Focus on pharmacological variability and monitoring of long-term drug therapy in children is therefore needed.

**INTRODUCTION**

Children constitute a vulnerable group of patients of special importance regarding pharmacological therapy. They differ considerably from the adult population due to rapid physiological changes during infancy and early childhood. These changes affect all pharmacokinetic processes, from absorption and distribution, to metabolism and excretion [1-3], as well as target organs for pharmacotherapy and therefore pharmacodynamics. Newly approved drugs are often scarcely studied in children. A narrow spectrum and unpredictable relationships between efficacy and tolerability for many drugs call for careful clinical considerations, where antiepileptic drugs will be used as examples in this text. Focus on pharmacological variability and monitoring of long-term drug therapy in children is therefore needed.

**Pharmacological variability**

Pharmacological variability implies variability with regards to pharmacokinetic, pharmacodynamic or pharmacogenetic factors. Regarding pharmacokinetic variability, there are age-related changes in all major processes [1-4]. Physiological changes are particularly rapid early in life. In neonates, absorption and elimination (metabolism and excretion) of many drugs are reduced. From birth to early infancy there are major changes in body tissue composition and body water compartments, affecting distribution of various drugs [4] (Table 1). From one year of age, the capacity for elimination is improved. For children from two to nine years of age, the blood flow and elimination processes are more efficient than in adults, resulting in shorter half-lives of many drugs and a need for a higher dose per kg body weight than in adults. Older children and adolescents have similar pharmacokinetic properties as compared to adults.

Pharmacokinetic modelling gives new opportunities to study factors contributing to variability in the pediatric population as a non-invasive alternative to multiple serum samples, and they also include physiological factors, where age-specific changes may contribute [5].

Pharmacodynamic changes may also be explained by maturation of the brain, where neuronal development and neurotransmission are changing during the first two years of life, and the body may react differently to drugs in this period. Paradoxical effects are known to occur in children with benzodiazepines due to changes in GABA receptors and their composition.

Pharmacogenetic/genetic variability is independent of age, but early determination of genetic mutations will guide the right treatment. Examples include GLUT-1 deficiency that requires ketogenic diet, and mutations in voltage-gated sodium channels causing epilepsy, where sodium channel blockers should be avoided. There is a rapid development of methods for genetic screening and thus, mapping of the genetic landscape of neurological disorders [6]. This will become more important regarding search for new drugs that may modulate the pathophysiological processes, such as the recently approved immunosuppressant drug everolimus for tuberous sclerosis [7]. Mutations in metabolic enzymes (eg CYP2C9, 2C19 or 2D6) give rise to phenotypes as ultra-rapid or slow metabolizers. Another implication of pharmacogenetics is screening of HLA*-mutations prior to initiation of treatment due to increased risk of Stevens-Johnson syndrome with carbamazepine, especially in the Asian population [1].

Other factors that may affect treatment outcome include drug interactions and poor adherence. In many chronic disorders comorbidity is common, and a patient may need several concomitant drugs, often resulting in pharmacokinetic interactions or excessive adverse effect load.

Among neurological disorders, epilepsy is the most commonly occurring, affecting 0.1-1% of children [8]. Antiepileptic drugs show pronounced pharmacokinetic variability between individuals, and age is an important contributing factor. In a recent population-based study, more than 40% of all children with epilepsy had neurological or psychiatric comorbidity [9]. This complex group of patients highlights the importance of careful clinical and pharmacological considerations for optimal therapy.

**When is monitoring needed?**

One cannot use a “one dose fits all” approach to pharmacotherapy. Pharmacokinetic variability between individuals can be extensive, and every patient does not attain...
In long-term pharmacological treatment, an important aim is to avoid adverse effects on physical and cognitive development. TDM has a long tradition as part of a comprehensive care approach in epilepsy in children (and adults) in many countries [2]. For treatment with drugs with a narrow spectrum of efficacy/tolerability, monitoring of therapy for children in all age groups may improve patient safety. It was recently pointed out that physicians should be mindful of pharmacokinetic properties and the potential of certain antiepileptic drugs (e.g., valproate) to cause hepatotoxicity, and monitoring of biochemical markers such as liver enzymes is recommended [12]. Additional pharmacogenetic testing may also improve safety of the treatment (Table 1).

Firstly, all new drugs are approved for adults, and the initial use in pediatric populations is often off-label, where careful monitoring of efficacy and tolerability is essential [13,14]. More clinical and pharmacokinetic studies are needed in children, with active and standardized surveillance and follow-up [1,10,11].

CONCLUSION

There is extensive pharmacological variability between individuals, and age-specific physiological changes contribute to this variability. In children using long-term pharmacological treatment, there is often a narrow spectrum between efficacy and tolerability and thus a risk for adverse effects affecting development and maturation. The use of TDM, biochemical markers of toxicity, and pharmacogenetic testing are useful supplements to clinical evaluation to individualise therapy for an optimal treatment outcome. This will improve patient safety in pediatric populations.

REFERENCES


Cite this article