WORKSHOP ON REGULATORY AND SCIENTIFIC ISSUES RELATED TO THE INVESTIGATION OF MEDICINAL PRODUCTS INTENDED FOR NEONATAL USE

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CONSIDERATIONS ON METHODOLOGY, STUDY DESIGN AND STATISTICAL APPROACHES

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AGE CLASSES
(ICH E-11)

- NEONATES (0-28 DAYS)

  * PREMATURE (<37 w G.A.) OR TERM
  * 0-7 DAYS ; 8-28 JOURS

- INFANTS (29 DAYS-23 MONTHS)

- CHILDREN (2 YEARS – 11 ANS)

- ADOLESCENTS (12 YEARS - 16-18 YEARS)

NEONATES ARE DIFFERENT

AS COMPARED TO ADULTS

THEREFORE DATA OBTAINED IN ADULTS

CANNOT SIMPLY BE EXTRAPOLATED

TO NEONATES

using a proportionality rule

based upon body size
(weight or body surface area)

NEONATES ARE DIFFERENT

BECAUSE DRUGS BEHAVE DIFFERENTLY IN THEIR BODY

1/ the fate of drugs is different in the body of neonates

2/ the effect of drugs is different in neonates

- the magnitude of the response may be different

- the nature of the response may be different:

some side effects only occur in neonates as their immature body undergoes growth and maturation

NEONATES ARE DIFFERENT

BECAUSE DISEASES MAY BE DIFFERENT IN NEONATES

1/ some diseases only exist in neonates

2/ other diseases differ from what is observed in adults

- infectious diseases :
  - different epidemiology of micro-organisms
- malignancies :
  - different histological types
  - different prognosis
  - different response to drug therapy

NEONATES ARE DIFFERENT

THEREFORE CLINICAL STUDIES HAVE TO BE PERFORMED SPECIFICALLY IN NEONATES

BUT THEY …

1/ are more difficult to perform

2/ take longer

3) are more costly

… than in adults

NEONATES ARE DIFFERENT

AND CLINICAL STUDIES ARE MORE DIFFICULT TO PERFORM

WHY ?

1/ invasiness is a limiting factor and has to be restricted as much as possible

2/ the recruitment is more difficult than in adults

3) appropriate tools have to be developped for the measurement of drug effect

ISSUES TO BE FACED

PROBLEM: INVASIVENESS

- ➔ pain, stress
- ➔ blood deprivation
- ➔ irradiation
- ➔ exposure to clinical trials and to investigational new drugs … should be limited to the minimum required

INVASIVENESS HAS TO BE RESTRICTED

PROPOSED / USED CLUES

1- PREVENT PAIN AND STRESS

- ***BLOOD SAMPLING***

  - **local anesthesia (EMLA cream),**
  - **catheters**

- ***ASSESSMENT OF EFFICACY***

  - **non invasive procedures**
    (transcutaneous methods) (*)

ALTERNATIVES IN CLINICAL TRIALS / PD STUDIES

TO PREVENT PAIN AND ANXIETY

TRANSCUTANEOUS MEASUREMENTS :

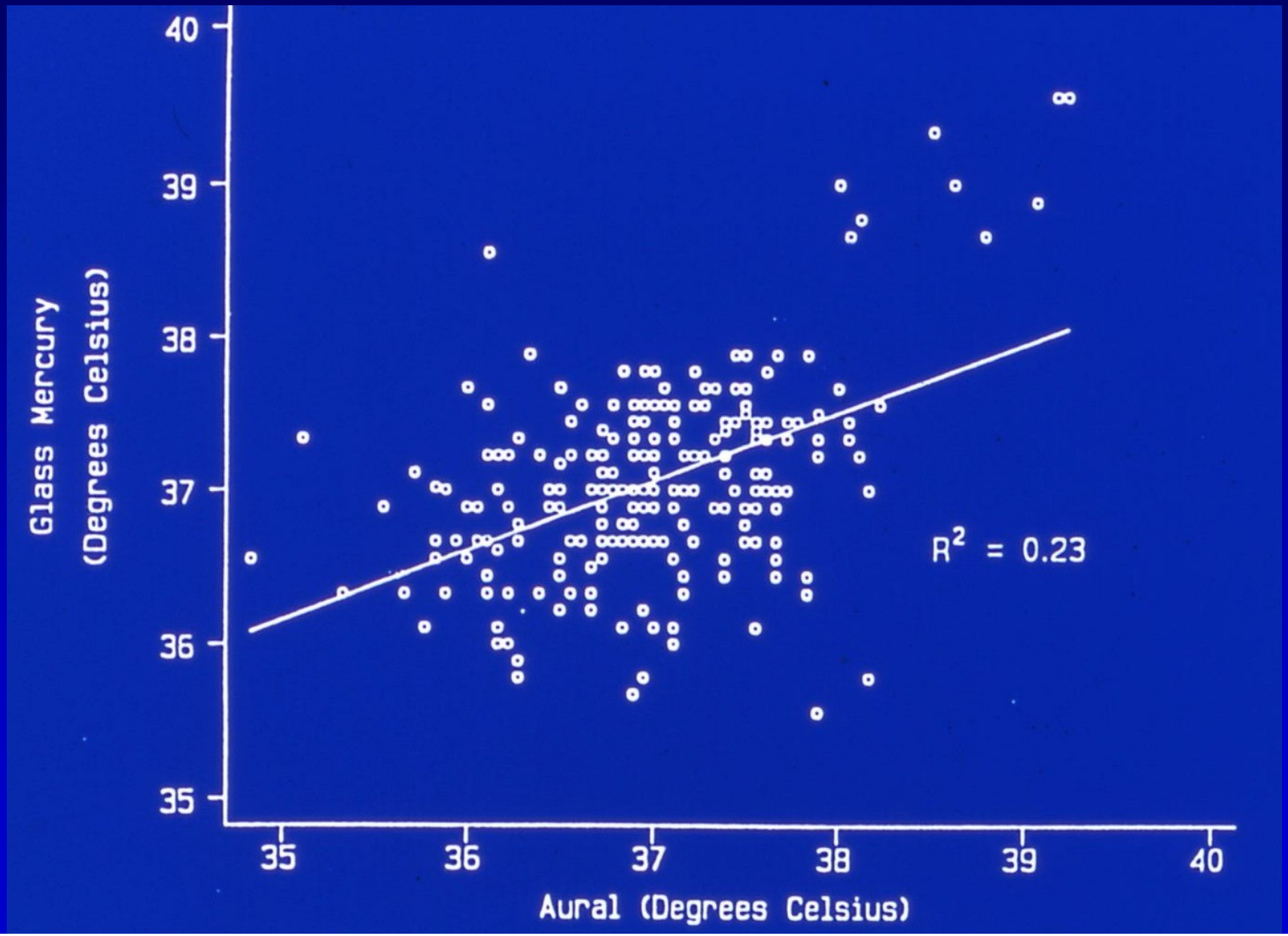
- PO_2, PCO_2, SaO_2, TEMPERATURE, BILIRUBINE

- ECHODOPPLER : CEREBRAL BLOOD FLOW, HEART, VESSELS

- NEURO-IMAGING
  - BUT ...

