

Nitrazepam 1mg/ml solutions to avoid Clinical-Therapeutic Error



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

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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 probable 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-physic-microbiological stability analysis of Nitrazepam 1mg/ml. Samples stored 30 days 2-8°C and/or ambient 25°C.

Chemical-physic stability by quantitative determination of molecular ions Nitrazepam C₂₈H₂₇N₃O₂, in High Pressure Liquid

Chromatography (HPLC), equipped with a UV detector, interfaced with a triple quadrupole mass detector (Mass Spectrometer, MS/MS).

Column Luna C18 50mm. Standard Nitrazepam D5100mcg/ml(3).

Microbiological stability according to Italian Official 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):

- Nitrazepam 1mg/ml Simple Syrup Methylcellulose 1%;
- Nitrazepam 1mg/ml suspension tragacanth gum;
- Nitrazepam 1mg/ml Syrspend® SFAIkaDry (5);

HPLC MS/MS analysis confirmed, uniform and steady dosage, 30 days stability for: Nitrazepam 1mg/ml suspension tragacanth gum and Nitrazepam 1mg/ml Syrspend® SFAIkaDry. (Fig. n 4)

Conclusion

Good clinical practice and collaboration between departments allows a better management of epileptic seizures in children affected by severe EDR.

Reproducible and safe therapy means improving patient's life and therapeutic compliance.

