26. Farrell PM, Lai HJ, Li Z, Laxova A, Green CG, Collins J, et al. Evidence on improved outcomes with early diagnosis of cystic fibrosis through neonatal screening: enough is enough!. J Pediatr 2005;147:S30-6.
27. Accurso FJ, Sontag MK, Wagener JS. Complications associated with symptomatic diagnosis in infants with cystic fibrosis. J Pediatr 2005;147:S37-41.
28. Rosenstein BJ, Cutting GR. The diagnosis of cystic fibrosis: a consensus statement. Cystic Fibrosis Foundation Consensus Panel. J Pediatr 1998;132:589-95.
29. Davis PB. Therapy for cystic fibrosis—the end of the beginning? N Engl J Med 2011;365:1734-5.

Acyclovir Dosing and Acute Kidney Injury: Deviations and Direction

The decades-long pursuit of optimized antimicrobial dosing to improve response and avoid toxicity has yielded major benefits in the care of children. Advances have included dose-ranging studies to assess predefined clinical end points, and pharmacokinetic (PK) modeling to construct and validate dose and drug concentration targets associated with successful outcomes, laboratory improvements, or altered surrogate disease markers.[1] Although precise forecasting of dosing needs for the individual patient can be accomplished through population modeling methods and employing Bayesian PK application,[1] much of the dosing for the bedside clinician still remains handbook- or guideline-driven, based on age or size categories, and/or organ function groupings specific to the elimination pathway of the drug. More precise individualized dosing, both to meet target pharmacodynamics (PD) exposure (for example, peak concentration or area under the curve relative to minimum inhibitory concentration) for the specific infection site, organism susceptibility, and prevention of resistance is necessary for the narrow therapeutic range drugs such as vancomycin and aminoglycosides.[2] These strategies, however, are not routinely employed for antivirals such as acyclovir. Although the Food and Drug Administration has approved 60 mg/kg/d dosing of intravenous (IV) acyclovir for infants and children 3 months to 12 years of age, professional guidance generally has restricted the use of this higher dosage to neonatal herpes simplex virus disease based upon a large clinical trial conducted by the Collaborative Antiviral Study Group that demonstrated significant and specific improvements in clinical outcomes compared with lower doses of parenteral acyclovir, without increases in toxicity.[3] The study in this issue of *The Journal* by Rao et al assesses the nephrotoxic consequences and risk factors associated with these higher doses in a pediatric cohort receiving IV acyclovir.[4]

See related article, p 1462

Using pediatric modified RIFLE criteria, risk, injury, failure, loss of kidney function, and end-stage kidney disease (pRIFLE) for acute kidney injury (AKI), and univariate and multivariate analysis, the investigators establish demographic and clinical factors associated with presumed acyclovir-induced AKI in comparison with a matched cohort of children treated with acyclovir who did not develop AKI.[4] Patients who had no pretreatment serum creatinine (Scr) or height measured were given median Scr and 50th percentile height for age so that estimated glomerular filtration rates (GFR) could be calculated using the modified Schwartz equation. The study revealed the dose-dependent nature of acyclovir use and the development of AKI, where the greatest severity was seen in older age children (median = 14.4 years old), compared with the risk and injury categories, where the median ages were 8 and 7.5 weeks of age, respectively. In the multivariate analysis, age >8 years and concomitant ceftriaxone therapy, but not dose—which was highly predictive in the univariate analysis—were statistically strong risk factors for renal failure, whereas doses >15 mg/kg and a metric for doses >500 mg/m^2 were predictor variables for the risk and injury categories, respectively. Because of the selection of different numbers of controls for each AKI class, true incidence may be elusive, but the percentages of patients developing risk, injury, and failure were reported as 22%, 9.7%, and 3.8% of the acyclovir-treatment courses. For these classes, the median time to worst level of impairment was only 0.8, 0.7, and 1.4 days, but ranged out to 14.4, 13, and 4.4 days.

This study can be compared with two recent retrospective reports. Schreiber et al used estimated GFR in 126 children beyond 7 days of age, receiving IV or oral (PO) acyclovir.[5] Their highest acyclovir dosing reported was 45 mg/kg/day for IV administration (1500 mg/m^2/day IV for zoster in patients who were immunosuppressed), and 80 mg/kg/d for PO administration. Although no classification or definition

AKI	Acute kidney injury
GFR	Glomerular filtration rates
IV	Intravenous
OAT	Organic acid transporter
PD	Pharmacodynamics
PK	Pharmacokinetic
PO	Oral
pRIFLE	Pediatric modified RIFLE criteria
Scr	Serum creatinine

The authors declare no conflicts of interest.