VALIDATION OF NON INVASIVE METHODS AND SURROGATE MARKERS (*)

NON INVASIVE METHODS IN CHILDREN



INVASIVENESS HAS TO BE RESTRICTED

2- RESTRICT BLOOD LOSS

- ***SMALL BLOOD VOLUMES***

  - **micro-assays**

INVASIVENESS OF PK STUDIES

VOLUME OF BLOOD DRAWN

THE PROBLEM

- 80 ml/kg (NN : 85-90 ml/kg)
- NN : 2 kg BV = 170 ml

  3 % BV = 5.1 ml

  1 % BV = 1.7 ml

THE SOLUTIONS :

- SENSITIVE ASSAYS
- SMALL NUMBER OF SAMPLES

INVASIVENESS HAS TO BE RESTRICTED

2- RESTRICT BLOOD LOSS

- ***SMALL BLOOD VOLUMES***

  - **micro-assays**

- ***SMALL NUMBER OF SAMPLES***

  - **PK and PK/PD:**

    population approaches (⁎)

INVASIVENESS HAS TO BE RESTRICTED

ALTERNATIVES FOR PK STUDIES

1) POPULATION APPROACH (POP-PK)
   - few blood samples/patient
   - many patients

2) RICH DATA INDIVIDUAL APPROACH
   - many blood samples
   - few patients

INVASIVENESS HAS TO BE RESTRICTED

2- RESTRICT BLOOD LOSS

- ***SMALL BLOOD VOLUMES***

  - **micro-assays**

- ***SMALL NUMBER OF SAMPLES***

  - **PK and PK/PD:**
    population approaches

- ***ALTERNATIVE APPROACHES*** **?: saliva ?..**

ALTERNATIVES FOR PK / METABOLIC STUDIES

. SALIVA

. CO_2 BREATH TEST

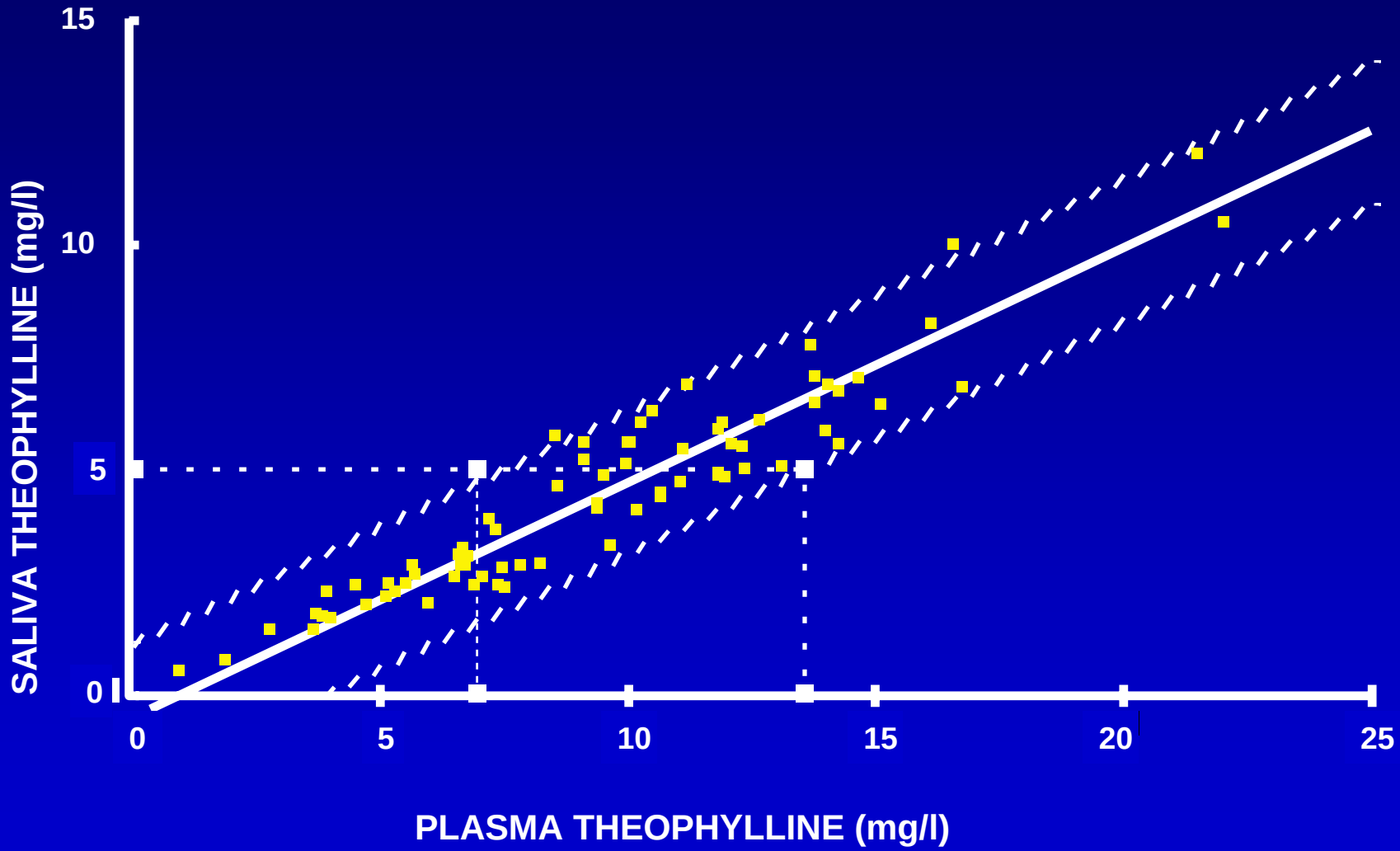
. URINES

. HAIR, MECONIUM

BUT ...

VALIDATION OF NON INVASIVE METHODS

Group II - Citric acid salivette



INVASIVENESS HAS TO BE RESTRICTED

3 - RESTRICT EXPOSURE TO CLINICAL STUDIES AND INVESTIGATIONAL NEW DRUGS whenever possible

- *AVOID UNECESSARY STUDIES*

  - extrapolation from adult data to the lowest possible age limit

  - use of the already available pediatric data (literature, data on file …)

- *ALTERNATIVE APPROACHES*

AVOID UNNECESSARY STUDIES

1- EXTRAPOLATION FROM ADULT DATA

- adjust the dose for a similar drug systemic « exposure » (plasma concentration, AUC) using data on the maturational profiles on:

- PK : dose-concentration relationship
- renal elimination
- metabolic pathways

- PK-PD: plasma-concentration relationship

AVOID UNNECESSARY STUDIES

b) THE KNOWLEDGE OF THE ONTOGENY OF THE PROCESSES INVOLVED IN DRUG ELIMINATION (RENAL, HEPATIC, METABOL. PATHWAYS)

determine the lower age limit for extrapolation

➡ **PLANNING PEDIATRIC PK STUDIES**

(OPTIMISATION OF AGE DISTRIBUTION IN RECRUITMENT OF PATIENTS)

➡ **MODELING OF THE INFLUENCE OF MATURATION (*)**

(SIMULATION (*)– VALIDATION) Ex : SIMCYP

AVOID UNNECESSARY STUDIES

2- USE OF AVAILABLE DATA

- bio-avalability studies
- population PK on published data
- meta-analysis (*)

