Cefazolin disposition in special populations

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Abstract: Physiological changes during pregnancy and in early life result in alterations in pharmacokinetics (PK) and pharmacodynamics (PD). Cefazolin (CFZ) is a frequently administered drug, also in special populations as pregnant woman and neonates, but PK data in these patients are limited. We aimed to focus on CFZ disposition in these two special patient groups. CFZ protein binding saturability was hereby established in both cohorts, however neonates display a markedly higher unbound CFZ fraction compared to adults. CFZ clearance (Cl) during pregnancy is twice as high as in the normal setting and clearance in neonates is lower compared to older children. To compare our data with other ‘special’ populations, we provided an overview of recalculated CFZ volume of distribution (Vd) and Cl values from reported datasets in literature.


1. Introduction: cefazolin disposition

The general pharmacokinetic principles of disposition and elimination of exogenous compounds apply, irrespective of population specific or individual characteristics [1,2]. However, characteristics like pregnancy or infancy warrant a focussed approach because important alterations in physiology affect drug disposition in a clinical relevant way. Pregnancy results in alterations in pharmacokinetics (PK, concentration-time profile) with a subsequent extensive inter-individual variability in drug response (pharmacodynamics, PD, concentration-effect profile) [1,2]. In neonates, inter-individual variability in drug disposition is mainly based on changes in body composition and maturational aspects.

CFZ is a first generation cephalosporin, to be administered intravenously. The drug has a narrow bactericidal spectrum, mainly covering Gram positive bacteria. After administration, beta-lactam antibiotics are localized in the extracellular water space and highly bound to albumin (75-85%) in both intravascular and interstitial fluids in non-disposing organs, although, in disposing organs such as liver and kidney, these compounds are also distributed in intracellular fluid [3].

As part of routine clinical care, special populations are also exposed to frequently used drugs like CFZ, however, PK data (needed for safe and effective drug administration) in these patients are limited. Therefore we aim to focus on CFZ disposition in pregnant woman and neonates.

2. Cefazolin disposition during pregnancy

CFZ is administered as prophylactic antibiotic drug during a variety of surgical interventions, including interventions during pregnancy [4,5]. Its clearance is almost exclusively renal and consequently depends on glomerular filtration rate (GFR) and renal tubular functions. GFR increases approximately 50% in the first trimester of pregnancy and continues to increase up to a gestational age (GA) of 37 weeks [1,2]. Data on alterations of renal tubular functions during pregnancy are not available. Pregnancy also affects protein binding capacity.

CFZ protein binding in human plasma is high but displays important intra- and inter-individual variability in adults as Vella Brincat

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et al. described [6]. This is of clinical relevance, since only the unbound drug fraction is pharmacologically active.

To document CFZ plasma protein binding and its covariates during pregnancy and to compare these observations with already reported observations in non-pregnant adults, maternal CFZ plasma samples were collected during in utero surgery [4,5]. Plasma samples (n=130) were collected during 30 interventions. Median unbound CFZ fraction was 0.25 (range 0.14–0.41). Correlations between the unbound CFZ fraction and total CFZ plasma concentration (r=0.46), time after CFZ administration (r=−0.38), albuminaemia (r=−0.39) and gestational age (r=−0.19) were significant. Median unbound CFZ fraction was higher during pregnancy when compared to observations in non-pregnant adults (0.25 vs 0.19, p<0.001). In a multiple regression model, total CFZ plasma concentration and albuminaemia were covariates of the unbound CFZ fraction (r²=0.4). We therefore concluded that the saturability of CFZ plasma protein binding as described in non-pregnant adults was confirmed during pregnancy, but CFZ free fraction is higher, likely explained by the lower albuminaemia during pregnancy [4].

To study CFZ PK in maternal plasma and during pregnancy, newly collected concentration-time profiles and reported observations concerning CFZ disposition were pooled [5]. Based on 187 plasma samples collected during pregnancy (GA 17-40 weeks), CFZ clearance (Cl) and distribution volume (Vd) estimates were 7.44 l/h and 12.04 l respectively, about twice as high compared to the non-pregnant setting. However, a GA-dependent trend was not observed although there is a progressive increase in renal function (GFR) throughout pregnancy and a progressive reduction in albumin plasma binding capacity throughout pregnancy. These in vivo observations suggest that the increase in GFR is compensated by a similar increase in tubular drug resorption activity during pregnancy.

3. Cefazolin disposition in neonates

Compared to adults and older children, neonates are characterised by a higher body water content (influencing Vd) and lower GFR (influencing renal drug elimination). GFR increases during the first two weeks of life to reach adult values at the age of 8-12 months [7]. Renal tubular functions are less active in neonates and their specific role in neonatal drug clearance needs further investigation.

Human serum albumin is the only plasma protein that binds CFZ. Since neonates frequently display hypoalbuminaemia, determination of CFZ protein binding and its covariates in this population is of relevance and is expected to differ from adults. We collected plasma samples (n=131) of 40 neonates, to whom 50 mg/kg CFZ was administered as routine prophylactic drug prior to a surgical procedure. The study population, 25 male and 15 female neonates, had a median postmenstrual age (PMA) of 39 (range 25-45) weeks, median postnatal age (PNA) of 9 (range 1-108) days and median body weight of 2767 (range 830-4200) grams. Median unbound CFZ fraction was 0.39 (range 0.10-0.73), which is higher than reported values in adults. Linear regression analyses between unbound CFZ fraction and total CFZ concentration (r=0.32), PMA (r=−0.54), PNA (r=−0.42), GA (r=−0.21), albuminaemia (r=−0.35) and indirect bilirubinaemia (r=−0.32) were significant. In a multiple regression analysis, 4 independent covariates of unbound CFZ fraction (i.e. total CFZ concentration, PMA, albuminaemia and indirect bilirubinaemia) were determined and explained 50% of inter-individual variability in neonatal unbound CFZ fraction.

