Integrating functional GI observations into toxicology studies

Jean-Pierre Valentin, PhD
Louise Marks, PhD

Drug Safety & Metabolism
Translational Safety
Alderley Park, Cheshire
United Kingdom

jean-pierre.valentin@astrazeneca.com
Aims of presentation

• Highlight the scope of the problem surrounding GI adverse effects in preclinical and clinical development

• Present an overview of the GI system and types of GI adverse effects

• Highlight current Regulatory Guidance for assessing GI liability

• Discuss what we can do to help to investigate this liability more thoroughly

• Summarise the available methods for assessing drug-induced changes to GI function

• Describe 3 methods amenable to inclusion on toxicology studies

• Describe 4 real life examples of where GI endpoints have been used

• Conclusion and discussion
Impact of adverse effects of drugs by organ function throughout the pharmaceutical life cycle

<table>
<thead>
<tr>
<th>Phase</th>
<th>'Nonclinical'</th>
<th>Phase I</th>
<th>Phase I-III</th>
<th>Phase III/Marketing</th>
<th>Post-Marketing</th>
<th>Post-Marketing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Information:</td>
<td>Causes of attrition</td>
<td>Serious ADRs</td>
<td>Causes of attrition</td>
<td>ADRs on label</td>
<td>Serious ADRs</td>
<td>Withdrawal from sale</td>
</tr>
<tr>
<td>Sample size:</td>
<td>88 CDs stopped</td>
<td>1,015 subjects</td>
<td>82 CDs stopped</td>
<td>1,138 drugs</td>
<td>21,298 patients</td>
<td>47 drugs</td>
</tr>
<tr>
<td>Cardiovascular:</td>
<td>27%</td>
<td>9%</td>
<td>21%</td>
<td>36%</td>
<td>15%</td>
<td>45%</td>
</tr>
<tr>
<td>Hepatotoxicity:</td>
<td>8%</td>
<td>7%</td>
<td>21%</td>
<td>13%</td>
<td>0%</td>
<td>32%</td>
</tr>
<tr>
<td>Haematology/BM:</td>
<td>7%</td>
<td>2%</td>
<td>4%</td>
<td>16%</td>
<td>10%</td>
<td>9%</td>
</tr>
<tr>
<td>Nervous system:</td>
<td>14%</td>
<td>28%</td>
<td>21%</td>
<td>67%</td>
<td>39%</td>
<td>2%</td>
</tr>
<tr>
<td>Immunotox; photosensitivity:</td>
<td>7%</td>
<td>16%</td>
<td>11%</td>
<td>25%</td>
<td>34%</td>
<td>2%</td>
</tr>
<tr>
<td>Gastrointestinal:</td>
<td>3%</td>
<td>23%</td>
<td>5%</td>
<td>67%</td>
<td>14%</td>
<td>2%</td>
</tr>
</tbody>
</table>

2010 Update (lower number of CDs):
- Trials halted/delayed/development stopped 2010 (18 CDs)
  - GI related – 11% (↑)
- Prescribing restrictions/labelling 2010 (40 CDs)
  - GI related – 5% (↓)
- Withdrawal from sale 2010 (8 CDs)
  - GI related – 0% (↓)

The various toxicity domains have been ranked first by contribution to products withdrawn from sale, then by attrition during clinical development.

Adapted from Redfern WS et al. SOT, 2010; SOT 2011
Scale of clinical GI adverse reactions

18
The % of total ADRs associated with the GI system
Lewis, 1986

20-40
The % of patients hospitalised with GI effects
Lewis, 1986

700
The number of drugs implicated in causing diarrhoea
Chassany et al 2000

80
The % of GI ADRs that are predictable Type A pharmacological reactions
Gatenby et al 1995

7
The % of all ADRs associated with diarrhoea
Chassany et al 2000

20
In a study of Phase 1 clinical trial data (1986-95)¹ % of subjects reporting severe ADRs with GI-associated ADRs

38
In a review of AZ portfolio Phase 1 (SAD) clinical trial data the % of compounds with at least one reported GI AE

¹ADR data referenced from Redfern WS et al 2010. The Toxicologist 114(S1):1081
Clinical GI adverse reactions

The majority of GI effects are functional in nature, with fewer of pathological causation.

- Effects on mouth, gums, tooth discolouration, taste, ulcers
- Inflammation, ulceration, fibrosis
- Nausea and vomiting
- Motor dysfunction
- Pancreatitis
- Ulceration, inflammation, bleeding, colitis
- Diarrhoea/constipation
- Abdominal cramps/discomfort
### Drug classes commonly reported to have GI side effects