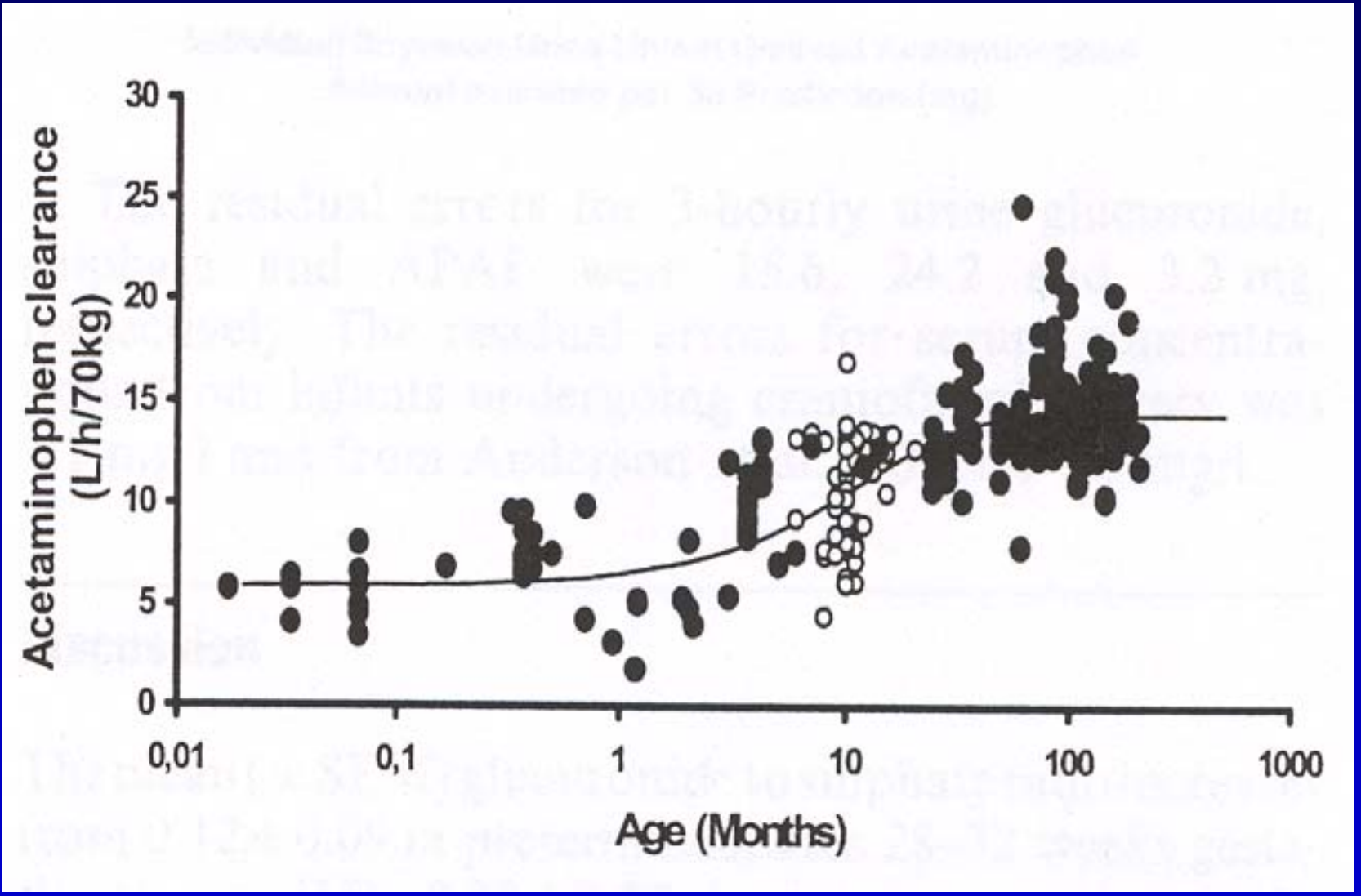
INVASIVENESS OF PK STUDIES

3- APPROPRIATE DRUG DEVELOPMENT PLAN

- **BIOAVAILABILITY OF NEONATAL FORMULATIONS**

IN HEALTHY *ADULT VOLUNTEERS*

- POPULATION PK

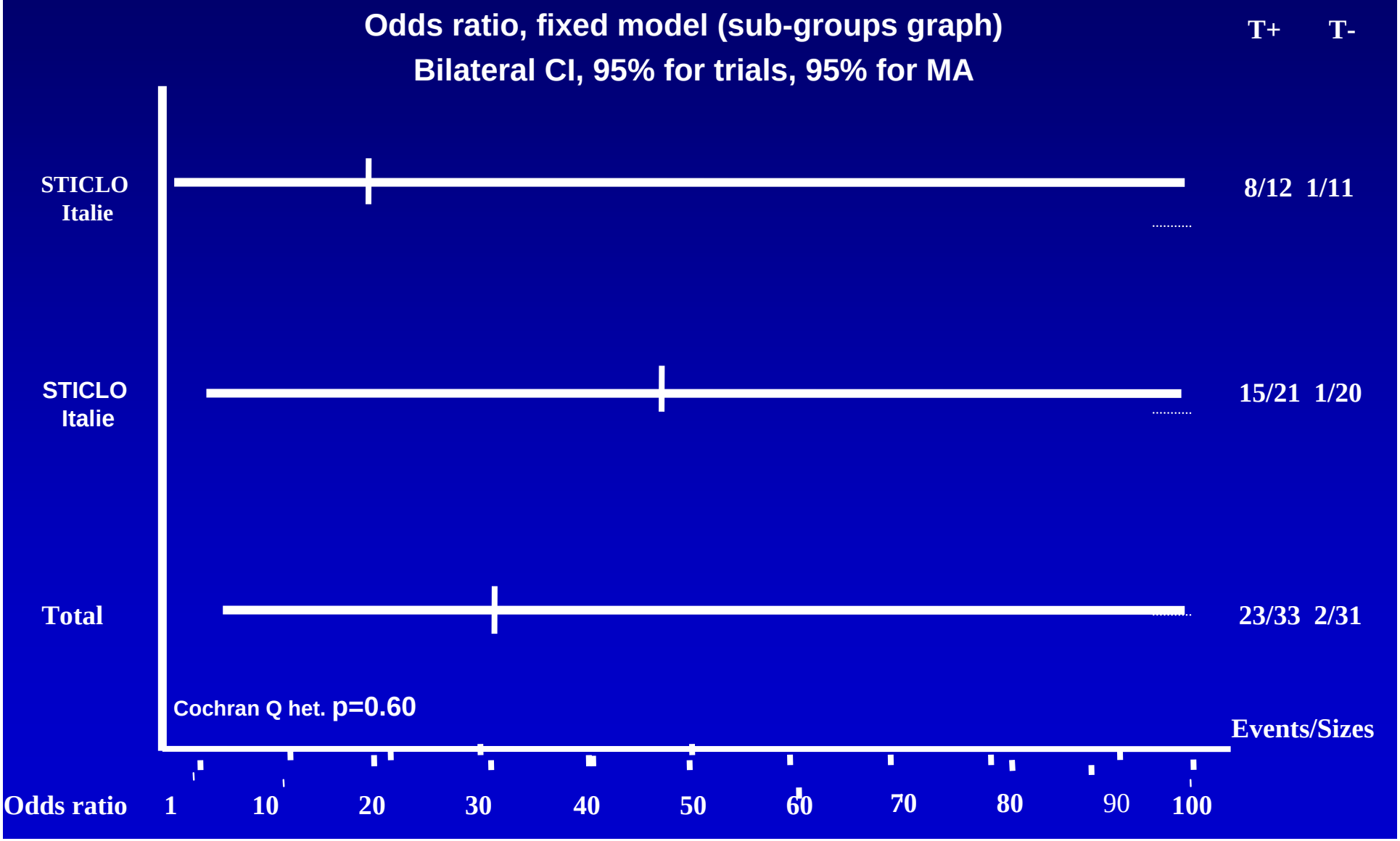


Anderson B, Pons G et al, Paediatr. Anaesth, 2005, 15, 282-92

Odds ratio of responders in STP group compared to placebo

- META-ANALYSIS (Kassaï B. et al., 2006)

