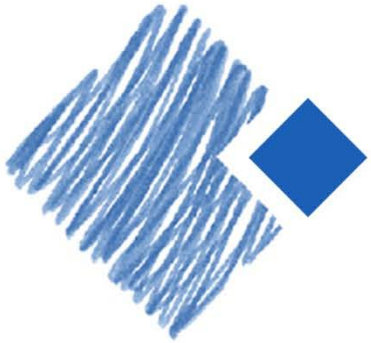


SocraTec R&D

We make it work

Protocol development, definition of in/ex criteria and clinical conduct of BA/BE studies in patients

Challenges and solutions, e.g. in case of oncological, HIV or psychiatric patients

Dr. Barbara Schug/ Dr. Frank Donath
SocraTec R&D, Oberursel / Erfurt, Germany
www.socratec-pharma.de

AGAH Workshop: Bad Homburg, May 16th, 2013

Bioequivalence: population

SocraTec R&D

General concept

- characterisation of the dosage form
  - quality parameter
  - “living paddle – apparatus”
- standardisation of the study conditions
  - administration
  - food intake
  - behaviour
  - and consequently: subjects

Selection of healthy subjects is based on a high level of standardisation as availability is not a limiting factor for recruitment

Bioequivalence: population

SocraTec R&D

Healthy subjects

- *reduction of variability:* Which parameters are of relevance?
  - interest of the sponsor to increase the power of the study
- *safety:* When is a subject healthy?
  - ongoing discussion with authorities initiated in Germany by AGAH
- *tolerability:* Which drugs/doses can be administered?
  - relevant issue in drugs with narrow therapeutic range
- *suitability:* Do we need patients to reach the aim?
  - of relevance for PD parameters
- *discriminating:* Can we detect product differences?
  - of relevance for special population

To be defined by pharmacokineticist and PI

When is a subject healthy?

SocraTec R&D

Background information

- BfArM repeatedly exacerbated criteria in phase-I-protocols
- AGAH initiated discussion: authorities, industry and CROs
- risk-based approach depending on the level of experience with the drug substance to be tested
- for approved drugs:
  - screening within -21 to -1 days before dosing
  - heart rate: 50-90 bpm manually determined
  - ALT/GPT: up to 10 % above normal
  - AST/ GOT: up to 20 % above normal
  - Bilirubin: up to 20 % above normal
  - Creatinin: up to 0,1 mg/dl above normal
  - ECG: QT_cF normal, AV-block first degree acceptable

BE studies in patients

SocraTec R&D

Drugs which might endanger the participating healthy subject

- anticancer drugs
  - cytotoxic drugs: alkylating agents, antimetabolites, anthracyclines, plant alkaloids, topoisomerase inhibitors, monoclonal antibodies, tyrosine kinase inhibitors
  - cytostatic drugs
  - chemosensitizer
- immunosuppressants
- opioids
- psychiatric drugs
- drugs for treatment of Parkinson s disease

Decision may depend on the design

SocraTec R&D

HIV - HAART: Standard therapy

- combination of at least 3 antiretroviral drugs
  - PI: protease inhibitors
  - NRTI: nucleoside reverse transcriptase inhibitors
  - NNRTI: non-nucleoside reverse transcriptase inhibitors
- flexible combinations of different products ...
- ... or meanwhile also fixed combinations

Bioequivalence studies with antiretroviral drugs

- immediate release formulations
  - single dose, fasted studies

Safety profile allows BE testing in healthy subjects

HIV – DDI

SocraTec R&D

Combined therapy – potential interactions

- Antiretroviral drugs show high potential for drug-drug-interactions (primarily CYP3A4)
- DDI studies require steady state conditions

Safety concerns for steady state studies in healthy volunteers

- Potential liver toxicity
- Potential nephrolithiasis

DDI studies preferably to be performed in patients

BE studies in patients

SocraTec R&D

Drugs for which there is reason to assume that healthy subjects might be less discriminatory than the intended patient population

- inflammatory bowl disease (Crohn s disease, Colitis ulcerosa)
- asthma when treated with inhalatives
- enteric coated dosage forms in population with increased gastric pH

Characteristics of the special population interfere with absorption site / formulation properties

BE studies in patients

SocraTec R&D

Studies with PD-surrogates for BE assessment

- underlying disease mandatory for expressing the PD parameter
  - increased cholesterol for lipid-lowering drugs (CSE)
  - reduced CD4-count for anti-HIV-drugs
  - exhaled NO for locally acting anti-inflammatory drugs in asthmatics
  - ...

But we will focus on PK!

Bioequivalence trials in oncology

SocraTec R&D

When may BE (BA) studies become necessary?

- scale up
- post-approval changes / formulation development
- generic development
- DDI and food effect studies as subtype of BE studies

For which types of formulations?

- (solid) oral dosage forms (IR / MR)
- liposomal formulations
- general: dosage form characteristics influencing systemic exposure of active moiety
- but also for biosimilars even if they are intended for iv administration

Well known examples of relevance for BE-studies:

- capecitabine (Xeloda®)
- doxorubicin (Doxil®)

FDA-Guidances have been published

Caelyx®: Side-effects

SocraTec R&D

Cardiac toxicity
Myelosuppression
Infusion-related reactions
Palmar-plantar erythrodysesthesia (PPE, hand-food syndrome)
GI-reactions: nausea, vomiting, constipation, diarrhea)
Neutropenia
Alopecia
Mucositis / Stomatitis

Primarily in patients

After two to three cycles of treatment

More common with Caelyx® than with doxorubicin

Pre-clinical safety: mutagenic and carcinogenic

Phase-I-study in healthy subjects acceptable ?

