS/MS). Column LunaC1850mm. Standard Nitrazepam D5100mcg/ml(3). Microbiological stability according to Italian Ufficiale Farmacopea(FUI)(4).

Results
101 children EDR (54 males, 47 females), age mainly affected 3-4(20%) and 9-10(33%).

Classification (Fig. n 2): Focal Onset 34,86%, Focal to Bilateral Tonic-Clonic 17,10%, Generalized Onset 47,36%, Unclassified 0,65%.

31 Drugs prescribed, the most used (Fig. n 3): Levetiracetam(27%), Clobazam(25%), Topiramate (21%), Nitrazepam (12%).

Required dosages of NTR difficult to administer: 0.625mg, 0.83mg, 1.25mg, 1.66mg and 2.5mg.

Set up three liquid galenic formulations (Nitrazepam from Mogadon® 5mg tablets):
- Nitrazepam1mg/ml Simple Syrup Methylcellulose1%;
- Nitrazepam1mg/ml suspension tragacanth gum;
- Nitrazepam1mg/ml Syrspend®SFAlkaDry (5);

HPLC MS/MS analysis confirmed, uniform and steady dosage, 30 days stability for: Nitrazepam1mg/ml suspension tragacanth gum and Nitrazepam1mg/ml Syrspend®SFAlkaDry.(Fig. n 4)

Conclusion
Good clinical practice and collaboration between departments allows better management of epileptic seizures in children affected by severe EDR.
Reproducible and safe therapy means improving patient's life and therapeutic compliance.