Responders



INVASIVENESS HAS TO BE RESTRICTED

3- AVOID IRRADIATION

- **THE PROBLEM**
  - IRRADIATION FROM RADIO-ACTIVE ISOTOPES

- **THE SOLUTIONS** :
  - USE OF STABLE ISOTOPES (*) :
    - BIOAVAILABILITY STUDIES
    - PK REPEATED DOSES
    - METABOLIC STUDIES
    - CO_2 BREATH TEST
    - COMPLIANCE

NEONATES ARE DIFFERENT

AND CLINICAL STUDIES ARE MORE DIFFICULT TO PERFORM

1/ invasiness is a limiting factor and has to be restricted as much as possible

2/ the recruitment is more difficult than in adults

RECRUITMENT HAS TO BE FACILITATED

PROBLEMS

1- NUMBER OF PATIENTS OFTEN LIMITED

2- INFORMED CONSENT MORE DIFFICULT TO OBTAIN

⇨ clinical trials takes longer

⇨ clinical trials may cost more

RECRUITMENT HAS TO BE FACILITATED

PROBLEMS

3- EXPOSURE TO CLINICAL TRIALS AND TO INVESTIGATIONAL NEW DRUGS SHOULD BE LIMITED TO THE MINIMUM REQUIRED

⇨ **Ethical issue: smallest possible numbers**

⇨ **Validity of scientific data / acceptance by regulatory bodies: numbers not too small**

RECRUITMENT HAS TO BE FACILITATED

INNOVATIVE METHODOLOGICAL APPROACHES

➔limit the number of patients

PROPOSALS :

- **Sequential approaches (⁕)**
  - **dose-finding studies (phase II)**
  - **comparative trials (phase III)**
- **Enrichment methods (⁕)**
- **Clinical trial modeling and *in silico* simulation**

avenue to explore (⁕) :

a relatively new effort to devise *in silico* simulations of human physiology and genetic variation.

1 - DOSE-FINDING STUDIES IN NEONATES (PHASE II)

a) <u>DOSE FINDING PARALLEL GROUP STUDIES ARE DIFFICULT TO PERFORM IN CHILDREN</u>

- RELATIVELY NARROW DOSE RANGE

AND SMALL INTERVAL BETWEEN TESTED DOSES

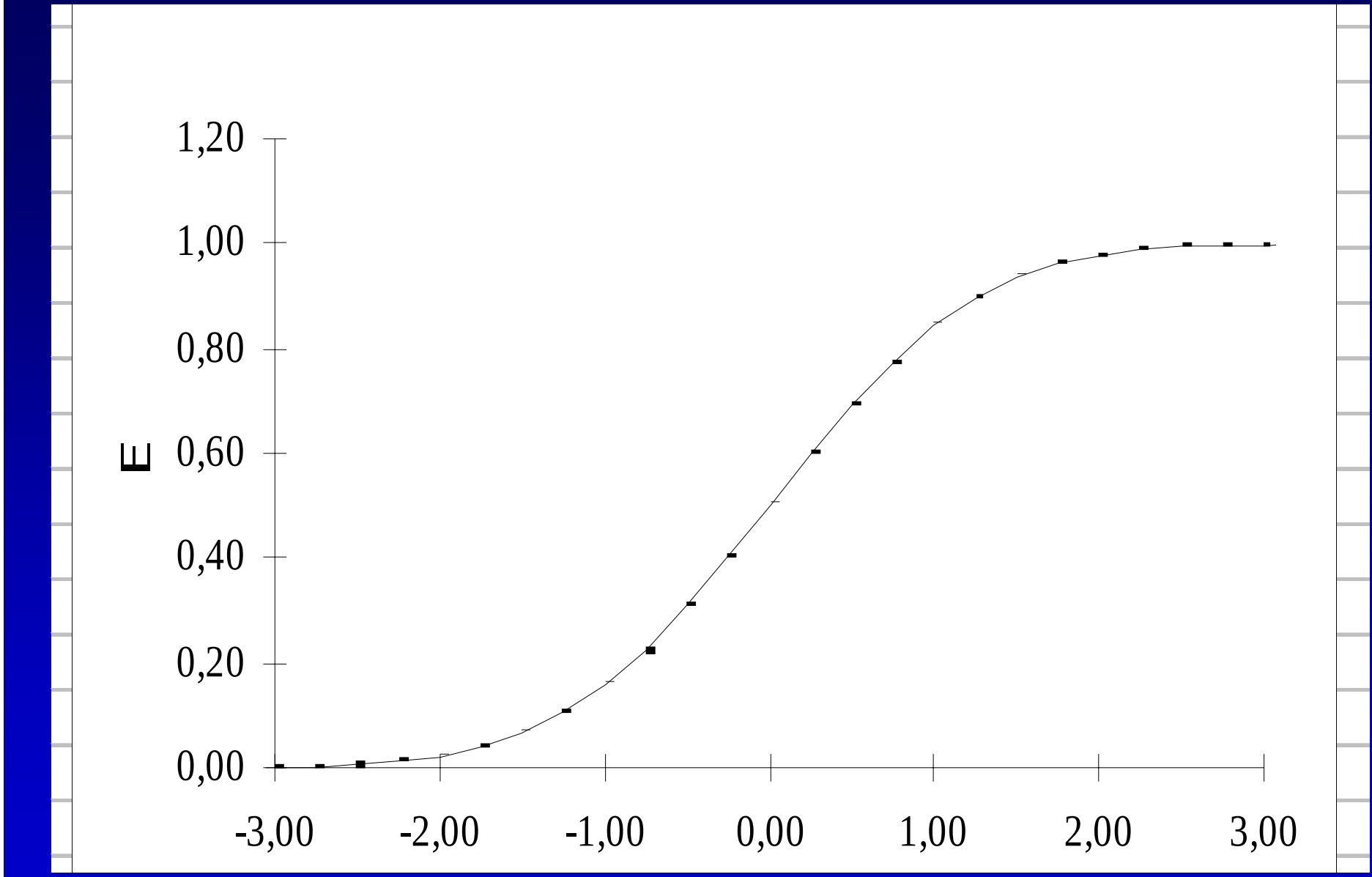
- IMPORTANT INTERINDIVIDUAL VARIABILITY OF THE PARAMETERS MEASURED

- LARGE NUMBER OF PATIENTS REQUIRED

1 - DOSE-FINDING STUDIES IN NEONATES (PHASE II)

NEW PROMISING METHOD :