US-FDA design requirements

SocraTec R&D

Clinical Study:

1. Type of study: Fasting*
   Design: Single-dose, two-way crossover *in vivo*
   Strength: 50 mg/vial
   Dose: 50 mg/m^2
   Subjects: Ovarian cancer patients whose disease has progressed or recurred after platinum-based chemotherapy.
   Additional Comments: Patients who have a history of hypersensitivity reactions to a conventional formulation of doxorubicin HCl or the components of Doxil should not be entered into the study. Females should not be pregnant or lactating. Other exclusion criteria include: total cumulative dose of doxorubicin HCl approaches 550 mg/m^2; patient is < 18 years of age or > 75 years of age; active opportunistic infection with mycobacteria, cytomegalovirus, toxoplasma, P. carinii or other microorganism if under treatment with myelotoxic drugs; clinically significant cardiac, liver or kidney disease.

   * If the health conditions of patients prevent fasting, the sponsor can provide a non-high-fat diet during the proposed study. Alternatively, the treatment can be initiated 2 hours after a standard (non-high-fat) breakfast.

Draft Guidance on Doxorubicin Hydrochloride, US-FDA, Februar 2010

In/ Ex criteria - cancer

SocraTec R&D

Criteria differ completely from healthy subjects

- Covering different aspects
  - the disease for which the drug is approved in order to stay within the indication (often off-label-use not accepted)
  - CNS status which allows informed consent: no relevant brain metastases
  - a hematology status which allows continuation of the treatment
  - a physical performance status which allows trial participation
  - a heart status which does not mean direct risks (NYHA I or II)
  - life-expectancy considering the duration of the trial
  - physical conditions which allow administration: no metastases preventing from swallowing
  - acceptable hepatic and renal function which allows adequate clearance

Crossover design allows high inter-subject variabilities !

Typical doxorubicin criteria

SocraTec R&D

Protocol example

Inclusion criteria

1. Have histologically confirmed ovarian cancer that is potentially sensitive to DOXIL/CAELYX
2. Have a normal left ventricular ejection fraction (LVEF) based on institutional ranges.
3. Have an Eastern Cooperative Oncology Group (ECOG) performance status of </= 2
4. Have an estimated life expectancy of ≥ 3 months
5. Have acceptable liver function:
   - Bilirubin </= upper limit of normal (ULN)
   - AST (SGOT), ALT (SGPT) and Alkaline phosphatase </= 1.5 times upper limit of normal
6. Have acceptable renal function:
   - Serum creatinine within normal limits, OR calculated creatinine clearance >/= 60 mL/min/1.73 m2 for patients with creatinine levels above institutional normal.
7. Have acceptable hematologic status:
   - Neutrophils >/= 1500 cells/mm3
   - Platelet count >/= 100,000 (plt/mm3)
   - Hemoglobin >/= 9 g/dL

Exclusion criteria

1. Have New York Heart Association (NYHA) Class III or IV cardiac disease, myocardial infarction within the past 6 months prior to Day 1, unstable arrhythmia, or evidence of ischemia on electrocardiogram (ECG) or during Cardiac Stress Testing within 14 days prior to Day 1
2. Have received radiotherapy to the mediastinal area or concomitant therapy with other potentially cardiotoxic agents
3. Have seizure disorders requiring anticonvulsant therapy
4. Have known brain metastases (unless previously treated and well controlled for a period of >/= 3 months)
5. Have severe chronic obstructive pulmonary disease with hypoxemia
6. Have had major surgery, other than diagnostic surgery, within 4 weeks prior to Day 1
7. Have received treatment with radiation therapy, surgery, chemotherapy, or investigational therapy within one month prior to study entry (6 weeks for nitrosoureas or Mitomycin C).
8. Have received radiation therapy to >25% of her total bone marrow during her lifetime

Example from Clintrial.gov

Ty eria

SocraTec R&D

Selection of

Inclusion criteria

1. Have histologically confirmed ovarian cancer that is potentially sensitive to DOXIL/CAELYX
2. Have a normal left ventricular ejection fraction (LVEF) based on institutional ranges.
3. Have an Eastern Cooperative Oncology Group (ECOG) performance status of </= 2
4. Have an estimated life expectancy of ≥ 3 months
5. Have acceptable liver function:
   - Bilirubin </= upper limit of normal (ULN)
   - AST (SGOT), ALT (SGPT) and Alkaline phosphatase </= 1.5 times upper limit of normal
6. Have acceptable renal function:
   - Serum creatinine within normal limits, OR calculated creatinine clearance >/= 60 mL/min/1.73 m2 for patients with creatinine levels above institutional normal.
7. Have acceptable hematologic status:
   - Neutrophils >/= 1500 cells/mm3
   - Platelet count >/= 100,000 (plt/mm3)
   - Hemoglobin >/= 9 g/dL

Exclusion criteria

1. Have New York Heart Association (NYHA) Class III or IV cardiac disease, myocardial infarction within the past 6 months prior to Day 1, unstable arrhythmia, or evidence of ischemia on electrocardiogram (ECG) or during Cardiac Stress Testing within 14 days prior to Day 1
2. Have received radiotherapy to the mediastinal area or concomitant therapy with other potentially cardiotoxic agents
3. Have seizure disorders requiring anticonvulsant therapy
4. Have known brain metastases (unless previously treated and well controlled for a period of >/= 3 months)
5. Have severe chronic obstructive pulmonary disease with hypoxemia
6. Have had major surgery, other than diagnostic surgery, within 4 weeks prior to Day 1
7. Have received treatment with radiation therapy, surgery, chemotherapy, or investigational therapy within one month prior to study entry (6 weeks for nitrosoureas or Mitomycin C).
8. Have received radiation therapy to >25% of her total bone marrow during her lifetime