<table>
<thead>
<tr>
<th>Drug class</th>
<th>GI effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti depressants</td>
<td>Nausea, diarrhoea, constipation</td>
</tr>
<tr>
<td>SSRIs and TCAs</td>
<td></td>
</tr>
<tr>
<td>Anti inflammatories</td>
<td>Gastroduodenal ulceration</td>
</tr>
<tr>
<td>NSAIDs</td>
<td></td>
</tr>
<tr>
<td>Anti psychotics</td>
<td>Dry mouth</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td></td>
</tr>
<tr>
<td>Anti microbials</td>
<td>Diarrhoea</td>
</tr>
<tr>
<td>Penicillin, erythromy</td>
<td></td>
</tr>
<tr>
<td>Anti bacterials</td>
<td>Oesophageal</td>
</tr>
<tr>
<td>Doxycycline, tetracycline</td>
<td></td>
</tr>
<tr>
<td>Anti bacterials</td>
<td>Oesophageal</td>
</tr>
<tr>
<td>Cytotoxics</td>
<td>Diarrhoea</td>
</tr>
<tr>
<td>5-fluoro-2'-deoxyuridine</td>
<td></td>
</tr>
<tr>
<td>Wide range of drug classes, therapy areas and chemical classes have GI AEs/ ADRs which can lead to:</td>
<td></td>
</tr>
<tr>
<td>Drug withdrawal</td>
<td></td>
</tr>
<tr>
<td>Reduced patient compliance</td>
<td></td>
</tr>
<tr>
<td>Dose-limiting toxicity</td>
<td></td>
</tr>
<tr>
<td>Not always primary pharmacology driven</td>
<td></td>
</tr>
<tr>
<td>constipation</td>
<td></td>
</tr>
</tbody>
</table>
Regulatory guidelines for assessing GI liability

Supplemental Safety Pharmacology Studies

‘Effects of the test substance on the gastrointestinal system should be assessed. For example, gastric secretion, gastrointestinal injury potential, bile secretion, transit time in vivo, ileal contraction in vitro, gastric pH measurement and pooling can be used’

ICH S7A
Safety Pharmacology Studies for Human Pharmaceuticals

Supplemental Safety Pharmacology Studies

‘Effects of the test substance on gastrointestinal transit should be assessed. Intestinal transit time should be investigated; gastric emptying should also be examined if appropriate…..Effects of test substance on secretion of gastric juice, saliva, bile….on the motility, in vitro of stomach and intestine…..motility of the gastrointestinal tract in situ….on gastroduodenal mucous membrane…should all be assessed in light of results of studies in category A’


Are we doing enough??
Clearly more scope than just the measurement of intestinal transit and gastric emptying
USE the techniques available to FULLY assess GI liability
What can we do to reduce GI safety liability?

- Early *in vitro* screens
- Augment data yield from early discovery studies
- Incorporation of functional endpoints
- SP strategies now routinely include functional endpoints including GI assessments
- Expand pool of GI investigative tools
Is animal data a good predictor of clinical GI effects?

Where data is available for translation there is a good concordance between in vivo data and clinical data for GI AEs.

FIG. 3. Concordance of human toxicity from animals.

FIG. 4. Concordance rates versus species.

Figure from Greaves et al., 2004; Data from Fletcher, 1978

Figures from Olson et al., 2000
Available avenues for assessing altered GI function

A number of methods are available which allow the assessment of drug-induced altered GI function at the membrane, cellular and whole animal levels.

In silico
- Computer simulation and modelling

In vitro
- Histology
- Morphometry/stereology
- Cellular transport and flux studies
- Electrolyte transport
- Solute uptake
- Motility studies

In vivo
- Charcoal meal
- Endoscopy
- Measure of gastric acid secretion
- Imaging
- Emesis models
- Wireless motility/pH devices
- Faecal pellet assessment
- Marker studies
Criteria for inclusion into early discovery studies

- Non or minimally invasive method
- No anaesthesia
- Portable equipment
- Robust endpoint compatible with reduced group sizes
- Translatable endpoints
- Minimal scientific / technical expertise required
- Offers value vs resource
Available avenues for assessing altered GI function

A number of methods are available which allow the assessment of drug-induced altered GI function at the membrane, cellular and whole animal levels.

- **In silico**
  - Computer simulation and modelling

- **In vitro**
  - Histology
  - Morphometry/stereology
  - Cellular transport and flux studies
  - Electrolyte transport
  - Solute uptake
  - Motility studies

- **In vivo**
  - Charcoal meal
  - Endoscopy
  - Measure of gastric acid secretion
  - Imaging
  - Emesis models
  - Wireless motility/pH devices
  - Faecal pellet assessment
  - Marker studies

Illustration of the digestive system with labeled parts including teeth, tongue, salivary glands, pharynx, epiglottis, esophagus, liver, gall bladder, duodenum, stomach, pyloric sphincter, pancreas, large intestine, small intestine, rectum, and anus.
Current methods/technologies: Pellet assessment

- Used as an indice of intestinal / colonic transit
- Number, weight and appearance of faecal pellets assessed
- Can be performed in metabolism cages, home cage, e.g. during condensed Irwin, or in WBP chambers
- Single snap shot or time course
- Non invasive

Current methods/technologies: Wireless capsules

- Animal orally administered a SmartPill® capsule (26 x 13 mm) or Bravo capsule (6 x 5 x 25 mm)
- Temperature, pressure and pH data acquired and transmitted (wirelessly) to pc
  - Increase in pressure and/or pH indicates time of entry into duodenum
  - Drop in temperature indicates exit from rectum
- Multiple endpoints can be measured with SmartPill® – GE, SIT, colonic transit and total transit times, antral and duodenal pressure changes and motility indices
- Published data (e.g. transit times) variable and technique not widely used
- Non invasive but costly; size of capsule may limit size of animals used
Current methods/technologies: X-ray Imaging