- BAYESIAN SEQUENTIAL ANALYSIS


E
1,20
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-2,00
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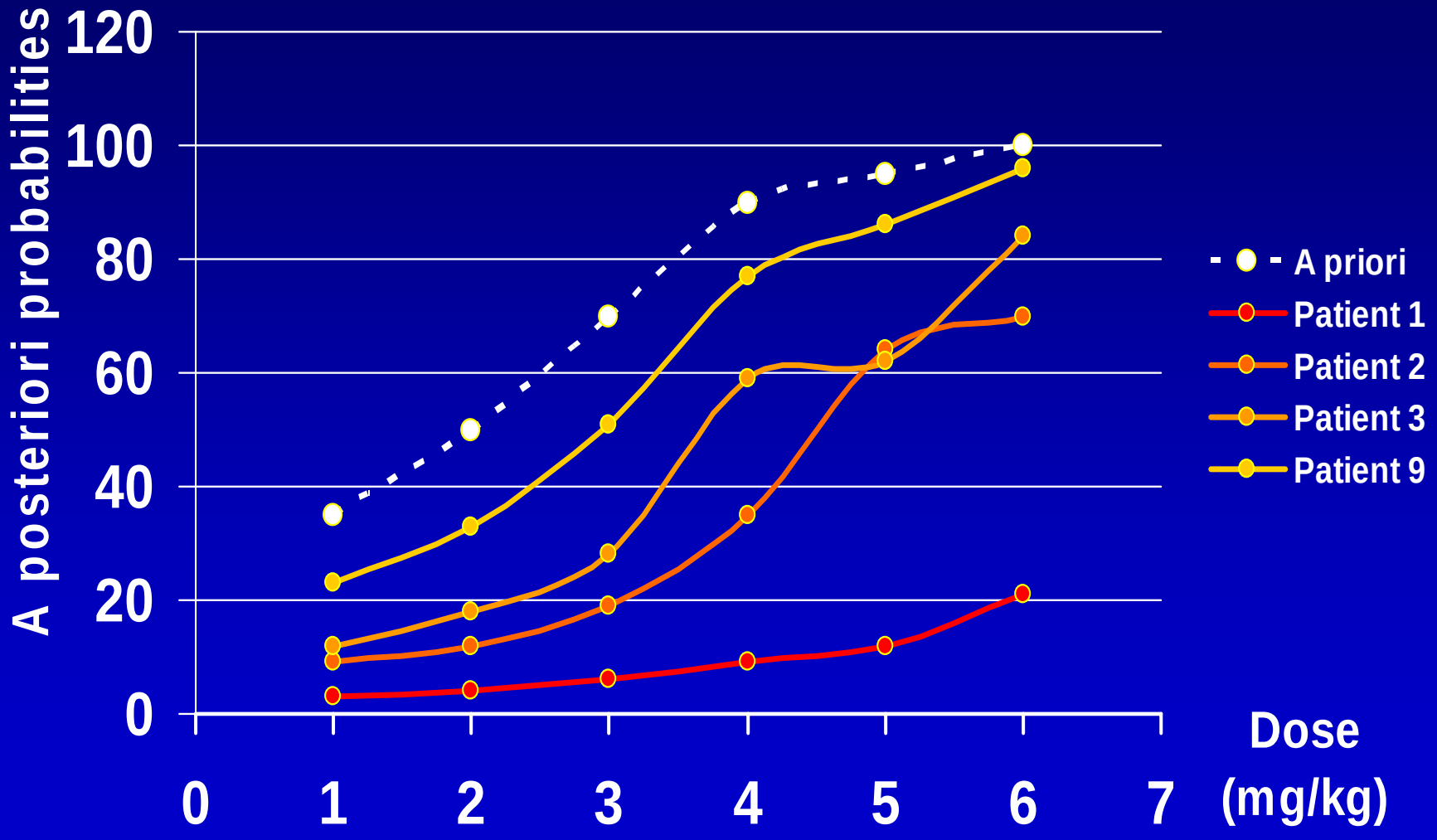
3,00

BAYESIAN SEQUENTIAL APPROACH

A posteriori estimated probabilities of success of the six tested doses, updated after each included patient

Subject	Administered dose (n°)	Clinical response	Dose-range studied					
			1	2	3	4	5	6
			A priori probabilities of success (%)					
			35	50	70	90	95	100
			A posteriori estimated probabilities of success (%)					
1	3	Failure	3	4	6	9	12	21
2	6	Success	9	12	19	35	64	70
3	6	Success	12	18	28	59	62	84
9	6	Success	23	33	51	77	86	96
10	5	Success	25	37	56	81	89	97
13	5	Success	31	45	65	87	93	99
14	4	Success	33	47	67	88	94	99

BAYESIAN SEQUENTIAL APPROACH



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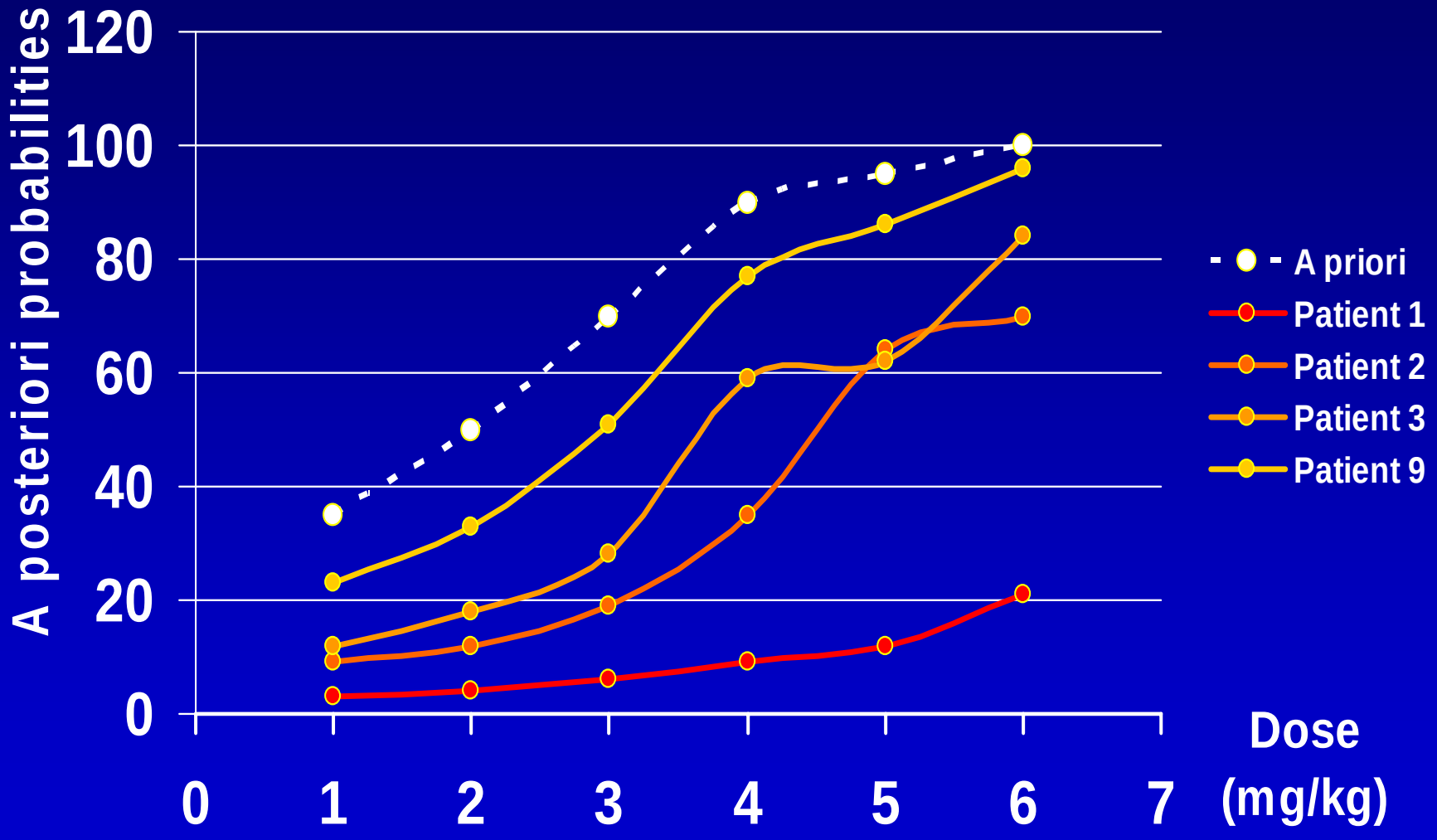
			A priori probabilities of success (%)					
			35	50	70	90	95	100
			A posteriori estimated probabilities of success (%)					
15	4	Success	35	49	69	90	95	99
16	4	Failure	26	38	56	81	89	97
17	5	Success	27	39	58	82	90	98
22	5	Success	31	44	64	87	93	98
23	5	Success	31	45	65	87	93	99
24	4	Success	32	47	67	88	94	99
25	4	Success	33	48	68	89	94	99