Example from Clintrial.gov

Patient selection

SocraTec R&D

ECOG Performance Status

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self care. Totally confined to bed or chair
5	Dead

As published in Am. J. Clin. Oncol.: Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982

Alternatives for patient selection

SocraTec R&D

Karnofsky Performance Status Scale

100	normal, no complaints, no signs of disease
90	capable of normal activity, few symptoms or signs of disease
80	normal activity with some difficulty, some symptoms or signs
70	caring for self, not capable of normal activity or work
60	requiring some help, can take care of most personal requirements
50	requires help often, requires frequent medical care
40	disabled, requires special care and help
30	severely disabled, hospital admission indicated but no risk of death
20	very ill, urgently requiring admission, requires supportive measures or treatment
10	moribund, rapidly progressive fatal disease processes
0	death

Challenges for BE-trial - doxorubicin

SocraTec R&D

Availability of subjects - breast and ovarian cancer

- high - at least in countries with a highly developed medical care system
- phase-I-cancer studies are often realised in Universities - there recruitment / performance might be limited:
  - infrastructure not optimum for the needs of the trial
  - high level of competition with other trials
  - often little interest of oncologists (catchwords: Citation Index of publication • scientific reputation • lack of therapeutic benefit)

AIDS-related Kaposi's - sarcoma

- lower dose recommended: 20 mg/m^2
- patients are more difficult to recruit – unfeasible in countries with highly developed medical care system

Challenges for BE-trials in oncology

SocraTec R&D

Often relatively high number of patients needed

Study ID	Dose/patient population	Reference product	Number analysed (n)
PKD/08/038	50mg/m^2 ovarian cancer	Caelyx (Europe)	23
PKD/09/031	30mg/m^2 multiple myeloma	Caelyx (Europe)	26
PKD/09/030	50mg/m^2 ovarian cancer	Doxil (US)	41

CHMP Assessment Report: Doxorubicin Sun (EMEA/H/C/002049)

Demands for trial (planning and performance)

- high number of subjects...
- ...to be recruited in a short time
- high level of standardisation during performance
- ...to be realised only in a setting with adequate QMS (professional CPU)

Challenges for BE-trials in oncology

SocraTec R&D

Often relatively high number of patients needed

Study ID	Dose/patient population	Reference product	Number analysed (n)
PKD/08/038	50mg/m^2 ovarian cancer	Caelyx (Europe)	23
PKD/09/031	30mg/m^2 multiple myeloma	Caelyx (Europe)	26
PKD/09/030	50mg/m^2 ovarian cancer	Doxil (US)	41

CHMP Assessment Report: Doxorubicin Sun (EMEA/H/C/002049)

Demands for trial (planning and performance)

- high number of subjects...
- ...to be recruited in a short time
- high level of standardisation during performance
- ...to be realised only in a setting with adequate QMS (professional CPU)

Adequate selection of In/Ex criteria relevant for success

Opiods: co-medication in cancer

SocraTec R&D

Pharmacodynamic effects on the GI-tract

- stomach
  - mobility ↓ ⇨
  - tonus of pylorus ↑ ⇨

  ⇨ Delayed gastric emptying
- small intestine
  - pancreatic secretion ↓ ⇨ digestive disorder
  - biliary secretion ↓ ⇨ digestive disorder
  - propulsion ↓ ⇨ delayed transit
  - water uptake ↑ ⇨ faecal impaction
- colon
  - propulsion ↓ ⇨ delayed transit
  - non-propulsive contraction ↑ ⇨ spasms, colic
  - water uptake ↑ ⇨ faecal impaction
  - tonus of anal sphincter ↑ ⇨ defecation

