To prevent adverse events from drug combinations
or
Prediction of adverse events from drug combinations

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About me

- Trained as biologist/zoophysiologist, PhD at Göteborg University 1993
- Affiliations at Göteborg University and Vanderbilt University
- Industry affiliations since 1996
- Project toxicologist at AZ, based in Mölndal, aligned to CVGI R&D
- Support drug projects by:
  - identifying toxicological hazards,
  - initiate and evaluate preclinical study programmes
  - provide safety assessments before clinical studies in man

Disclaimer

- This presentation represents my own personal opinions, and is by no means reflecting the positions or considerations of AstraZeneca

Introduction to drug combinations

- Treatment of disease may benefit from concomittant medications
  - Act on several targets/mechanisms
  - Individual drug component doses may be lowered
  - Sum of all drug components in the combination may act synergistically
- Patient compliance may benefit from having to deal with fewer separate medications
  - More then one drug component in the same dosage form
  - Fewer prescriptions, easier handling
- Quality of Life in may improve
  - Side effects from one drug component may be minimised by concomittant treatment with another drug component

FOLFIRINOX

- Therapy in patients with metastatic pancreatic cancer
- combination chemotherapy regimen consisting of
  - Oxaliplatin (organoplatinum complex, where oxalate as ”leaving group” form DNA crosslink – inhibition of replication and trasncription)
  - Irinotecan (inhibits topoisomerase; DNA breaks then leads to apoptopic cell death)
  - Fluorouracil (inhibits RNA processing, thereby inhibiting cell growth)
  - Leucovorin (folinic acid; to ”rescue” bone marrow and GI epithelium)

Treatment of hypertension

- Tribenzor for patients unable to get their blood pressure controlled with any two of the three classes of drugs that make up the combination
  - angiotensin-receptor blockerolmesartan (40 mg)
  - calcium-channel blocker amlodipine (10 mg)
  - diuretic hydrochlorothiazide (HCTZ) (25 mg).
- American Society of Hypertension 2010 meeting:
  - 2492 patients with moderate to severe hypertension (>140/100 mm Hg; mean BP 168/101 mm Hg) were randomized to the triple combination product or one of three dual therapies using the same medications.
  - The triple combination had greater reductions in both systolic and diastolic blood pressure over the 12 weeks of the study compared with the three dual therapies
  - A significantly greater proportion of those receiving the triple therapy reached their goal blood pressure.
- Exforge - a three-drug combo of
  - amlodipine/valsartan/HCTZ—was approved by the FDA in 2011.

Complera

- A once-daily, 3-drug combination for treatment-naive HIV-infected patients.
  - Rilpivirine: a nonnucleoside reverse transcriptase inhibitor (NNRTI)
  - Tenofovir: anucleoside reverse transcriptase inhibitors (NRTI)
  - Emtricitabine: NRTI

Qnexa

- Once-per-day, weight-loss therapy of two approved drugs in a controlled-release formulation.
- Phentermine is an appetite suppressant and stimulant of the amphetamine and phenetylamine class.
  - Potential side effects: valvulopathy, increases in blood pressure and heart rate
- Topiramate is ananticonvulsant that has weight loss side effects.
  - Potential side effects: psychiatric side effects and increased incidence of cleft palate (teratogen)
- FDA likely to enforce conditions for post-market monitoring for cardiovascular risk and an indication against use by pregnant women

Disadvantages of combination products

- Less flexibility to adapt individual dosing
- More complicated to end treatment
- Fewer options in cases of intolerability
- Emergence of rare side effects

What is drug toxicity?