BAYESIAN SEQUENTIAL APPROACH

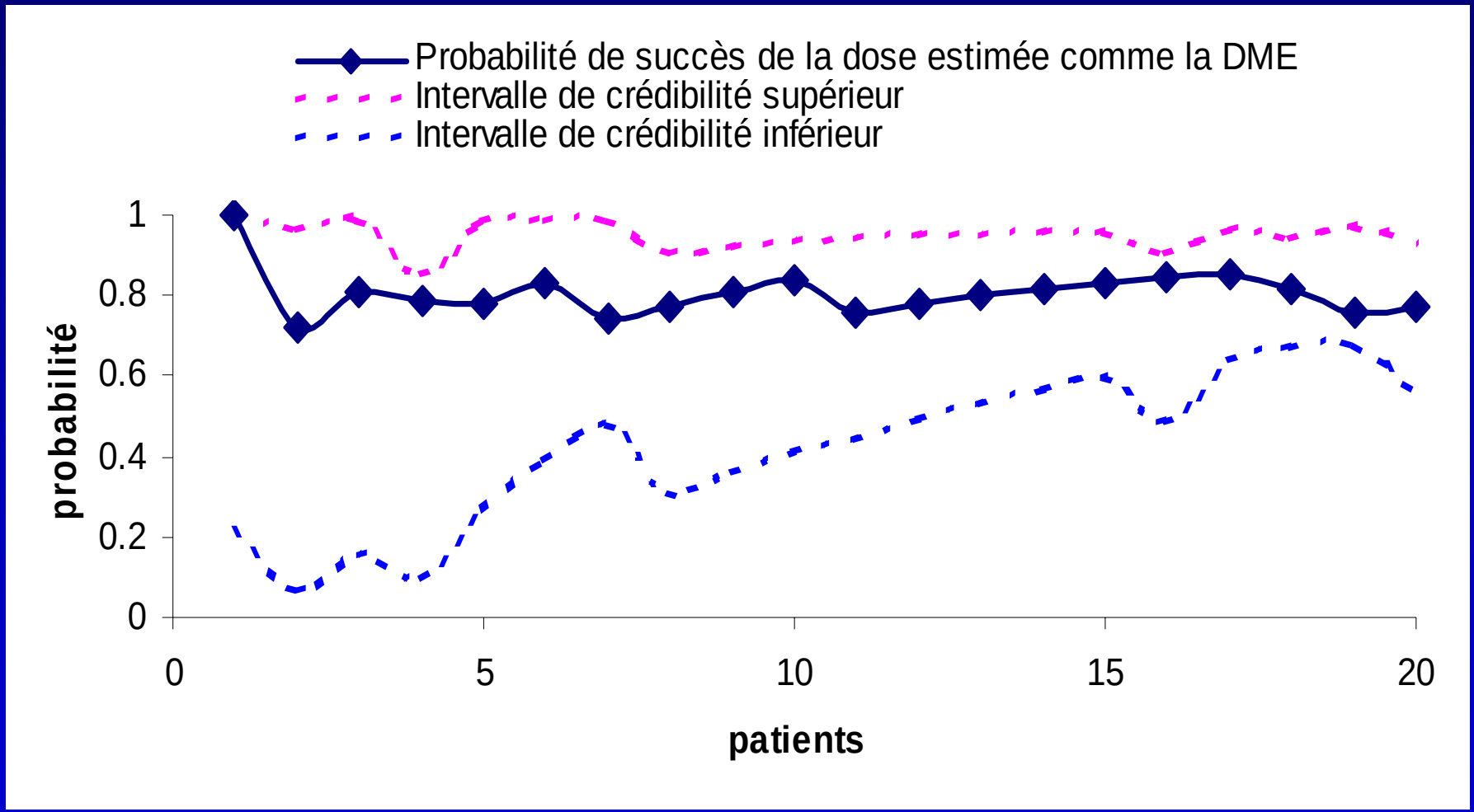


BAYESIAN SEQUENTIAL ANALYSIS
A posteriori estimated probabilities of success
Curative IV NSAID in patent ductus arteriosus

		Dose (mg/kg)			
		5	10	15	20
		A priori estimated probabilities of success (%)			
		0,6	0,8	0,9	0,95
Patients	Dose	*A posteriori* estimated probabilities of success (%)			
1	10	0,481	0,683	0,812	0,891
2	5	0,370	0,544	0,682	0,787
3	15	0,539	0,744	0,861	0,925
4	10	0,512	0,717	0,840	0,915
5	15	0,467	0,667	0,799	0,882
6	15	0,500	0,703	0,829	0,903
7	10	0,519	0,723	0,845	0,914
8	15	0,553	0,757	0,870	0,931
9	10	0,567	0,771	0,880	0,938

BAYESIAN SEQUENTIAL ANALYSIS

A posteriori estimated probability of success of the minimal efficient dose (95 % credibility interval)



BAYESIAN SEQUENTIAL ANALYSIS

- ADVANTAGES
  - NO PLACEBO GROUP REQUIRED
  - ETHICS
  - LIMITED NUMBER OF PATIENTS
- FLAWS
  - QUALITATIVE PARAMETER
  - RAPID EVALUATION OF RESPONSE
  - ORGANISATION

