

Significant Interactions in Treatment of Dravet Syndrome

¹Idoate A I, ¹Aldaz A, ¹Parra A, ²Sanchez-Carpintero R

¹Pharmacy Department. ²Neuropediatrics Department. Clínica Universidad de Navarra

Background

Standard combined treatment of Dravet Syndrome (DSy), which includes clobazam, stiripentol and valproate (VPA), frequently presents behavioural effects.

Purpose

To determinate the association between the presence and degree of behavioural alterations and other adverse digestive events and possible kinetic-dynamic interactions of Dravet Syndrome treatment.

Materials & Methods

- Single-centre retrospective observational study was carried out of the children treated at our centre for Dravet Syndrome for 4 years.
- Children selected had received simultaneous valproate (VPA), stiripentol (STI) and clobazam (CLO).
- Plasma concentrations CLO, NorCLO (*active demethylated metabolite of clobazam*) and VPA were analyzed before and at least 4 days after administration of STI.
- CDR (concentration dose normalized by weight) was calculated for CLO and Nor CLO.

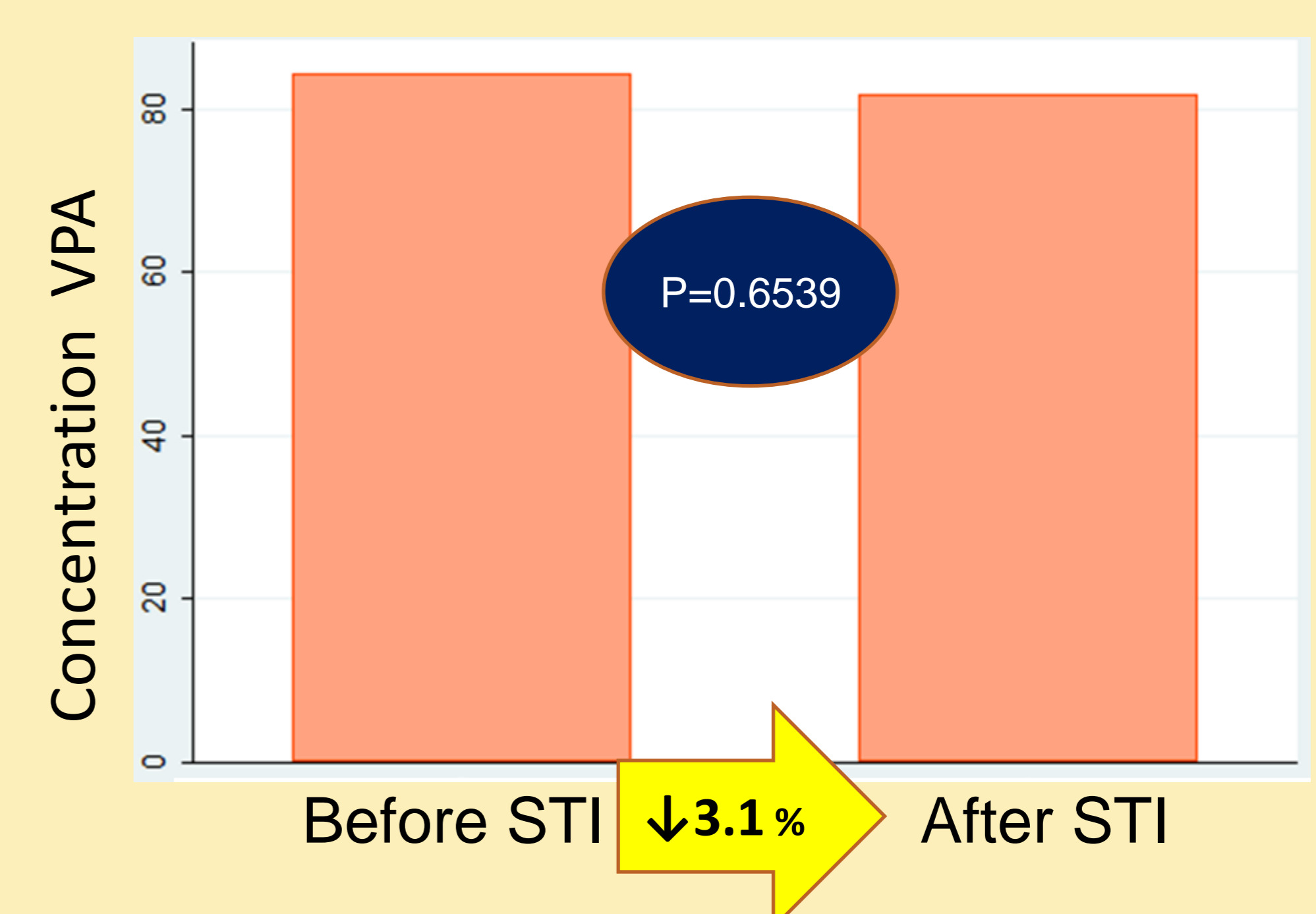
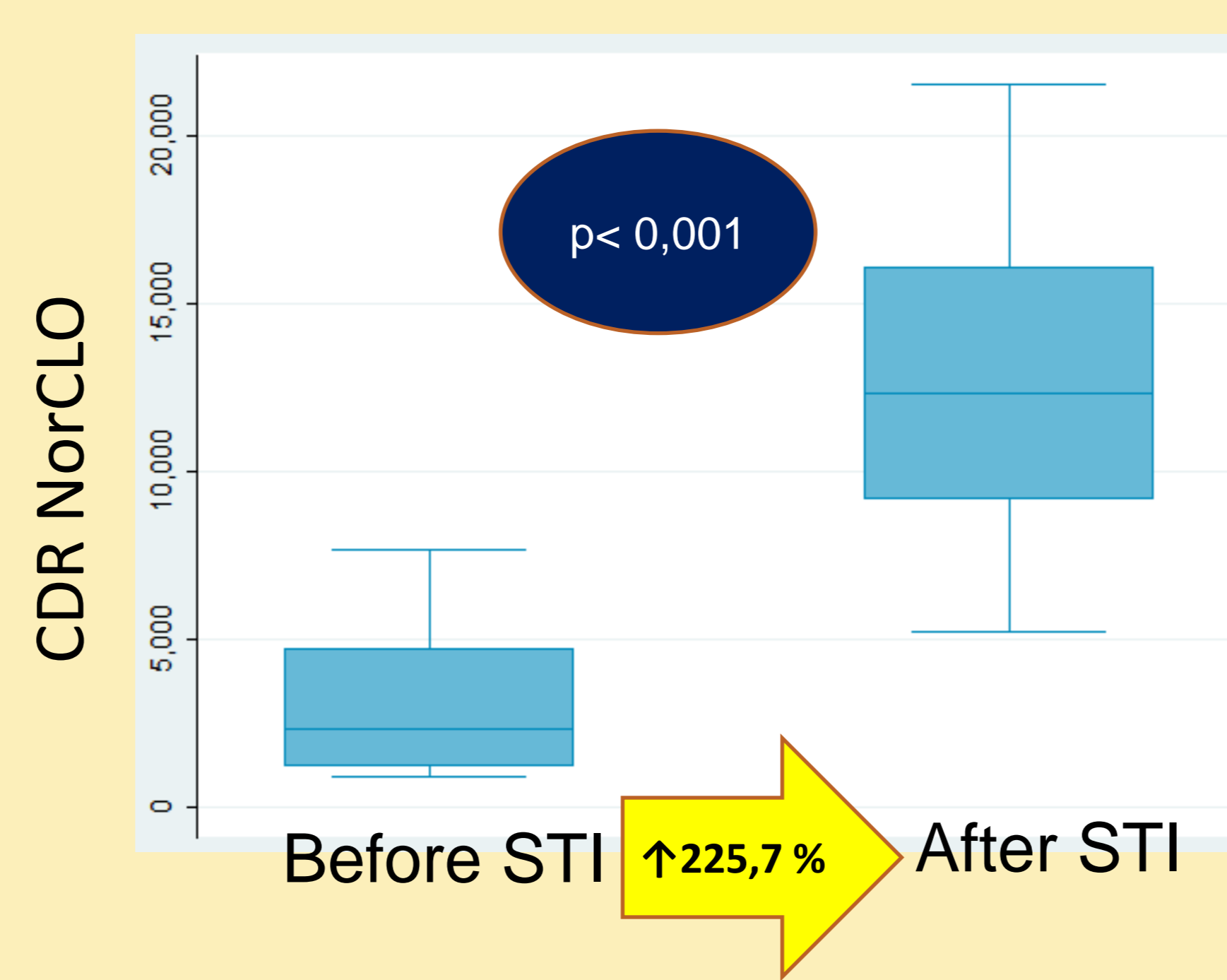
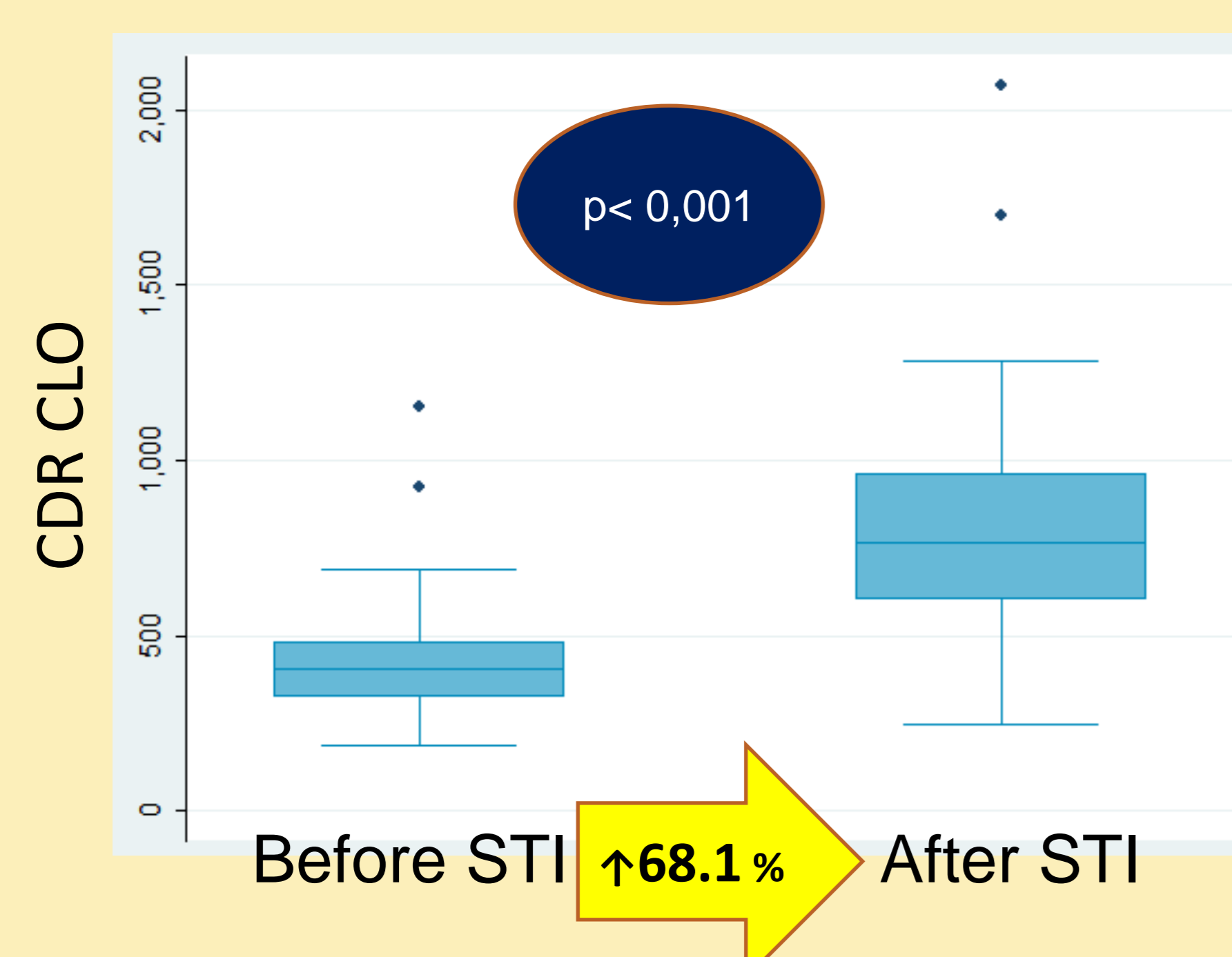
Nº patients DSy included	16 (57% female)
Nº patients (%) with STI	7 (43.8 %)
Mean age (range) patients (years)	9.5 [4-20]
Mean (SD) STI dose received (mg)	551.2 [250-1250]
Mean (SD) CLO dose received (mg)	12.1 [2.5-30]
Mean(SD) VPA dose received (mg)	771.9 [240-1600]

