A Novel Approach to Assess and Improve Palatability of an Inhaled Asset Using the Rat Brief Access Taste Aversion Assay and an In Silico Model of Salivary Flow

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All animal studies were ethically reviewed and carried out in accordance with the Animals (Scientific Procedures) Act 1986 and GSK Policy on the Care, Welfare and Treatment of Animals.

Introduction

Inhaled medications for children are often delivered either via a spacer (dry powder) or nebulised (Figure 1). Despite training and monitoring being provided, self-administration is performed incorrectly by approximately 50% of patients. Even with correct administration, a significant proportion of the active pharmaceutical ingredient (API), typically between 30% to 40%, is deposited in the back of the mouth and throat. Here it has the potential to interact with receptors, eliciting a taste response.

The palatability of a medicine has a powerful impact on patient compliance (Figure 2), especially in children. Frequently, issues with taste aversion are not highlighted until the drug is in the clinic. By this stage any reformulation increases lead time to patients who could benefit from the medication or might prevent access completely if reformulation is not viable.

Objectives

• To determine the level of taste aversion to Compound A, an inhaled nebulised asset, with an intended clinical dose of 1mg/mL.
• To assess whether the addition of menthol, a TRPM8 agonist, is one excitant which has previously been accepted. There is circumstantial evidence that suggests activation of TRPM8 receptors, known to produce a cooling sensation, might reduce bitter taste perception.

Rat vs Human - Similarities

• Similar subsets of bitter taste receptors.
• Taste defined by flavour, smell, and texture.
• Both possess TRPM8 receptors.

Rat BATA assay

Maintain same rank order as in man.
Typical 0.5 log. offset.
Consistent, reproducible, and highly predictive.
Assay of API, individual components and complete formulation.
Non-invasive animal model with no expected adverse effects.
Greater accordance with clinical situation than non-clinical formulations.

Method

Two rat BATA trials (Figure 3) were run as described in Table 1. The initial study generated a dose response curve for Compound A presented in water alone. A subsequent study assessed the effect of adding 0.3mg/mL menthol to the Compound A formulations.

Table 1. Method Summary

<table>
<thead>
<tr>
<th>Study Description</th>
<th>Days</th>
<th>Test Compound</th>
<th>Compound A</th>
<th>0.3mg/mL Menthol</th>
<th>0.6mg/mL Menthol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>6</td>
<td>Compound A</td>
<td>0.3mg/mL</td>
<td>0.6mg/mL</td>
<td></td>
</tr>
<tr>
<td>Day 2</td>
<td>12</td>
<td>Compound A</td>
<td>0.6mg/mL</td>
<td>1.2mg/mL</td>
<td></td>
</tr>
</tbody>
</table>

Following completion of studies, rats were assessed by a Named Veterinary Surgeon and due to the minimal impact of the procedure were considered fit to be held in stock for use on future BATA studies.

Results

The results from both studies were collated on one graph with response presented as a percentage of maximum lick rate (Figure 4).

The dose response curve generated from the initial study for Compound A showed a high level of aversion in the rat, with an EC50 (determined tolerable limit) far lower than the intended clinical dose of 1mg/mL (Table 2). The curves generated in the second study show that the response to the menthol containing formulations was significantly higher (p<0.05) than the Compound A formulation presented in water alone (Table 2). The dose response curve for Compound A generated in the second study was significantly different (p<0.05) to that generated in the initial study, with an approximate offset of 0.5 log. The offset between Compound A in study 1 and 2 might be a consequence of a menthol pre-rinse type effect.

Table 2. Estimated rat and human EC50 values

<table>
<thead>
<tr>
<th>Compound</th>
<th>EC50 (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound A</td>
<td>0.07mg/mL</td>
</tr>
<tr>
<td>Compound A + Menthol</td>
<td>0.3mg/mL</td>
</tr>
<tr>
<td>Compound A + Menthol + Human</td>
<td>1mg/mL</td>
</tr>
</tbody>
</table>

Oral Concentration

Calculating the oral concentration of inhaled medicines is complex due to the continuous production and swallowing of saliva throughout the administration period. The following assumptions can be made based on historically available data:

• Typical nebuliser deposits 30 - 40% of API on back of tongue
• Salivary volume of 1.1mL induces swallow reflex
• 3.0mL post swallowing saliva volume
• 0.3mL minute saliva production rate

Menthol offers an improvement in taste acceptance but how much impact might this actually have on patient compliance with nebulised medicines?

How can this information be utilised to aid prediction of oral peak concentrations and potential aftertaste?

Conclusions

• The rat BATA was able to generate dose response curves for Compound A alone and with menthol.
• Menthol offers significant improvement to taste.
• The salivary flow model enables prediction of peak oral concentrations and rudimentary indication of aftertaste duration.
• Together, these models could aid appropriate clinical design, reducing patient compliance risk due to aversive taste.

Other Comments and Future Work

• Assess synergistic TRPM8 agonists without intense flavour.
• Inquire potential for a pre-rinse effect in the BATA.
• Build lipophilicity data into the salivary flow model, might enable us to better model the effects on lingering aftertaste.

References


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