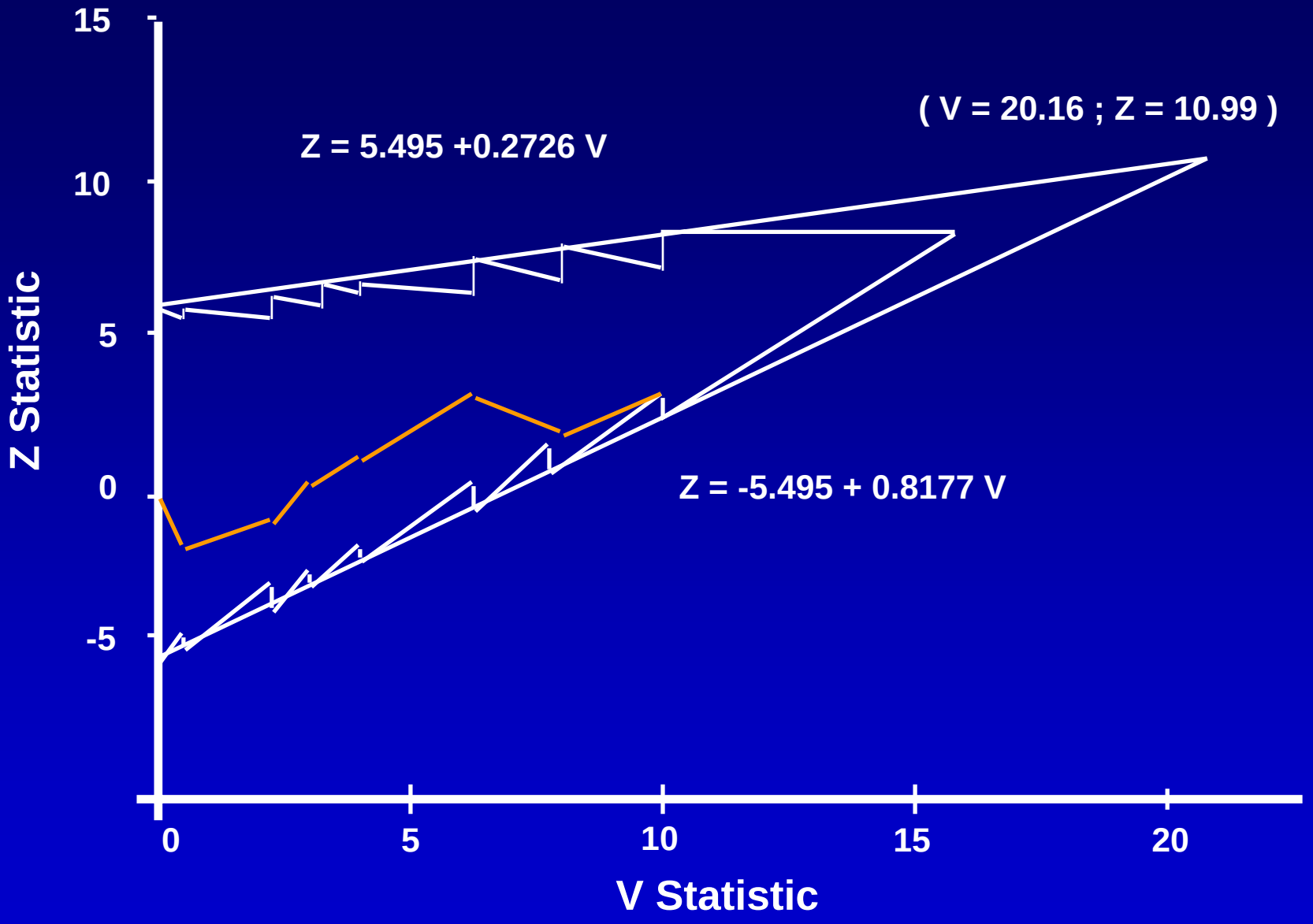
2 - EFFICACY STUDIES IN NEONATES (PHASE III)

POTENTIAL INTEREST IN METHODS THAT MAY LIMIT THE NUMBER OF PATIENTS TO BE RECRUITED

1- POTENTIAL INTEREST OF SEQUENTIAL METHODS (TRIANGULAR TEST)

2- RESPONDER PATIENT POPULATION ENRICHMENT - WITHDRAWAL

METOCLOPRAMIDE IN GASTROESOPHAGEAL REFLUX



TRIANGULAR TEST AND SAMPLE PATH

Bellissant E. et al.,Clin.Pharmacol. Ther.,1997,61,377-384

RECRUITMENT HAS TO BE FACILITATED

INNOVATIVE METHODOLOGICAL APPROACHES

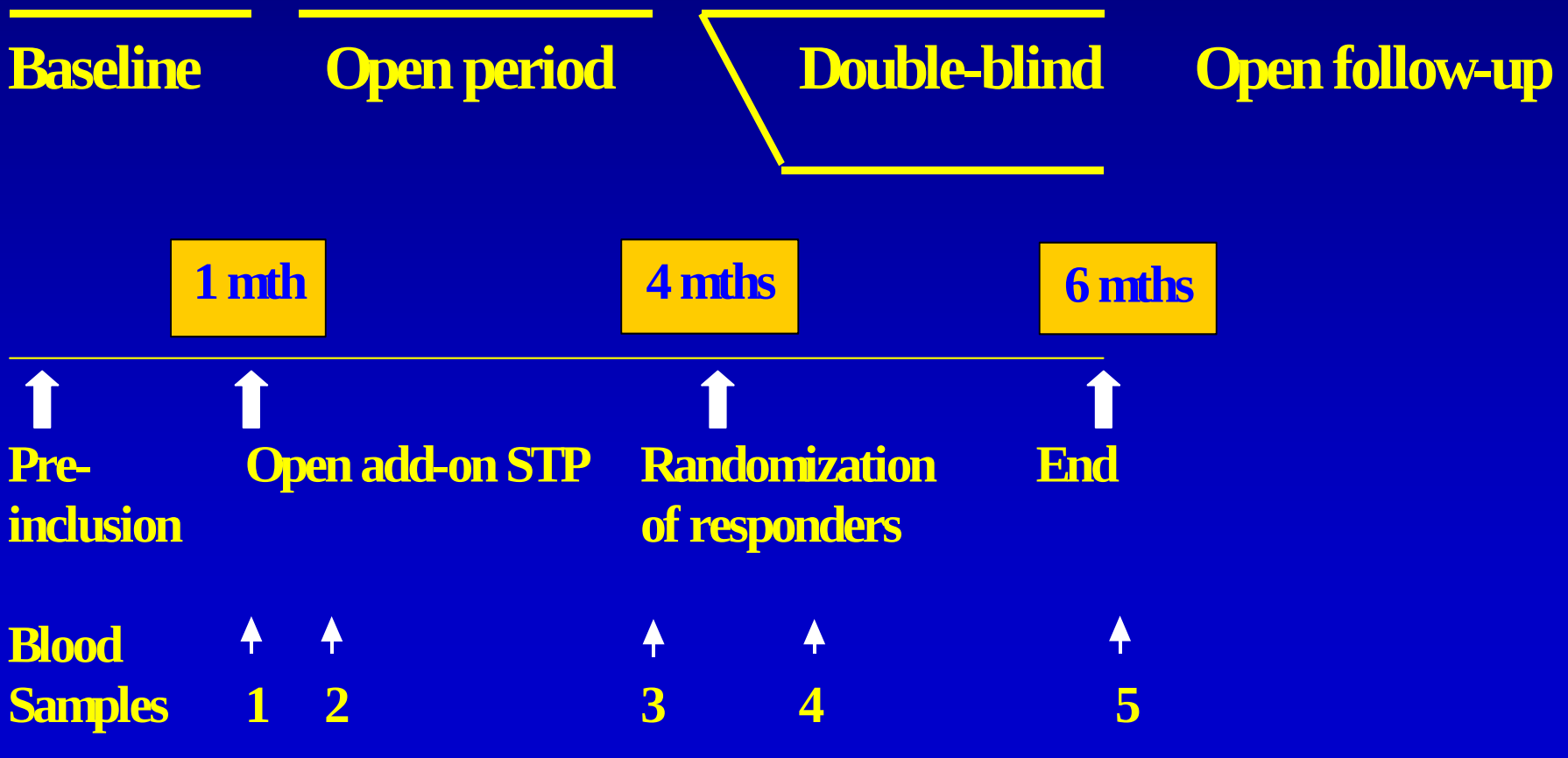
➔ limit the number of patients

- Sequential approaches
  - dose-finding studies (phase II)
  - comparative trials (phase III)

