Efficacy and safety of second-generation antipsychotics in pediatric patients: a progress report.

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Second generation antipsychotics (SGAs) Risperidone, Aripiprazole, Olanzapine and Quetiapine are increasingly used to treat pediatric patients. They are used mostly off label, because of the lack of adequate information from clinical trials, except for Risperidone. Information on pediatric ADME of Risperidone, however, is still scant. Current knowledge indicates that child and adolescent patients are more susceptible than adults to adverse drug reactions (ADRs). These are particularly serious with SGAs, ranging from metabolic alterations and organ toxicity (mostly liver), to neuroleptic malignant syndrome and extrapyramidal symptoms. A crucial aspect, both for efficacy and safety, is to define the appropriate therapeutic window of SGAs via pharmacokinetic and pharmacogenetic analyses.

We decided to tackle this issue by designing a multi-centric and non-interventional clinical study, in which we recorded in parallel pharmacokinetic and pharmacogenetic data alongside measures of clinical efficacy and safety reports, in order to define the actual risk-benefit profile of each SGA.

The sample size needed for such an evaluation was estimated to be 250 patients, enrolled from three different child and adolescent neuropsychiatry units distributed nationwide, i.e. the pediatric neuropsychiatric units of: Second University of Naples, IRCCS E. Medea of Bosisio Parini, University of Catania. We decided to centralize in a single laboratory the pharmacological tests, to be analyzed in collaboration by the clinical pharmacology units of the Universities of Catania, Milano and Naples. Patients monitoring is guaranteed by follow-up controls every three months and whenever the therapy has to be adjusted. During each follow-up visit psychiatric conditions and therapy effectiveness are evaluated by standard scoring scales, alongside SGA plasma concentrations and routine hematochemical parameters; occurring ADRs are evaluated for causality.

Presently, the study has nearly reached its target population and the enrolled patients are halfway through follow-up visits. The sample to date includes 160 patients of 12 years mean age, of which 81% are males. Predominant indications for use of SGAs are behavioral and conduct disorders (70%) and pervasive development disorders (25%). 76% patients are treated with Risperidone, 17% with Aripiprazole and 7% with Olanzapine or Quetiapine. Prescribed doses for Risperidone ranged from 0.01 to 0.04 mg/Kg per day, which were within the recommended reference range. A good correlation between dose and plasmatic levels of Risperidone was also observed. Strikingly, these values do not reflect the reference levels established from adult populations (around 10 ng/ml in children vs. 20-60 ng/ml in adults), indicating a possible different metabolism of Risperidone in children. The evaluation via the 'Clinical Global Impression' and 'Developmental Behavior Checklist' scales of therapeutic effectiveness, carried out so far, shows that these drugs, when effective, do act even at very low doses/plasma concentrations. This is of relevance as safety data depict a serious scenario with SGAs, where metabolic deterioration and hormonal imbalances affect a remarkable number of patients and are often cause for therapy withdrawal, even in a short-term perspective.

The preliminary results are encouraging and indicate that the study, once concluded, will provide valuable information on the overall reliability of SGAs, define appropriate therapeutic regimes and the risk-benefit profiles of SGAs in children.