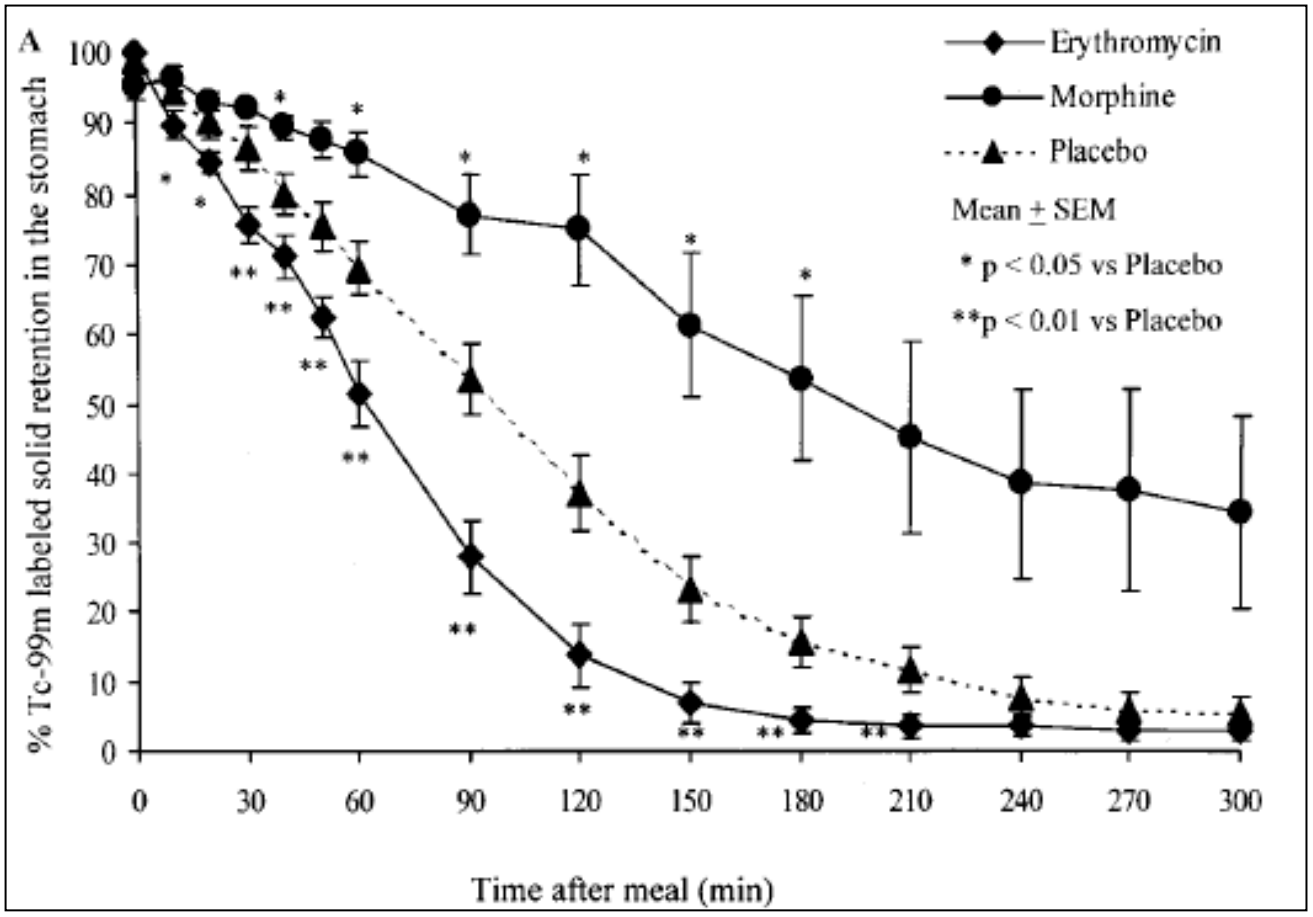
Total = Constipation

Modified from Klaschik, 2006

Opiods: effect on gastric emptying

SocraTec R&D

Solid retention

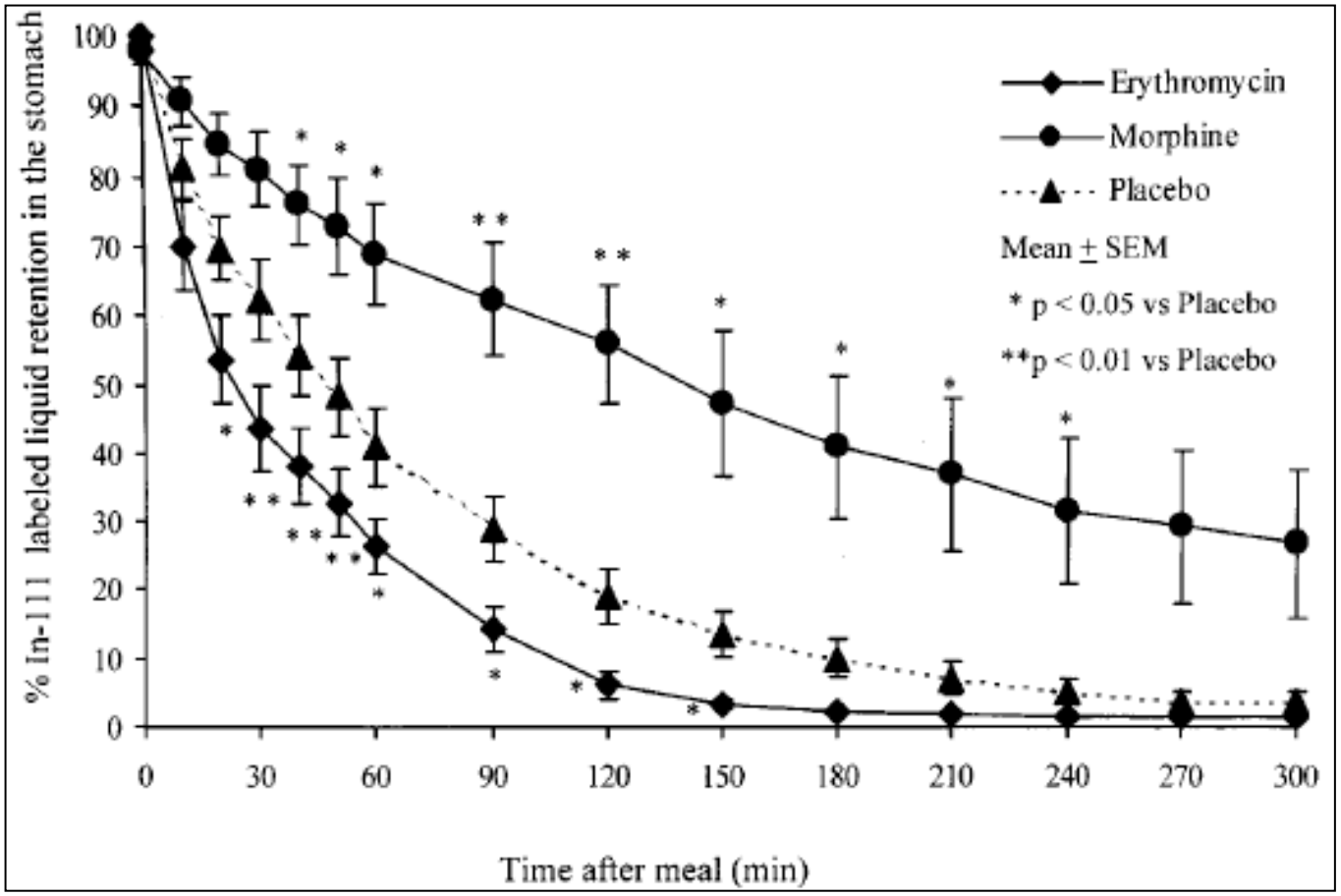


Gonlachanvit et al.: Dig Dis Sc, 48, 2003, 408-497

Opiods: effect on gastric emptying

SocraTec R&D

Liquid retention



Gonlachanvit et al.: Dig Dis Sc, 48, 2003, 408-497

In/Ex criteria that matter?