- Number of imaging techniques available including X-ray (shown above), PET
- X-ray methods can be used on restrained, non anaesthetised animals (fasted/non fasted)
- Can be performed in small and large animals
- Animals administered a contrast agent (e.g. barium meal)
- Image sequences are obtained at selected time points from restrained animals
- Multiple endpoints - measure of gastric emptying, intestinal transit and motility
- Non-invasive
Example 1: Early discovery screening and candidate selection

**Issue:**
Off target pharmacology related side effects
Poor tolerability in rats with lead compound (↓ body weight, ↓ faecal pellet count, stomach distension)

**Hypothesis:** Poor selectivity against IGF/IR *in vitro* translates to modulation of glucose homeostasis & inhibition of gastric emptying *in vivo*  Proven

**Impact on project:**
Single dose studies allowed rapid explanation for poor tolerability of leads
Compounds de-selected from shortlist
Project drives against IGF/IR activity
Current lead compound ‘2748 has 30 fold↑ IGF selectivity & improved *in vivo* tolerance

<table>
<thead>
<tr>
<th>AZ compound number</th>
<th>IGF cell IC₅₀ (uM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>‘0729</td>
<td>0.10</td>
</tr>
<tr>
<td>‘8357</td>
<td>0.16</td>
</tr>
<tr>
<td>‘0484</td>
<td>0.49</td>
</tr>
<tr>
<td>‘2748</td>
<td>3.30</td>
</tr>
</tbody>
</table>
Example 2: Inclusion of pellet endpoint on MTD/DRF studies

- Incorporation into the DRF phase of MTD/DRF studies performed as part of our SP functional endpoints package (Resp/CNS/GI)
- Faecal pellets removed from the whole body plethysmography (WBP) chambers at the end of the recording session
- Validated using theophylline and bethanechol
- Male rats only
- n=8 per group
- 45 min WBP session

Expected changes in ventilation were reported and effects on GI function could also be detected.
Example 3: Animal Model Framework Case Study

**Estimating nausea liability:**

- Decreased gastric emptying
- Body weight loss (24 h)
- Emesis

**At least 2 + nausea = true positive**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined</td>
<td>5</td>
<td>7</td>
<td>18</td>
<td>2</td>
<td>32</td>
<td>71%</td>
<td>72%</td>
<td>72%</td>
</tr>
</tbody>
</table>

- Potential to predict drug-induced nausea using existing data sets – also useful for other GI effects?
- Looking at other toxicology study endpoints may also provide information which may link back to nausea liability – e.g. food consumption data, clinical observations, GI pathology findings

**Cross company 3Rs assessment**

- Looking at marketed drugs with GI ADRs in the clinic:
  - 14% had emesis in dogs and nausea in man, 55% had neither
  - 18% had inhibition of gastric emptying in rat and nausea, 40% had neither
  - 10% had body weight loss and nausea, 63% had neither

The creation of an algorithm predicting that a drug would cause nausea in man if it had produced a response in at least 2 of the animal models studied enabled a more powerful approach to predicting nausea.

*Ewart et al, 2011. JPTM, 64(1):e57*
Vomiting, diarrhoea and salivary hypersecretion if seen alone are not indicative of nausea. If seen in combination, they are strong markers for nausea risk.

Example 4: A nausea algorithm

AZ internal algorithm built on:
86 marketed drugs

Algorithm tested on:
20 AZD compounds that have reached Phase I
Blinded validation
90% positive and negative prediction
Observations mapped onto "public" profile

Parkinson et al. 2012. Toxicological Sciences, 126(1), 275-284
Conclusions

• GI AEs and ADRs can result in delayed preclinical development, pre-clinical and clinical dose-limiting toxicity, contribute to reduced patient compliance and in extreme cases may lead to drug withdrawal and morbidity

• Increasing focus on understanding GI liability early in a compound’s development

• Industry needs to readdress what techniques are available to monitor and assess drug-induced changes in GI function and how they could be used to allow screening of candidate compounds
  • Identify methods that can be added to toxicology studies
  • Identify methods that can be used as follow up investigative models in early discovery

• Pellet and wireless device methods seem suitable for incorporation into toxicology studies and have demonstrated value and project impact

• X-ray and other imaging methods may also be suitable but may need more thought for the best timing
Thanks to those involved in the compilation of information for these slides, in any GI method evaluation performed or currently underway and with any associated presentations and/or publications .................

AstraZeneca Global Safety Assessment
Ahmad Al-Saffar
Mark Anderton
Elizabeth Beard
Des Cobey
Chris Drayton
Lorna Ewart
Nick Moore
Victoria Motyer
Will Redfern
Jason Schofield

AstraZeneca Discovery, Integrative Medicines
Leif Hultin

AstraZeneca Computational Toxicology
Daniel Muthas
Joanna Parkinson

..................and thanks to the SPS for the opportunity to present as part of this webinar series