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GH-05 Exploring Drug Efficacy in the Pediatric Population: Determining the Differences Among Various Drug Classes

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Exploring Drug Efficacy in the Pediatric Population: Determining the Differences Among Various Drug Classes

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Introduction

Pharmacodynamics is commonly defined as what the drug does to the body. The pharmacodynamic effects of a drug are required to determine its efficacy and safety. Due to the unique nature of pediatric development, and the challenges in doing research on children, the efficacy and safety of many drugs are not well defined in the pediatric population. The current study was designed to assess previously published pediatric pharmacodynamic studies to determine the commonly researched classes of drugs, how the usage of drugs may change with age, and pediatric drug efficacy.

Methods

Over 60 scientific research articles were evaluated to assess the safety and efficacy of drugs in children. The pediatric data that were obtained included age, body weight, race, dosing, adverse effects, efficacy, and safety. Antibiotics, analgesics, anti-inflammatory, chemotherapeutics, and other medications were compiled to evaluate the usage and activity of each drug during development.

Figure 1

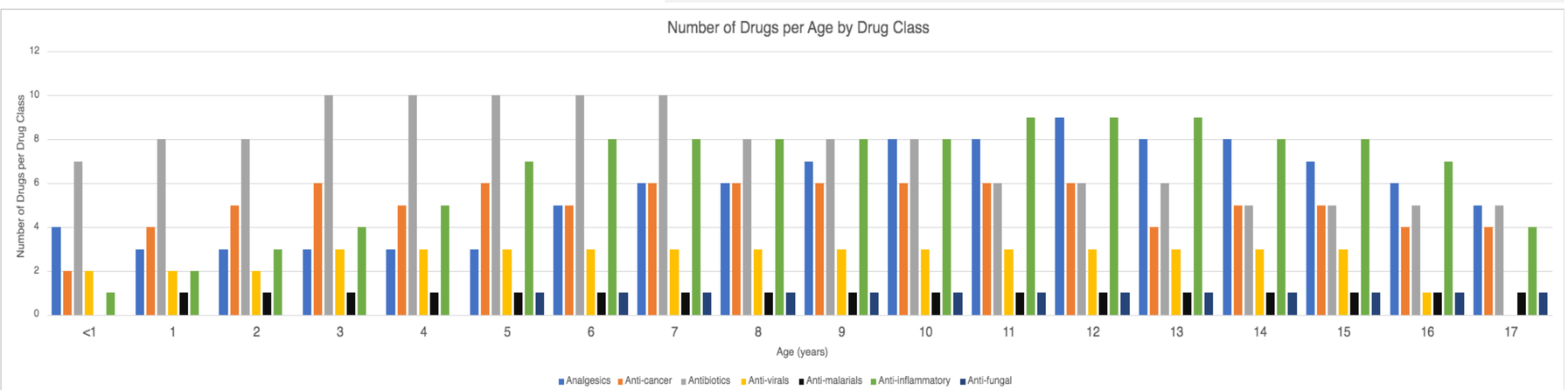

Table 1

Drug	Efficacy
Anti-inflammatory	
ATG (anti-thymocyte globulin)	Regimens of dosage and timing of ATG with respect to a hematopoietic stem cell transplant need serious improvements. ATG exposure needs to be significantly higher before transplantation occurs. This can be achieved by giving lower doses further in advance, due to the long half-life of ATG.
Rituximab	A lower dose than the current recommendation can achieve desired CD19 levels with less expense to the patients. Lowering the dose to 375 mg/m^2 for children above age 4 can effectively treat autoimmune disease for up to 6 months while lowering the cost of treatment and lowering the risk of infection.
Pravastatin	The plasma pravastatin concentrations are ten-fold higher in patients ages 4-18 years old undergoing triple immunosuppressive therapy following a cardiac transplant when compared to control patients. Even so, short term pravastatin therapy was effective in lowering cholesterol levels. Doses higher than 10 mg/day need to be monitored for side effects due to significant interindividual variability in adverse drug responses. Longer follow up time is also necessary to evaluate myocardial rejection and long-term cholesterol levels following myocardial transplantation.
Antibiotics	
Cefepime	50 mg/kg Cefepime q8h and q12h is not sufficient to absolve gram-negative bacterial infections in children older than 30 days. This is largely because Cefepime clearance is increased by Postmenstrual age and serum creatinine.
Amikacin	Oncology patients have altered PK of amikacin and need higher doses to achieve desired effects. 45 mg/kg twice daily is suggested by simulation in order to keep bacteriological counts low in immunocompromised oncology patients. Using 15 mg/kg/day, not a single patient was calculated to reach a sufficient maximum concentration of the drug.
Sulfadoxine-pyrimethamine	Study shows that current dosing for children ages 2-5 is inadequate and leads to treatment failure. The current 500 mg/25 mg dose combination does not achieve adequate AUC values. Increasing to 2 tablets per day is recommended to reach adequate AUC.
