Setting Permitted Daily Exposures for Pharmaceutical Agents Administered via the Intravitreal Route

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Ocular Anatomy and Clearance Mechanisms

The eye is comprised of three chambers:
- Anterior chamber – area between cornea and iris, filled with aqueous humor
- Posterior chamber – area between iris and lens, filled with aqueous humor
- Vitreous chamber – area which houses the retina, filled with vitreous humor (VH); the largest chamber

Other important structures within the eye:
- Blood-Aqueous Barrier (BAB) – controls migration of substances from the VH into the aqueous humor (anterior clearance pathway) with subsequent elimination via normal clearance mechanisms, or from initial blood vessels in the posterior chamber
- Inner Limiting Membrane (ILM) – controls migration of substances from the VH into the retina
- Blood Retinal Barrier (BRB) – controls migration of substances from the VH into the retina and subsequently the systemic vasculature (posterior clearance pathway)

Methods

An effort was undertaken to characterize processes by which foreign materials, such as IVT APIs, migrate through and ultimately leave the eye. This characterization was given to how, or whether, APIs injected into the eye are capable of migrating from the VH to the general bloodstream. Both small- and large-molecule APIs were reviewed.

The primary concern for the setting of IVT PDEs is being able to successfully predict the systemic bioavailability of IVT-administered APIs. To begin, a set of antibiotics given both systemically and IVT was assessed in an attempt to establish a list of APIs that can be used to estimate the IVT clearance of APIs that can be introduced into the bloodstream in toxicologically meaningful amounts. The results are shown below:

<table>
<thead>
<tr>
<th>Compound</th>
<th>IVT Max Dose (mg)</th>
<th>IVT Max Dose (µg)</th>
<th>IVT PDE (µg/day)</th>
<th>IVT PDE (µg/day) (low)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin</td>
<td>1.5</td>
<td>10</td>
<td>0.0007</td>
<td>0.0007</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>4</td>
<td>28</td>
<td>0.0028</td>
<td>0.0028</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>0.5</td>
<td>3.5</td>
<td>0.0023</td>
<td>0.0023</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>0.25</td>
<td>1</td>
<td>0.0005</td>
<td>0.0005</td>
</tr>
</tbody>
</table>

For this approach, a systemic PDE is calculated using the lowest systemic dose with a corresponding adjustment factor of 10. It is assumed that the IVT dose, when it is transferred to the bloodstream, will have negligible clinical consequences. An IVT PDE is calculated according to ICH QS10 guidance for organic impurities in drug products, which recommend identification limits of 0.1% or 1 mg/day (whichever is lower) for drug substances with a dose ≤ 5 mg. For the maximum dosing volume of an IVT drug at 0.1-0.2 mL, (corresponding to 100-200 mg), 0.1 µg/day is considered a more appropriate threshold for these drug products than 1 mg/day. In almost all cases, the IVT PDE for the APIs is 0.1 µg/day.

Limitation: may be more appropriate for APIs which are not given systemically

Comparison of Approaches

Three approaches to IVT PDEs can be taken by risk assessors for IVT drugs. They typically target large molecules which cannot be absorbed directly to the VH. As they are often given by IV injection, their potential bioavailability is essentially limited to no bioavailability. This may be achieved after IVT injection, even if there is 100% migration of the API from the VH to the blood.

For this approach, the IVT dose is selected with a composite adjustment factor of 30-100. Alternatively, PDEs may be set using the Threshold of Toxicological Concern (TTC), which recommends PDEs of 1 µg/kg bw (or 0.036 µg/day for a 70-kg adult). No TTC approach is appropriate for IVT drugs as their maximum dosing volume is often limited to no in vivo data. These values are adjusted downward by an additional factor of 10 in lead to toxicity for IV dosing volumes, and thus would achieve a lower PDE. Knowing that large molecules have low bioavailability of interacting with VH, PDEs of 1-10 µg/day would be considered scientifically defensible.

Limitation: assumes that all tissues are potential targets for the API