SocraTec R&D

BMI > 30: hypotheses found in literature

- obese subjects habitually ingest food with higher energy density
  - deceleration of gastric emptying related to calorie intake
- adaptation to regular higher calorie intake results in down regulation of feed-back sensitivity
  - acceleration of gastric emptying related to calorie intake
- gastric volume is larger in subjects with high BMI
  - deceleration of gastric emptying related to calorie intake
- safety signals are not adequately triggered
  - acceleration of gastric emptying related to calorie intake

Obesity and gastric emptying

SocraTec R&D

Literature survey

Authors	Year	Meal	Energy (kJ)	GE
Wright et al.	1983	Solid / liquid	882 / 336	+ / 0
Sasahl et al.	1983	Liquid	1260	0
Horowitz et al.	1983	Solid / liquid	1134 / 0	- / 0
Sasahl et al.	1984	Liquid	0	0
Horowitz et al.	1086	Solid / liquid	1134 / 0	- / 0
Zahorsk-Markiewicz et al.	1986	Solid / liquid	1722 – 1848	+
Maddox et al.	1989	Solid / liquid	1134 / 252	- / -
Wisén et al.	1992	Liquid	1814.5	+
French et al.	1993	Liquid	302.5 – 1331.5	0
Verdich et al.	2000	Solid	2500	- / +

Contradictory results in literature

Wisen and Hellström: J Int Med. (1995)237: 411-418
Verdich et al: Int J. Obesity (2000) 24: 899-905

Obesity and GI motility

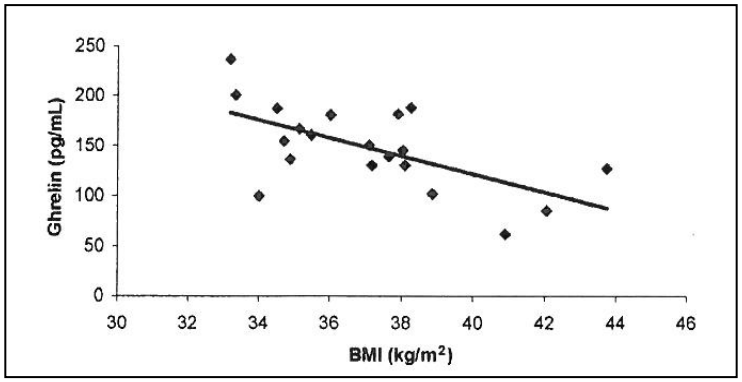
SocraTec R&D

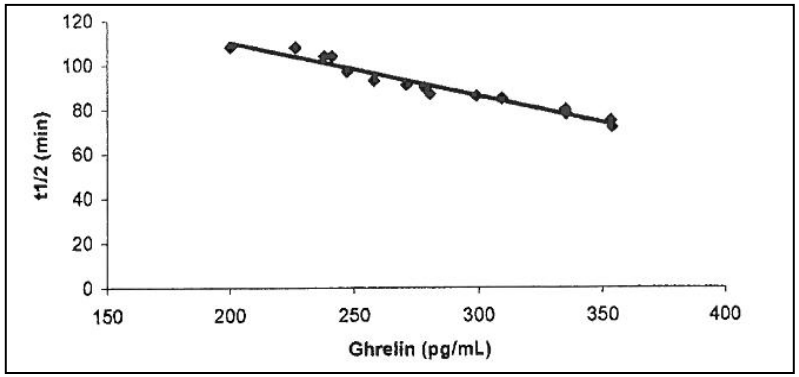
Gastric emptying rates in obese and lean subjects

- emptying after a solid test meal (99mTc marked)
- correlation with Grhelin as prokinetic factor

	obese men	**obese women**	**lean men**	**lean woman**
t ½	67,8 ± 14,79	66,6 ± 13,56	88,09 ± 11,72	97,25 ± 10,31

p < 0,001





Mora et al: Obesity Res (2005) 4: 739-744

Obesity vs. normal body weight range

SocraTec R&D

Situation in obese subjects

- newer data indicate that gastric emptying might be faster in obese compared with lean subjects
- data should be interpreted in the context of earlier contradictory data

But as long we perform our studies with a crossover design, body weight should not be an issue in the patient population !