Ceftaroline Fosamil	Standard dosing for ages 2 months and up can be administered via IV anywhere from 5 minute to one hour duration without compromising PK/PD target attainment for S. aureus and S. pneumoniae or exposure of the drug. While the probability of adverse events increases as infusion duration decreases, the infusion can be given in as little time as 5 minutes without significantly increasing the chances of an adverse reaction.
Cyclodextrin Itracanazole	CD-ITRA was well tolerated and efficacious in children older than 5 years. As drug concentration goes up, anti-fungal efficacy also does in a linear fashion based on an oropharyngeal candidiasis scoring system. A dose of 2.5 mg/kg twice daily is recommended for the treatment of oropharyngeal candidiasis in HIV positive patients older than 5 years old.
Miscellaneous	
Esomeprazole	In children under 1 year, esomeprazole, as well as all other proton pump inhibitors, has not been shown to be effective in treating GERD. Possible explanations include the lack of a diagnostic test that can distinguish acid-related disorders such as GERD from symptoms caused by allergies, motility issues, or other underlying causes.
Etelcalcitide	Single IV dose of 0.035 mg/kg was well tolerated in children ages 2-18 with secondary hyperparathyroidism receiving hemodialysis. This study suggests that Etelcalcetide could be an important addition to standard of care in pediatric patients with hyperparathyroidism and chronic kidney disease receiving hemodialysis.
Enoxaparin	Doses of at least 1.5 mg/kg were necessary to reach peak anti-Factor Xa activity, which measures anticoagulant levels. Single daily doses were correlated with lower drug exposure when compared to the adult population, so twice daily dosing is recommended for pediatric standard of care. This is largely due to the short half life of Enoxaparin.
Fosfaprepitant	A single IV dose was well tolerated in patients receiving emetogenic chemotherapy. Fosfaprepitant exposures were dose proportional. Subjects under 12 required higher weight-based doses to reach adult level exposures. This is likely due to faster clearance of the drug as a result of immature CYP3A4-based metabolism.

Results

The data in Figure 1 suggest that the number of anti-inflammatory and analgesic drugs both increased with age. The number of antibiotics administered decreases with age. Antiviral and anti-cancer drugs both had a consistent number studied across age groups, while limited studies were available for anti-fungal and anti-malarial drugs (1 study each). In the current study, data suggest that the efficacy of anti-inflammatory, antibiotics, and other drugs may differ between adults and children at various ages (Table 1). For example, the administration of sulfadoxine-pyrimethamine (age 2 -5 years), anti-thymocyte globulin (ATG) (ages 0-18), and esomeprazole (<1 year) did not result in adequate treatment in children at every age.

Conclusion

Limited studies are available regarding the pharmacodynamics of drugs in children throughout development. The current study suggests that the number of drugs administered may change with age. For example, younger children (0-8 years) may receive more antibiotics when compared to older children (9-18 years). However, children are not small adults. There may be “windows of vulnerability” that may alter their development or increase their susceptibility to adverse effects. The lack of pediatric pharmacodynamic data for many drugs may produce gaps in knowledge that could impact the clinical care of children.

References

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