0022-3476//$ - see front matter. Copyright © 2015 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.jpeds.2015.03.053

of renal impairment was provided, multivariate analysis suggested that impaired GFR at treatment initiation and concomitant nephrotoxic drug use were risk factors for AKI. These factors are especially relevant given the inclusion of patients who were immunosuppressed (mainly cancer) making up about one-half of this cohort, and who had the greatest decrease in GFR from baseline. Patients with pediatric cancer were excluded in the paper by Rao et al, and the other recent retrospective study by Kendrick et al,[6] mainly to avoid potential confounding variables to acyclovir as causational of AKI. Kendrick et al compared standard dose (30 mg/kg/d IV) acyclovir with high dose (60 mg/kg/d), in patients beyond the neonatal period (1 month to 18 years of age) empirically treated for herpes encephalitis. Unlike Rao et al, in the absence of height data for 95% of their patients, these investigators used the urine output classes in the pRIFLE criteria along with the multiples of Scr elevation for the severity categories of AKI, and the 61 analyzed patients had both pre- and post-acyclovir initiation Scr values. AKI was seen in 13.1% of the patients, with no difference reported between dosing groups and renal impairment categories. No univariate or multivariate analysis was presented, and median time to AKI was 1 day.[6]

Rao et al[4] add considerably to the surprisingly limited data regarding the toxicity of acyclovir in children. Although the rapid onset of AKI when using acyclovir is substantiated in this study, little is revealed regarding the mechanism. Prior observations have concluded that crystalluria and tubular obstruction of this relatively less soluble parenteral drug causes rapid renal impairment.[7] It would be easy to suggest that high-dose ceftriaxone adds to the solute burden to accelerate that obstruction. Yet, in the study by Vomiero et al,[8] of 17 cases of combined acyclovir and ceftriaxone use, 12 patients has a significant decrease in estimated GFR in 3 to 5 days (median = 3), and the range in the publication by Rao et al is up to 4.4 days in the failure group, and up to 2 weeks in the risk and injury groups.[4] Moreover, renal failure from ceftriaxone alone in 31 patients was noted to occur 5.2 days after initiation,[9] with the pathology (urolithiasis, anuria) and interventional therapy vastly different from the acyclovir-induced severe AKI. Therefore, the possibility exists of early and late versions of acyclovir-associated AKI. A prospective clinical trial could better capture this, along with which predictive factors contribute to different times of AKI onset and peak. The study by Vomiero et al,[8] did demonstrate a correlation between the rise in Scr and acyclovir dose, with the greatest rise in those with doses at or above 1500 mg/m^2/d, similar to AKI evaluated by Rao et al.[4]

Other potential mechanisms of acyclovir-induced AKI expand on these observations. The lack of crystalluria in numerous case reports and histology reflective of tubulopathy in the face of non-oliguric renal impairment[8] have led translational researchers to seek other explanations for AKI, using in-situ kidney preparations and in-vitro testing with transfected human kidney cells. Although the 9-carboxymethoxymethylguanine metabolite may be the offending moiety in producing the neurotoxicity of acyclovir (often accumulating in renal failure),[10] the precursor acyclovir aldehyde metabolite that is produced by alcohol dehydrogenase in a stoichiometric manner can be toxic to renal tubule cells, and may explain dose-dependent nephrotoxicity.[11] Proteomics experiments of acyclovir-induced AKI in mice demonstrated the increased kidney production of peroxiredoxins and several other antioxidant and anti-inflammatory proteins in a dose-dependent fashion, whereas decreased expression of vascular endothelial growth factor and its receptor potentially may relate to reduced tissue repair capability.[12] Additionally, acyclovir and beta-lactam antibiotics (with varying affinities) are substrates for specific organic acid transporters (OAT1 and OAT3) that are present in the basolateral surface of the renal tubular cell and whose contribution to tubular cell uptake and excretion of these and many other drugs is under genetic control.[13] Benzylpenicillin reduced the rat renal acyclovir clearance via diminished tubular secretion resulting in an increased area-under the curve, and doubled the elimination half-life and mean residence time. The in-vitro affinity of uptake by OAT in kidney slices and transfected cells was markedly reduced when benzylpenicillin was co-administered.[14] One can speculate that ceftriaxone, which is a substrate for the same OATs as acyclovir, may impair the latter's clearance and contribute to enhanced renal risk.

Polymorphisms and ontogeny of OATs[15] can also specify differential risks of toxicity that may inform the results of Rao et al. It is interesting that despite not entering into the multivariate analysis, cefotaxime had a "protective" effect in the injury group (OR = 0.29; $P < .01$), and conjecture whether differences in these cephalosporins in binding calcium, solubility, or OAT affinity may play a role. PK and toxicity studies in children using modeling techniques and serum and urine markers of nephrotoxicity (eg, cystatin C, beta-microglobulin, metabolomic profiling) of the acyclovir–ceftriaxone drug interaction, and of local and systemic acyclovir aldehyde production, are encouraged. Practical concerns, such as fluid restriction and the presence of inappropriate antidiuretic hormone secretion in cases of suspected herpes, encephalitis, and meningitis treated with acyclovir, need to be quantified, particularly in the older children where it may amplify AKI.

Finally, the posology of antiviral therapy can be refined by using population PK models and employing doses based on the influential variables, as in the case of PO valgancyclovir, with a creatinine clearance and body surface area-based equation in the prescribing information for more precise clinical dosing.[16] The a-priori dosing of acyclovir can be similarly derived for the individual child from allometric size scaling and GFR estimation.[17] PK-PD linkage models likely can be advanced to meet drug concentration and viral DNA reduction endpoints for acyclovir.[18]

Download English Version:

https://daneshyari.com/en/article/6220779

Download Persian Version:

https://daneshyari.com/article/6220779

Daneshyari.com