Back to liposomal doxorubicin

SocraTec R&D

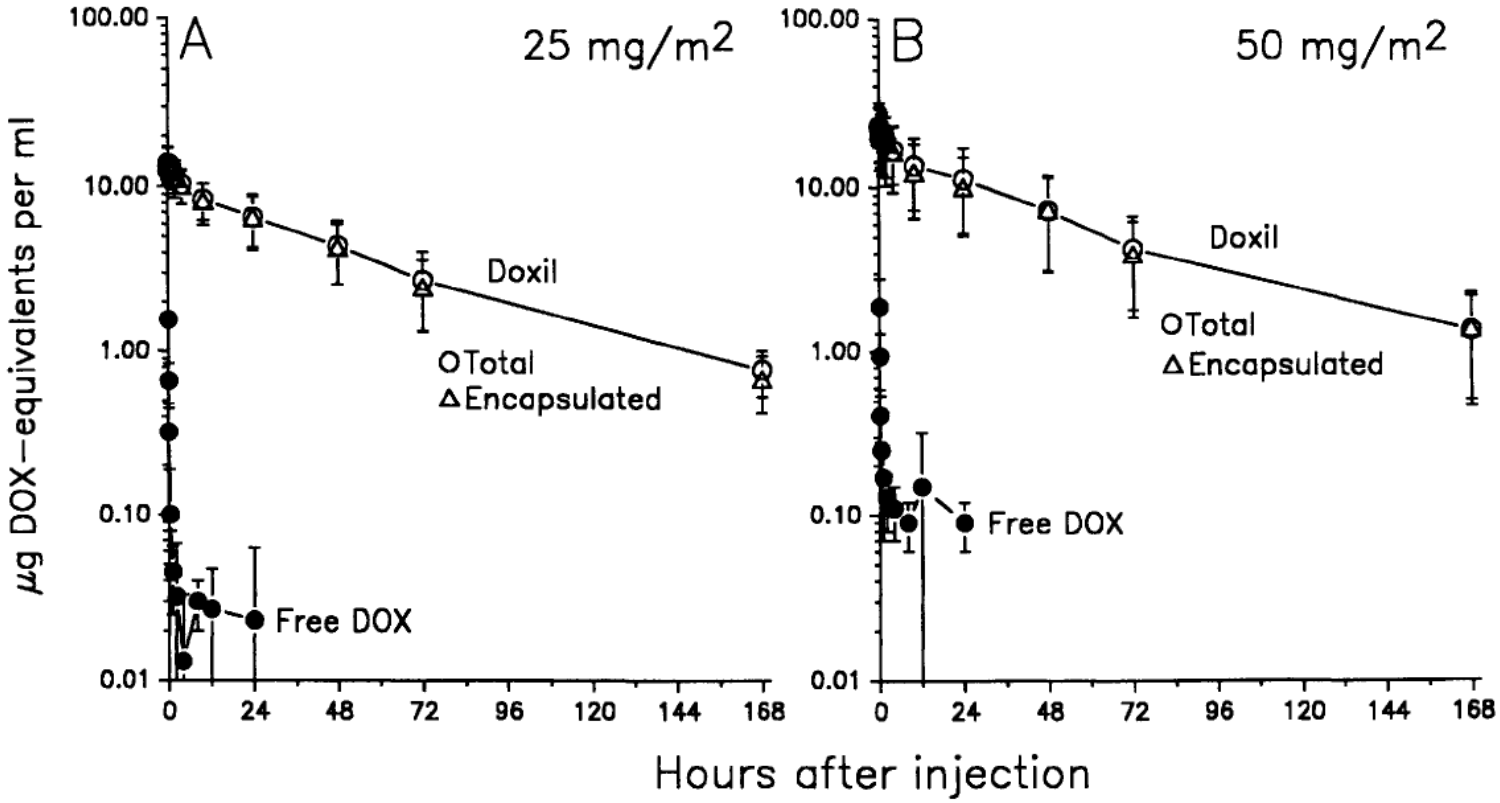


Fig. 1. Plasma levels of doxorubicin (total or liposome-encapsulated) in Doxil- and free DOX-treated patients. *A*, 25 mg/m^2 (n = 8 for Doxil; n = 3 for free DOX). *B*, 50 mg/m^2 (n = 14 for Doxil; n = 4 for free DOX).

Gabizon et al, 1994

PK of liposomal doxorubicin

SocraTec R&D

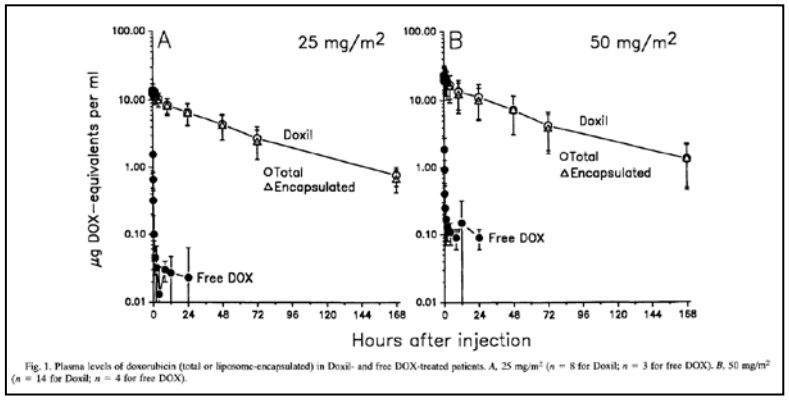


Fig. 1. Plasma levels of doxorubicin (total or liposome-encapsulated) in Doxil- and free DOX-treated patients. A, 25 mg/m² (n = 8 for Doxil; n = 3 for free DOX). B, 50 mg/m² (n = 14 for Doxil; n = 4 for free DOX).

Dosing regimen according to SmPC

- breast/ ovarian cancer
  - once every 4 weeks (50mg/m^2)
  - as long as the disease does not progress and the patient continues to tolerate treatment
- multiple myeloma
  - 30mg/m^2 on day 4 of bortezomib 3 week treatment regimen
  - as long as the patient responds satisfactorily and tolerates treatment

Gabizon et al, 1994

Caelyx® SmPC

Relevance of the quality dossier

SocraTec R&D

Situation for subjects and oncologists

- relevant interference with treatment due to long $t_{1/2}$
- lack of adequate efficacy could be fatal
- inadequately high release from liposomes could seriously endanger the patient
- thus, relevant interference with safety and tolerability

Against the background of missing therapeutic benefit the quality characterisation in-vitro and in animal studies is of particular relevance !