- Types of toxicity
- Target/chemistry related
- Idiosyncratic/synergistic effects
- Possible PD/PK interaction
- Testing for the unknown

Drug toxicity

- Target related
  - Exaggerated pharmacology
  - Interaction with related pathways and receptors/channels, …
- Structurally related
  - Genotoxic
  - Reactive metabolites
  - Chemical- & physical properties (surfactant)
  - Selectivity/specificity

Generic design of preclinical safety testing programmes

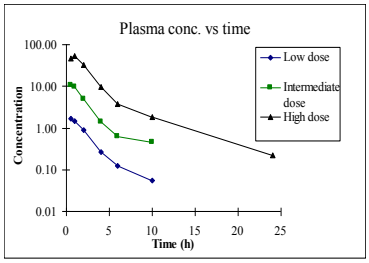
- FTIM/ Phase I
  - 14 days/1 month tox in rodent + non-rodent species, usually with recovery
  - Genotoxicity in vitro/in vivo
  - Safety pharmacology (CNS, CV, respiration, renal function, GI function)
- Up to 3 month clinical trial/ Phase II
  - 3 month general toxicity in rodent + non-rodent
  - Reprotoxicology, to support inclusion of women (WOCBP)
- Beyond 3 month clinical trials /Phase III /registration
  - 9 month non-rodent
  - 2y carcinogenicity to registration
- Special populations, eg pediatrics
  - If required, studies in juvenile animals
- Study designs should always be fit for purpose
  - Clincial context
  - 3R (refinement, reduction, replacement)

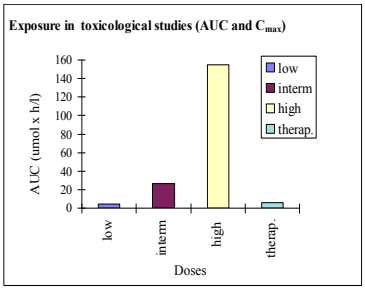
Pharmacokinetic considerations

- Expoures in animal tox studies should support exposures in man
- Adress metabolic patterns
- Adress distribution into tissues and organs (Quantitative Whole Body Autoradiography)
- Adress interactions with food, other drugs etc
- Provide assessment of safety margins

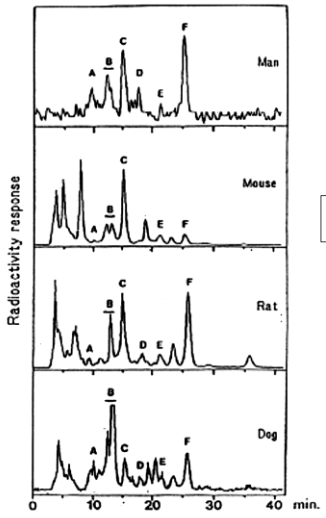
Purpose of toxicokinetic assessments

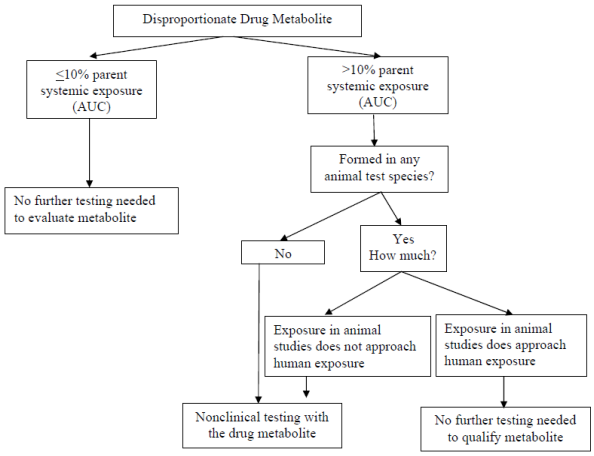
- Systemic exposure more important then the administred mass of drug
- Can be affected by drug properites, bioavailability, retention (or vomiting)
- Exposure at steady state
- Time and dose dependency
- Enzyme inductions
- Gender differences
- Exposure during recovery
- Potential to demonstrate exposure to metabolites