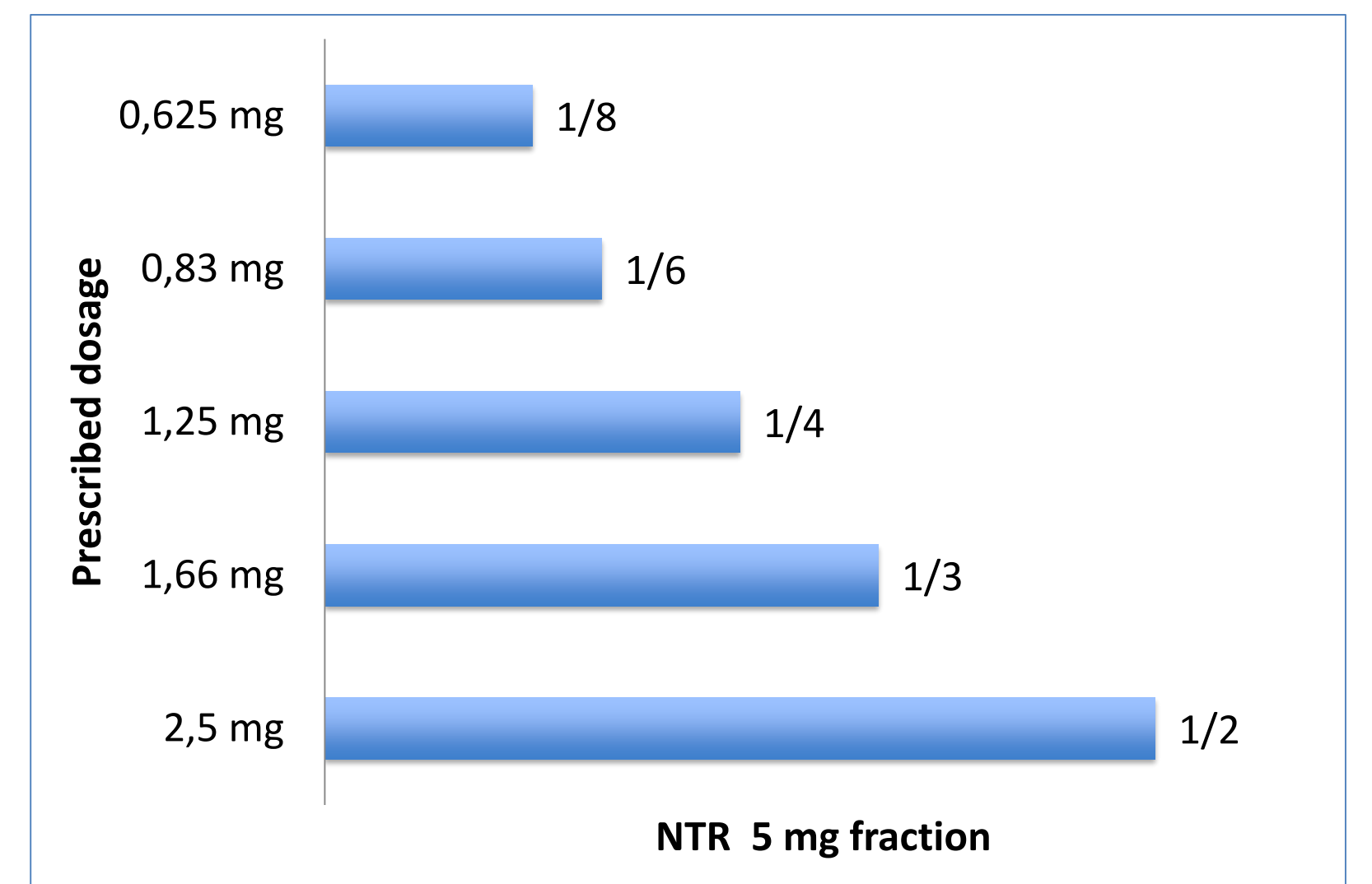
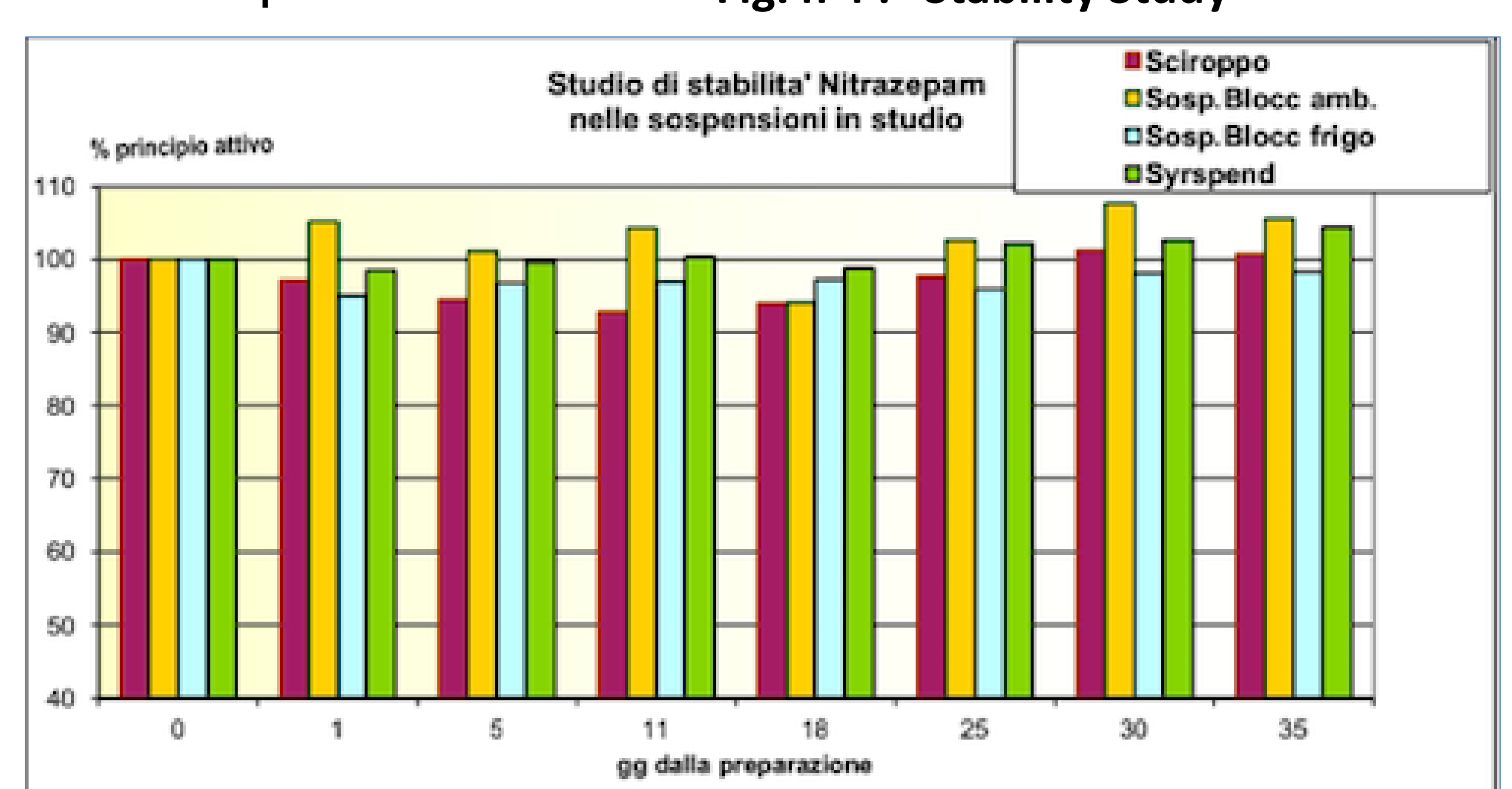
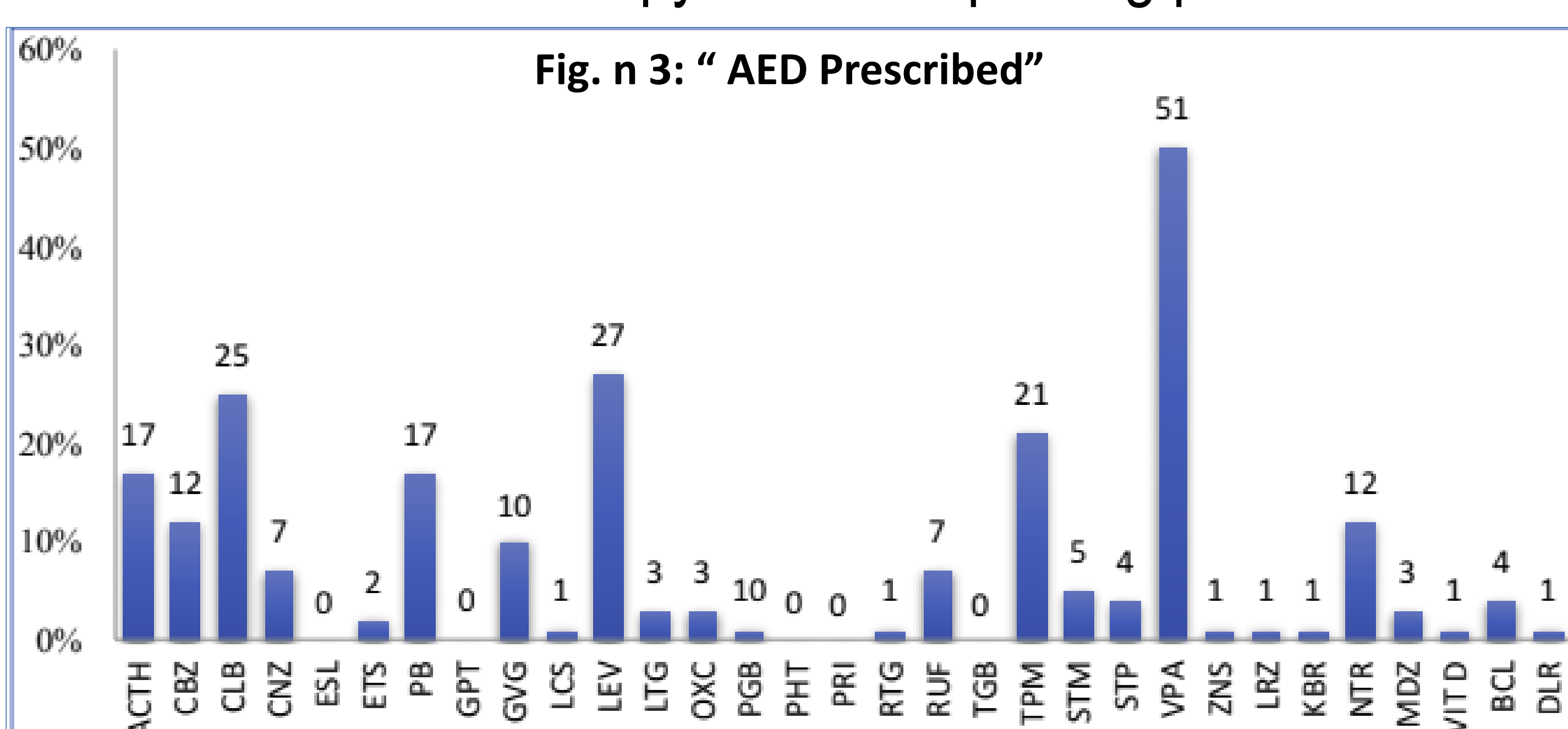


Fig.n 1 NTR Paediatric dosage

| Epilepsy Classification | % |
|-------------------------|--------|
| Focal | 34,86% |
| Generalized | 47,36% |
| Unknown | 0,63% |
| Focal to Bilateral | 17,10% |

Fig.n 2 Epilepsy-Classification ILAE Standards



References

(1) British National Formulary for Children 2014/(2) www.ilae.org/(3) www.sigmaaldrich.com/(4) Farmacopea Ufficiale Italiana XII ed./(5) www.fagron.com/en/product/syrspend-sf-alka-dry

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