Citation: CHMP assessment report

SocraTec R&D

Assessor s comment:

"The two original *("tissue")* distribution studies submitted with this application were deficient in terms of the doses utilised, study duration, choice of analyte, data analysis methods and interpretation of results. (…)"

"While the applicant concluded comparability of tissue distribution of the two products, there were major concerns regarding the reliability of the data and signals of a lack of equivalence between the two products."

"There remains an outstanding major objection regarding the reliability of the data and signals of lack of equivalence between the two products."

Citation: CHMP assessment report

SocraTec R&D

Assessor s comment:

"The two original *("tissue")* distribution studies submitted with this application were deficient in terms of the doses utilised, study duration, choice of analyte, data analysi esults. (…)"

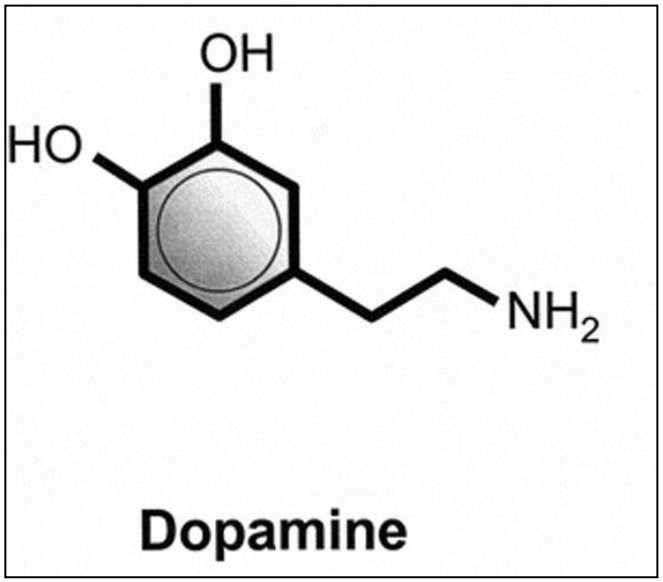
In how far is such an aspect of relevance for the study participants in the earlier BE-trial?

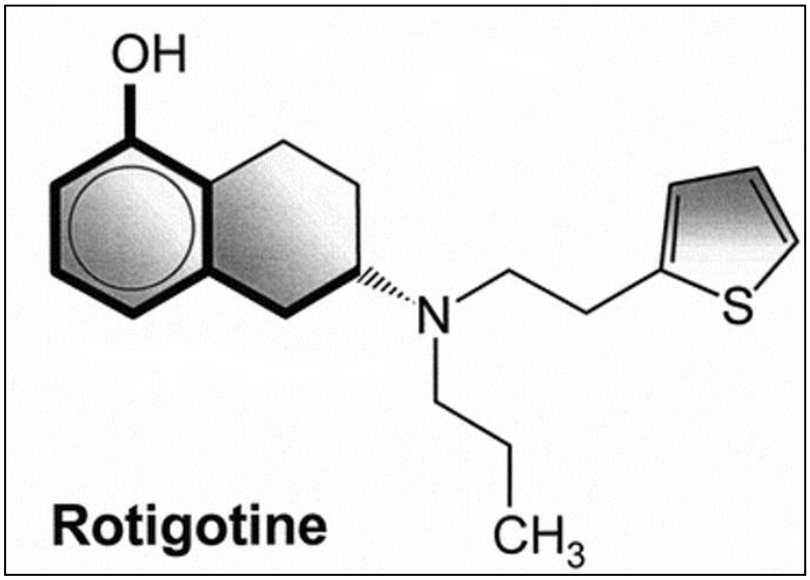
"While the applicant concluded n of the two products, there were majo y of the data and signals of a lack of equival between the two products."

"There remains an outstanding major objection regarding the reliability of the data and signals of lack of equivalence between the two products."

Another example: rotigotine

SocraTec R&D





- structural similarity with dopamine
- (also) high first-pass metabolism
- oral administration not meaningful

Initial development as transdermal therapeutic system

Pfeiffer RF, Neurology 2005, 65 6-10

Rotigotine – pharmacological profile

SocraTec R&D

Dose finding

- via titration, starting with 2 mg/ 24 h during one week increasing weekly in 2 mg steps up to 16 mg/ 24 h
- considering the narrow therapeutic range

Safety profile

- in the higher doses unacceptable for healthy subjects especially because of
  - Long time of titration combined with side effects disabling volunteers to perform common daily's activities

BE – trials should generally be realised in patients, maybe single doses of the 2 mg–patch acceptable for healthy subjects

Requirements for TDDS

SocraTec R&D

"Generally, the kinetics of drug delivery from TDDS' is determined by the interplay between the active substance, the formulation and the skin. Studies should be conducted to evaluate drug transport characteristics and the rate limiting step that determines systemic availability i.e. drug release and/or skin reservoir and/or other formulation related particularities.
Pharmacokinetic investigations should comprise single-dose and multiple-dose investigations considering particular aspects like e.g. application site-dependent absorption, fluctuation, lag-times and concentration time profile after patch removal. Aiming to establish an IVIVC is advisable. In case of several dose strengths, dose proportionality issues should be adequately addressed."

"In addition to conventional phase I studies skin irritation, sensitisation (see also appendix 1), phototoxicity, patch adhesion and, in general, the effect of sauna and sun cream on the patch adhesion (see also Guideline on quality of transdermal patches EMA/CHMP/QWP/911254/2011) should be investigated."

How to realise all these studies in patients?

Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/ CPMP/ EWP/ 280/ 96 Corr1). 12 March 2013

Challenges to overcome

SocraTec R&D

Single dose studies

- lowest dose to be realised at the beginning of the titration phase
  - wash-out phase acceptable?
  - or better a parallel group design?
- highest dose not acceptable, as titration phase is mandatory

⇨ A waiver of the 8 mg-single dose trial should be justifiable based on the properties of transdermal formulation (linear relationship of patch area to systemic exposure)

Linear PK: waiver of 8mg dose?