Results

Drug	CDR Before STI	CDR After STI
[CLO]	482.1 ± 203.7	810.3 ± 1950.2
[NorCLO]	3791.6 ± 367.6	12351.9 ± 4108.2

Drug	Before STI	After STI
[VPA] mcg/mL	84.3 ± 21.8	81.70 ± 21.4

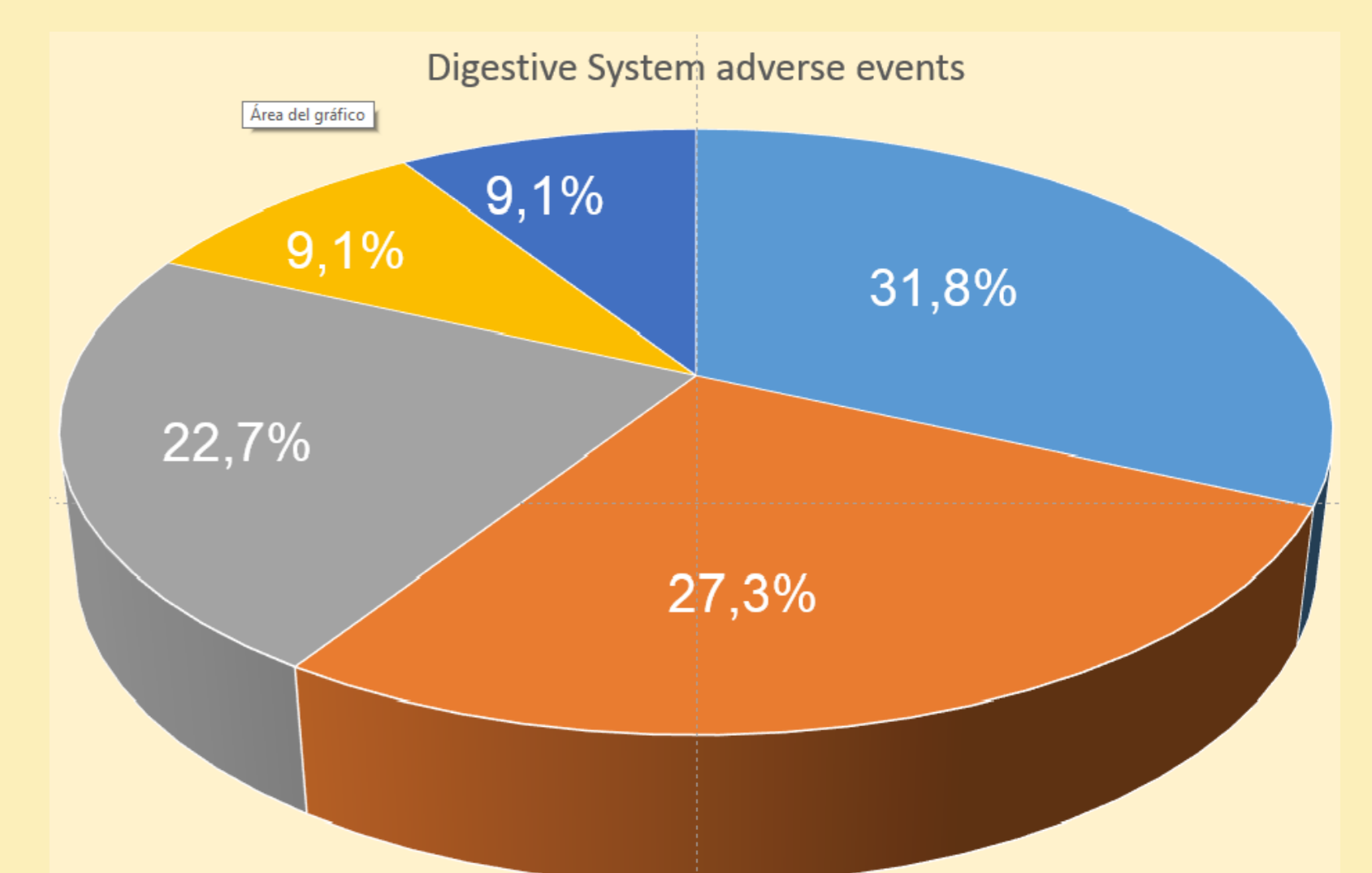
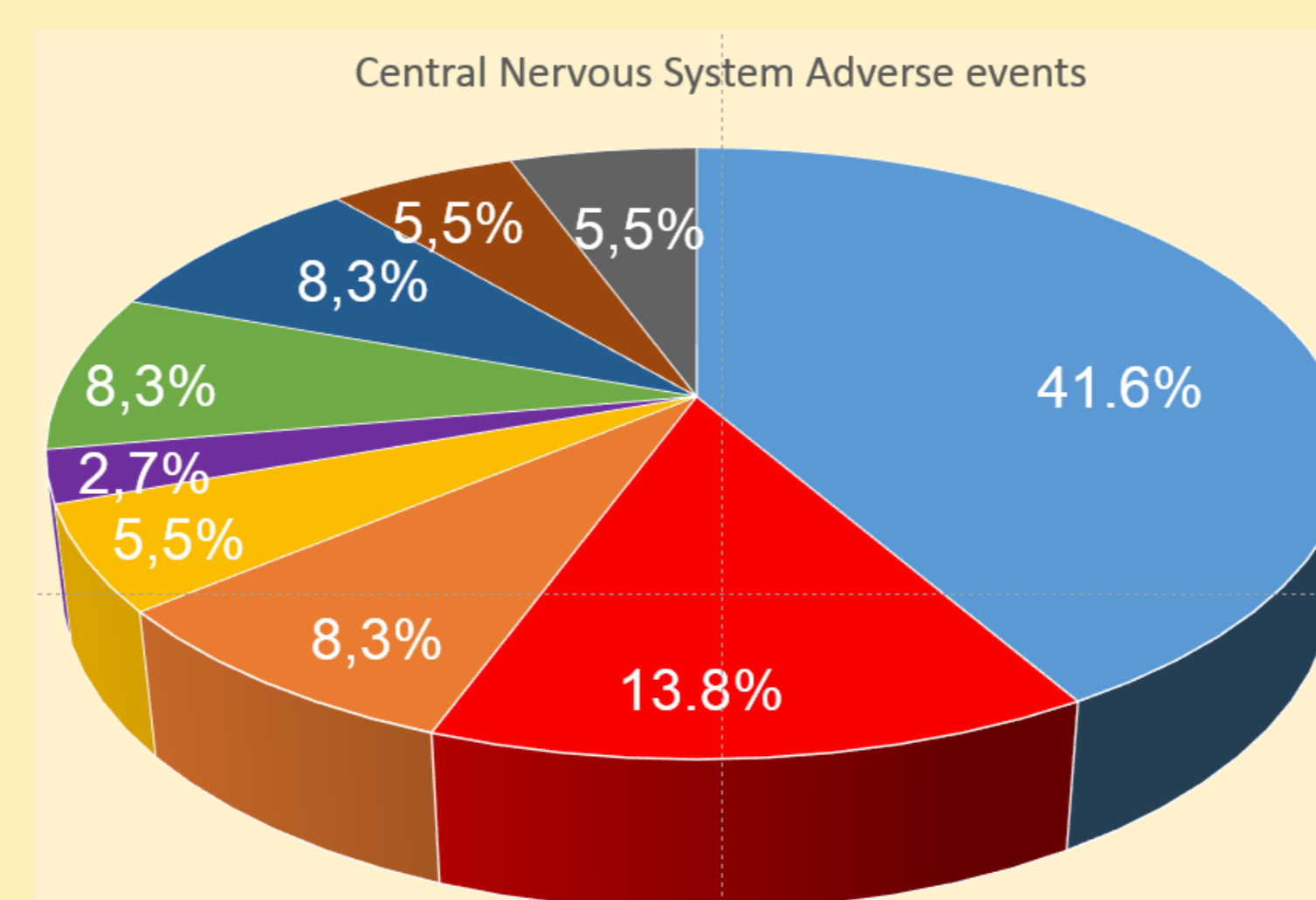
CDR= concentration/Dose normalized by weight index



- The addition of STI, with a mean ssCmin of 12.1 ng/mL, was associated with a significant increase in the concentration of CLO and NorCLO of 68.1% and 225.7%, respectively.

- STI treatment doesn't affect serum levels of VPA.

- Children with NorCLO concentrations higher than 5,000 ng/mL experienced major changes in their behavior.



■ drowsiness ■ hyperexcitability ■ aggressiveness ■ insomnia ■ intellectual slowness
■ ataxia ■ tremor ■ hypotoni ■ dysarthria

■ loss of appetite ■ loss of weight ■ weight gain ■ abdominal pain ■ nausea vomiting

Conclusions

- STI increases significantly serum concentrations of CLO and specially NorCLO due to a strong inhibitory effect on CYP2C19 and to a lesser degree on CYP3A4.
- Serum concentrations of VPA are not altered by STI.
- Potentially toxic values of CLO and NorCLO are associated with a marked deterioration of patient behaviour and other digestive alterations.
- Concentrations of CLO and NorCLO should be closely monitored in combined therapy with STI and the dose should be adjusted to clinical needs.