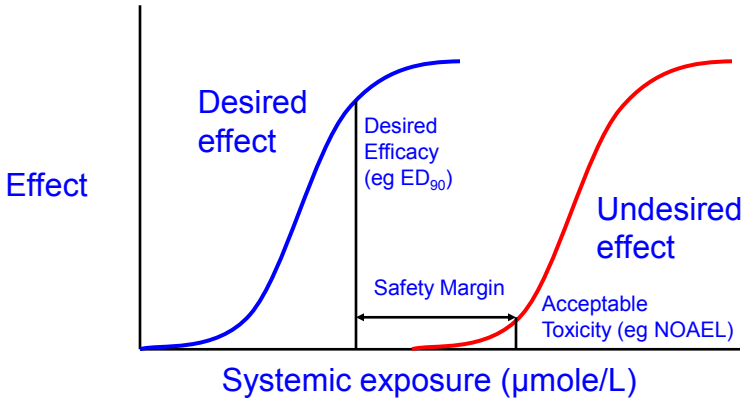
Safety Testing of Drug Metabolites





FDA guideline

Exposure safety margins



Entirely dependent on the toxicity of concern and the patient population to be treated

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

GUIDANCE ON NONCLINICAL SAFETY STUDIES FOR THE CONDUCT OF HUMAN CLINICAL TRIALS AND MARKETING AUTHORIZATION FOR PHARMACEUTICALS

M3(R2)

Current *Step 4* version

dated 11 June 2009

This guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the draft is recommended for adoption to the regulatory bodies of the European Union, Japan and the USA.

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Multidisciplinary/M3_R2/Step4/M3_R2__Guideline.pdf

Classification of combination drug products

- Combination drugs that are intended to be co-packaged or administered in a single dosage form ("fixed formulation").
- Products that with recommendations for co-use with a specific drug ("free combination")
- Two or more late stage entities (i.e., from Phase III studies and/ or post marketing)
- Late stage entities and early stage entities (i.e., Phase II studies or less)
- More than one early stage entity.

Toxicological testing recommendations

- Complete nonclinical development programs are needed on the individual entities
- Anonclinical combination toxicity study is warranted to support combination clinical trials,
- For combinations of an early stage entity(ies) with a late stage entity(ies), for which there is no significant toxicological concern
  - Combination toxicity studies usually not needed to support short clinical studies (1 month) and not longer than the clinical experience of the individual entities
  - Later stage or longer duration clinical should be supported by a nonclinical combination toxicity study.
- For combinations of early stage entities, nonclinical combination toxicity studies are recommended to support clinical trials.

Combination toxicological study

- The duration of the combination study should be equivalent to that of the clinical trial, up to a maximum duration of 90 days.
- A combination toxicity study of shorter duration can also be accepted, depending on the duration of the intended clinical use.

Design of the combination toxicology programmes

- Consideer pharmacological, toxicological and PK profiles of the individual entities, indication, patient population, and the available clinical data.
- Combination nonclinical studies are generally limited to a single relevant species.
  - If unexpected toxicity is identified, additional testing can be appropriate.
  - Genotoxicity, safety pharmacology, or carcinogenicity studies not recommended if individual agents have been tested according to current standards.
- If WOCBP are intended and the individual agent(s) have shown findings indicative of embryo-fetal risk, combination studies are not needed as the potential human developmental hazard has already been identified.
- If neither agent poses a potential human developmental risk, combination studies are not recommended unless concerns exist.

Design of a combination toxicology study

- Justification of choice of species, dose and dosing frequency
- Include end-points to evaluate additive and synergistic effects for known toxicities the individual entities should be included
- Address any identified cause for concern
- Be able to detect unexpected toxicities
- Explore exposure to the different entitties at relative proportions similar to those intended at therapeutic dose levels in man
- Provide exposure margins that are clinically relevant

Exposure ratios

Species	Dose level		AUC	AUC	AUC ratio
	ESO (mg/kg)	ASA (mg/kg)	ESO (µmol*h/L)	SA (µmol*h/L)	ESO/SA
Dog	42	42	**48**	**1900**	**41**
	42	-	61	-	-
	-	42	-	3100	-
Man	40[a]	325[a]	13	630	48

a Doses in humans are in mg, not mg/kg

ASA is rapidly hydrolysed to salicylic acid (SA) in blood and liver

Example Axanum

- The two components are available as separate products:
- Low-dose acetylsalicylic acid (ASA) used for prevention of thrombotic cardio- and cerebrovascular events
- ASA well known to induce gastric and/or duodenal ulcers
- Esomeprazole is a proton pump inhibitor which reduces acid secretion in gastric parietal cells. Used in treatment of dyspepsia, peptic ulcer disease and gastroesophageal reflux disease
- Clinical studies show that alleviation of ASA-induced gastric side effects with proton pump inhibitors is benefical

