Sickle cell anemia: time for personalized prescription of hydroxyurea? Focus on “Organic anion transporting polypeptide 1B transporters modulate hydroxyurea pharmacokinetics”

Courtney D. Thornburg
Department of Pediatrics, University of California-San Diego, La Jolla, California; and Hemophilia and Thrombosis Center, Rady Children’s Hospital-San Diego, San Diego, California

SICKLE CELL ANEMIA (SCA) is an inherited red blood disorder characterized by inevitable acute and chronic complications of vaso-occlusion and hemolysis in adults and children. SCA affects millions of people worldwide including 100,000 Americans. The only known preventive therapy for complications of SCA is hydroxyurea, a chemotherapeutic agent that induces fetal hemoglobin (HbF). Data are now available regarding the long-term safety and efficacy of hydroxyurea in both adults (11) and children (4). In addition, there are emerging data for the impact of hydroxyurea on chronic organ damage (3, 8). Most recently, the Pediatric Hydroxyurea Phase III Clinical Trial (BABY HUG, NCT00006400) demonstrated the safety and efficacy of hydroxyurea in children as young as 9 months of age (7, 9).

Although hydroxyurea improves hematologic parameters and reduces disease complications in all patients, individual laboratory and clinical responses are variable (13, 15). Hydroxyurea is rapidly absorbed from the gastrointestinal tract and primarily eliminated by kidney. Recent studies demonstrated interpatient variability in hydroxyurea pharmacokinetics (PK) (1, 2, 6, 14), and there is ongoing study of hydroxyurea PK in children (NCT 01506544). The underlying biology of this PK variability is unknown. In this issue of American Journal of Physiology-Cell Physiology, Walker et al. (12) examine the basis of interpatient variability of hydroxyurea.

The primary focus of this study was the cell membrane organic anion transporting polypeptide (OATP1B) transporter. OATP transporters are present in the cell membrane lipid bilayer. They transport organic anions across the cell membrane and belong to the solute carrier organic anion (SLCO) gene subfamily. They also transport a diverse group of other substances including drugs. The OATP1B transporter is known to influence the PK of a number of medications used in clinical practice.

The authors conducted a series of in vitro and in vivo experiments which demonstrate that the OATP1B transporters in the gastrointestinal tract, kidney, and liver may modulate hydroxyurea PK. Hydroxyurea PK was compared in wild-type and oatp1b<sup>−/−</sup> mice. Oatp1b<sup>−/−</sup> mice had significantly different hydroxyurea absorption, distribution, and elimination of hydroxyurea compared with wild-type mice (Fig. 1). Further study is warranted to determine how the contrasting effects of decreased absorption and reduced elimination impact hematology and efficacy of hydroxyurea. Further investigation may uncover other mediators of hydroxyurea PK.

The authors recommend pharmacogenetic (PGx) analysis of OATP1B transporter and other transporter mutations and polymorphisms. Single nucleotide polymorphisms that impact function of OAT1B transporters have previously been described (5, 10). Identification of PGx predictors of hydroxyurea PK and pharmacodynamics could eventually lead to dose prediction models and personalized prescription. Hydroxyurea therapy is already personalized in terms of individualizing the maximum tolerated dose (MTD) based on hematologic and clinical response and sharing response information (hemoglobin, hemoglobin F, and mean corpuscular volume and blood smear findings) with the patient. PK and PGx-based dosing models have the potential to further improve clinical care by allowing patients to achieve MTD through personalized dosing rather than with weight-based dosing. This could reduce the time to reach MTD and minimize family and clinician burden related to frequent monitoring every 2–4 weeks. This information could also define those patients who fail to respond owing to poor adherence versus those whose PK dictate a higher dose.

In summary, results are consistent with the previously demonstrated impact of cell membrane transporters in PK variation of xenobiotics. Ongoing studies in the field of cell membrane transporters such as OATP1B may lead to precision care for individuals with SCA and other acute and chronic medical conditions.

DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author.

AUTHOR CONTRIBUTIONS
C.D.T. prepared figure; drafted manuscript; edited and revised manuscript; approved final version of manuscript.

<table>
<thead>
<tr>
<th>Role in hydroxyurea PK</th>
<th>Intestine</th>
<th>Kidney</th>
<th>Liver</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid absorption</td>
<td>↑ absorption</td>
<td>↑ uptake in kidney</td>
<td>↑ uptake in liver</td>
</tr>
<tr>
<td>1° pathway of elimination</td>
<td>↑ urine excretion</td>
<td>hepatic metabolism</td>
<td></td>
</tr>
<tr>
<td>2° pathway of elimination</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PK in absence of OATP1B transporter

| Systemic exposure in absence of OATP1B transporter | ↑ exposure |

Fig. 1. Impact of organic anion transporting polypeptide 1B (OATP1B) transporters on hydroxyurea pharmacokinetics (PK).
REFERENCES