SocraTec R&D

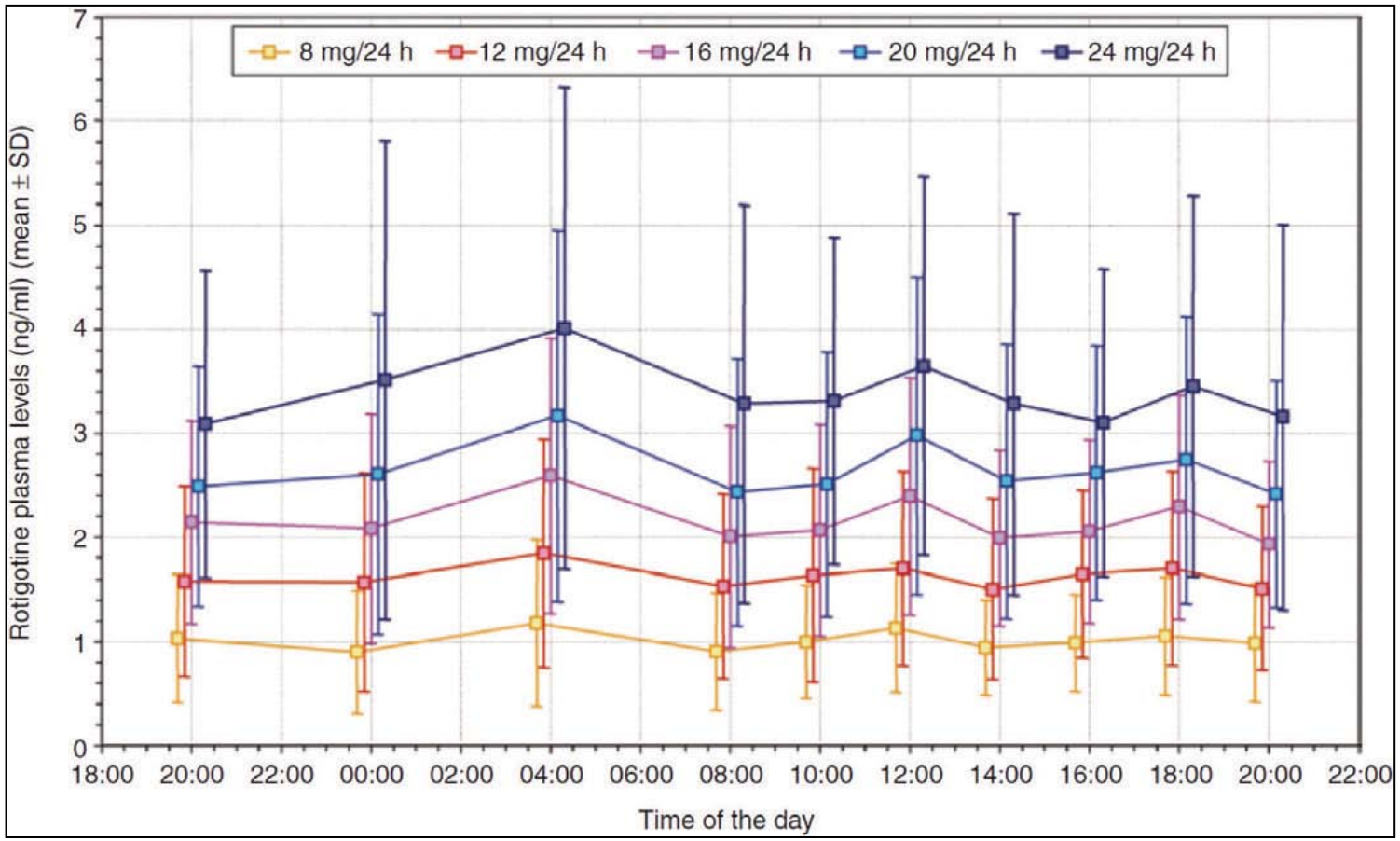


Fig. 1. Plasma concentration of rotigotine over 24 hours and after several days of treatment. Modified from Malik M, et al. [6]

Challenges to overcome

SocraTec R&D

Multiple dose studies

- favourable approach: direct switch-over in order to avoid treatment-free intervals
- problem: low predictive value of in-vitro-testing procedures (incl. Franz cell system)
  - single dose data should be available before in order to avoid inadequate treatment
  - testing for adequate efficacy by sensitive tests might be necessary e.g. finger tapping test
  - determination of duration of off-phenomena
  - determination of vigilance
- switch from Reference to Test
- consecutive treatment to be avoided
- crossover or even semi- or replicate design

Conclusion

SocraTec R&D

Inclusion / Exclusion criteria

- consider aim of the study and the safety of the subjects
- do not confound with criteria of phase II/ III studies
- avoid superfluous standardisation in crossover trials
- off-label use is often not accepted for formal reasons, however possible from scientific / medical perspective

Design issues

- again: careful balance between aim and safety
- as little interference with the therapy as possible
- adequate decision upon waiver whenever justifiable

SocraTec R&D
We make it work

Concepts in Drug Research and Development

Contact:

Prof. Dr. Henning Blume
Phone: +49-6171-5857-120
henning.blume@socratec-pharma.de

Dr. Barbara Schug
Phone: +49-6171-5857-111
barbara.schug@socratec-pharma.de

André Warnke
Phone: +49-6171-5857-122
andre.warnke@socratec-pharma.de

Fax +49-6171-5857-25; Postal Address: Im Setzling 35, 61440 Oberursel (Taunus), Germany