Testing strategy

- Two well established drugs on the market
- Both with well known safety data
  - (literature, PDR/FASS texts)
- Reliance on pre-existing labelling texts and literature data to avoid extensive additional studies on each component
- Following ICH guidelines for a 3-month combo tox aiming at similar exposure ratios as in man, but at higher exposure levels than those intended for therapeutic human use (safety margin)

Toxicological observations with *Esomeprazole*

- From the Swedish product summary text: http://www.fass.se/LIF/produktfakta/artikel_produkt.jsp?NplID=20100512000117&DocTypeID=6
- Pre-exsiting studies on Omeprazole/Esomeprazole alone:
- Repeat-dose toxicity, genotoxicity and reproduction toxicity studies did not indicate any particular risks for human use
- Carcinogenicity studies with the racemate omeprazole showed gastric ECL-cell hyperplasia and carcinoids in the rat. These effects are the result of prolonged and pronounced hypergastrinemia, secondary to reduced stomach acid secretion, as observed in rats after long-term treatment with inhibitors of gastric acid secretion.
- Esomeprazole findings in combination tox study were similar to those seen in previous comparable studies

Toxicological observations with *Acetylsalicylic acid*

- From the Swedish product summary text: http://www.fass.se/LIF/produktfakta/artikel_produkt.jsp?NplID=20100512000117&DocTypeID=6
- Single-dose oral studies have shown low toxicology
- Repeat-dose toxicity studies show that doses of up to 200 mg/kg are well tolerated in the rat
- Dogs are highly sensitive to ulcerogenic effects of NSAIDs.
- No genotoxicity or clastogenicity potentials. Several studies have shown that ASA is not a tumour promotor.
- Reproduction toxicity data show that ASA is teratogenic in several laboratory animal species.
  - Inhibitors of prostaglandin synthesis results in increased pre- and post-implantation losses and embryo-foetal deaths. Increased incidence of various malformations, among others cardiovascular malformations

Toxicological observations with an esomeprazole and acetylsalicylic acid combination

- From the Swedish product summary text: http://www.fass.se/LIF/produktfakta/artikel_produkt.jsp?NplID=20100512000117&DocTypeID=6
- 3 months' oral administration of a combination of esomeprazole and ASA in a repeat-dose toxicity study in dogs showed no new or unexpected toxicological changes.

Outcomes

- AXANUM, a fixed dose combination of 81 mg low-dose ASA (acetylsalicylic acid) and 20 mg esomeprazole, has received positive agreement for approval in 23 European Union member countries and in Norway. AXANUM is indicated for prevention of cardiovascular (CV) events such as heart attack or stroke, in high-risk CV patients in need of daily low-dose ASA treatment and who are at risk of gastric ulcers.
- The EU decision took place via the decentralised procedure (DCP), with Germany acting as reference member state. This process is now followed by national approvals.
- Clinical pharmacology studies confirmed that there is no PD or PK interaction between esomeprazole and ASA at therapeutic doses
- http://www.astrazeneca.com/Media/Press-releases/Article/20110802positive-approval-of-axanum-in-europe

Summary and conclusions

- Drug combination products drugs may provide increased compliance, adherence and convenience for the patient
- The use of combined therapies may increase clinical benefits by modifying several disease mechanisms simultanously
- Increasing interest for combination treatment of both chronic widespread disesese as well as serious conditions with short survival times
- A regulatory framework to adress preclinical/toxicological concerns in place

Sola dosis facit venenum

"The dose makes the poison"

Paracelsus
Theophrastus von Hohenheim
1493–1541
Swiss physician
Pioneered the use of chemicals and minerals in medicine