In 29 patients, paired peak (1h after CFZ administration) and trough (8h after CFZ administration) plasma samples were available. Median (range) unbound CFZ fraction at peak level (0.46, 0.28-0.69) was significantly higher compared to trough level (0.36 ,0.17-0.73) (p<0.001). In line with observations in adults, both between-patient and within-patient
saturability of CFZ protein binding were hereby also established in neonates.

From clinical point of view, the influence of CFZ protein binding on its PK and PD parameters need to be considered. Since the unbound CFZ fraction is higher in neonates compared to adults and only the free drug can pass the glomerular filter, one can assume that CFZ clearance is proportionally higher in neonates compared to the anticipated clearance based on the GFR.

Based on a pooled approach, the 131 CFZ concentration-time points were used to estimate CFZ clearance in our neonatal cohort. The study population was divided in 4 categories, i.e. early preterms, late preterms, early terms and late terms (Table 1). For every patient category, a pooled logarithmic trend line was calculated based on all plasma samples collected during the first 8 hours after CFZ administration. Subsequently, pharmacokinetic parameters were documented assuming a one compartment model with instantaneous input and first order output (Table 1). Overall, lower CFZ clearance values were documented in early life (i.e. <8 days of life) compared to neonates equal to or older than 8 days, regardless of their PMA. This likely reflects maturation of postnatal renal drug elimination capacity.

Table 1: CFZ volume of distribution (Vd) and clearance (Cl) in neonates

<table>
<thead>
<tr>
<th>Patients</th>
<th>Vd (L/kg)</th>
<th>Cl (ml/kg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm (PMA &lt;37 weeks)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early (PNA &lt;8 days)</td>
<td>0.249</td>
<td>0.491</td>
</tr>
<tr>
<td>Late (PNA ≥8 days)</td>
<td>0.243</td>
<td>0.623</td>
</tr>
<tr>
<td>Term (PMA ≥37 weeks)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vd (L/kg)</td>
<td>0.274</td>
<td>0.263</td>
</tr>
</tbody>
</table>

4. Discussion

As first generation cephalosporin, CFZ is a widely used antibiotic compound. Beside prophylactic indications also reports on effective therapeutic use of CFZ in adults (severe bacterial infections) as well as in neonates (coagulase - negative staphylococcal sepsis) are known [8]. Effective antimicrobial treatment requires optimal drug concentrations at the effect site. For CFZ, unbound drug concentrations in plasma are assumed to reflect drug concentrations at the target site, illustrating the relevance of CFZ protein binding and PK/PD data.

In this manuscript we focused on CFZ PK data in pregnant woman and neonates. Due to their specific physiological characteristics, these populations need special attention concerning drug dispostion. To compare our data with reports on CFZ disposition in other (special) populations, we collected (and recalculated) CFZ Vd and Cl values of published datasets (Table 2). A higher CFZ Vd is documented in neonates compared to older age groups, probably due to the relatively higher extracellular water content and the lower albuminaemia in babies compared to adults. To explain the inter-individual changes in CFZ Vd in neonates, Deguchi et al. reported the unbound CFZ fraction as main covariate [9].

Table 2: CFZ volume of distribution (Vd) and clearance (Cl) data recalculated from literature. Data are presented as median (range) or mean (±SD). *Interquartile range.

<table>
<thead>
<tr>
<th>Patients [ref]</th>
<th>Vd (L/kg)</th>
<th>Cl (ml/kg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonates [9]</td>
<td>0.28 (0.21-0.37)</td>
<td>0.78 (0.53-1.10)</td>
</tr>
<tr>
<td>Preterm neonates [10]</td>
<td>0.25 (0.18-0.34)</td>
<td>0.67 (0.52-1.21)</td>
</tr>
<tr>
<td>Children</td>
<td>0.19 (0.19-0.21)</td>
<td>2.27 (2.20-3.09)</td>
</tr>
<tr>
<td>Children [3]</td>
<td>0.13 (0.12-0.16)</td>
<td>1.06 (0.74-1.13)</td>
</tr>
<tr>
<td>Obese children [11]</td>
<td>0.14 (0.11-0.15)</td>
<td>0.92 (0.85-1.2)</td>
</tr>
<tr>
<td>Adults, pregnancy [5]</td>
<td>0.17</td>
<td>1.72</td>
</tr>
</tbody>
</table>
CFZ clearance in neonates is lower compared to older children and some adult populations. This is in line with clearance results of other compounds. Special ‘events’ or circumstances like pregnancy, surgery and/or obesity seem to contribute to the clearance differences observed between different adult (and pediatric) cohorts. Hemodynamic consequences (i.e. blood loss, co-medication, fluid administration) due to surgical procedures make it difficult to interpret and compare the results obtained from the different references.

Besides between-population comparison of clearance data, also evaluation within a population is needed. In this manuscript we estimated CFZ clearance data in neonates, based on a pooled approach of predefined PMA/PNA categories. We have to admit that a more detailed population PK analysis is warranted in the near future, to explore CFZ clearance covariates within the neonatal population in order to optimize drug dosage regimens.

With this overview, we also aim to stimulate clinicians and/or pharmacologists to perform further research on disposition of other frequently used (antibiotic) drugs in special populations, usually excluded from general pharmacology studies. This is extremely important to improve clinical care and to adapt treatments to the most vulnerable patients and/or during special periods of life.

References