- Enrichment methods (✳)(↘ variability, ↗ stat power)
  - enrichment in responders
  - withdrawal in the placebo group

RESPONDER POPULATION ENRICHMENT - WITHDRAWAL PLACEBO CONTROLLED TRIAL

Stiripentol in partial epilepsy in children



NEONATES ARE DIFFERENT

AND CLINICAL STUDIES ARE MORE DIFFICULT TO PERFORM

1/ invasiness is a limiting factor and has to be restricted as much as possible

2/ the recruitment is more difficult than in adults

3) appropriate tools have to be developped for the measurement of drug effect

APPROPRIATE TOOLS HAVE TO BE DEVELOPPED

FOR THE MEASUREMENT OF DRUG EFFECT

NEONATES DO NOT EXPRESS

THEIR DISTRESS

THE SAME WAY AS ADULTS

APPROPRIATE TOOLS HAVE TO BE USED / DEVELOPPED

FOR THE MEASUREMENT OF DRUG EFFECT

1/ **DEVELOPMENT OF SCALES (*)**

- PAIN
- SEDATION

2/ **DEVELOPMENT OF NEW END-POINTS AND SURROGATE MARKERS (*)**

- CLINICAL
- BIOLOGICAL

ASSESSMENT OF THE EFFECT OF DRUGS

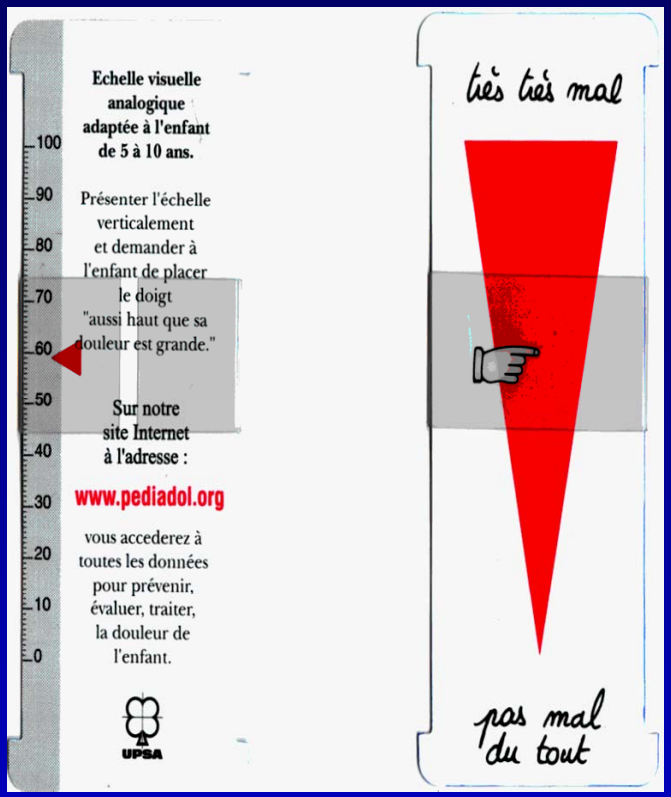
I - END-POINTS ADAPTED TO PATIENT 'S AGE

- ASSESSMENT OF PAIN

I - SELF-EVALUATION (>6 YEARS)

1) VISUAL ANALOGUE SCALE 4 - 6 YEARS
2) FACE SCALES 4 - 6 YEARS
3) « POKER CHIP » 4 - 6 YEARS

VISUAL ANALOGUE SCALES (VAS)



TOKENS

PAIN SCALES FPS-R

PAIN EVALUATION IN CHILDREN

II- HETERO-EVALUATION (<6 YEARS)

BEHAVIORAL MEASURES OF PAIN BIRTH – 6 YEARS

1/ POST-OPERATIVE PAIN :

- OBJECTIVE PAIN SCALE (OPS) > 2 MONTHS
- CHILDREN ’S HOSPITAL OF EASTERN ONTARIO PAIN SCALE (CHEOPS) : 1- 6 YEARS
- AMIEL-TISON SCALE : 1 MONTH - 3 YEARS

PAIN EVALUATION IN CHILDREN

II- HETERO-EVALUATION (<6 YEARS)

2/ OTHER ACUTE PAIN :

- NEONATAL FACIAL CODING SYSTEM (NFCS) : 0-18 MONTHS
- CHEOPS

3/ LONG - LASTING ACUTE PAIN :

- DEGR SCALE : 2-6 YEARS
- EDIN SCALE : PREMATURE NEONATES

APPROPRIATE TOOLS HAVE TO BE USED / DEVELOPPED

FOR THE MEASUREMENT OF DRUG EFFECT

FOR UNPREDICTED LATE TOXICITY

ON DEVELOPING ORGANS

➔POST MARKETING STUDIES

ARE OF PARTICULAR INTEREST IN NEONATES

POST MARKETING STUDIES

THERAPEUTIC CATASTROPHIES OF THE PAST :

- PHOCOMELIA : THALIDOMIDE
- ADENOCARDINOMA OF THE VAGINA : DIETHYLSTILBOESTROL
- RETROLENTAL FIBROPLASIA : O2
- BRONCHOPULMONARY DYSPLASIA : MECANICAL VENTILATION

MORE RECENT FINDINGS :

- DELAYED CARDIAC TOXICITY OF ANTHRACYCLINS
- DELAYED TESTICULAR TOXICITY OF HODGKIN-MOP CHEMOTHERAPY
- DELAYED OVARIAN TOXICITY OF HIGH DOSES BUSULFAN BEFORE BMT

POST MARKETING STUDIES

LONG TERM PROSPECTIVE FOLLOW UP STUDIES

- GROWTH AND MATURATION
- REPRODUCTIVE CAPACITY
- ABILITY TO LEARN ; COGNITIVE SKILLS
- EMOTIONALITY AND PSYCHOLOGICAL DEVELOPMENT

SIDE EFFECTS THAT OCCUR FAR BEYOND THE PERIOD OF DRUG EXPOSURE

APPROPRIATE METHODOLOGICAL APPROACHES HAVE TO BE USED / DEVELOPPED

FOR THE MEASUREMENT OF DRUG EFFECT

FOR UNPREDICTED LATE TOXICITY

ON DEVELOPING ORGANS

➔CASE-STUDIES NESTED IN COHORT STUDIES

ARE OF PARTICULAR INTEREST IN NEONATES

CONCLUSION (I)

- INNOVATIVE METHODOLOGIES ARE POTENTIAL USEFUL TOOLS TO FACILITATE DRUG EVALUATION IN NEONATES WHENEVER NECESSARY

- ARE NOT EXPECTED TO REPLACE CLASSICAL APPROACHES

- THE LIMITS OF VALIDITY OF THESE APPROACHES ARE TO EVALUATED FOR AN APPROPRIATE LEVEL OF PROOF OF EFFICACY AND SAFETY

CONCLUSION (II)

-DUE TO THE CONSTRAINTS OF DRUG EVALUATION IN NEONATES NEONATAL CLINICAL PHARMACOLOGY REPRESENTS A

CHALLENGING AREA FOR METHODOLOGICAL CREATIVITY

WHICH MAY ULTIMATELY BENEFIT TO OTHERS AREA OF CLINICAL PHARMACOLOGY INCLUDING ADULTS