
“Children and drugs” –
*About clinical trials in
children*

Ornella Della Casa Alberighi, MD
Basel, Switzerland

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Unapproved Uses of Approved Drugs

- Ä Pediatric disclaimers stating that safety and efficacy of a specified drug has not been studied in children frequently included in prescription information
- Ä Drugs with a pediatric disclaimer used in practice in an off label manner when given to children,
- Äand the safety responsibility is thus transferred to the prescribing physician
- Ä Three quarters of all medications marketed today do not carry FDA approved labelling for use in neonates, infants, children and adolescents

Introduction of several new Laws and Regulations in the late 1990s

- Ä 1997 - US Pediatric Exclusivity Provision Act (prolonged until 2007) enabled the FDA to create powerful incentives for pediatric research on patented drugs
- Ä 1997 - The European Council pediatric clinical trial directives comparable to those of the US published for consultation by the EU commission
- Ä 1998 - Pediatric Rule enabled the FDA to require studies if the drug in question is likely to be used in a substantial number of pediatric patients
- Ä 2000 - ICH guideline on pediatric clinical trials finalized
- Ä Since 2001, a pediatric plan has to be presented to FDA for all NCEs for which a pharmaceutical company requests an investigational new drug application
- Ä Incentives to generate clinical data on older drugs are created in the US with the "Pediatric Priority List"

Guidelines and Directives for Pediatric Clinical Trials

- Ä Ethical Principles for Medical Research Involving Human Subjects (Declaration of Helsinki as revised in Edinburgh, Scotland, October 2000): <http://www.wma.net>
- Ä ICH guidelines: <http://www.ifpma.org/ich1.html>
- Ä FDA: <http://www.fda.gov/cder/pediatric/index.htm>
- Ä EMEA: <http://www.emea.eu.int/>

Pediatric Drug Labeling: Improving the Safety and Efficacy of Pediatric Therapies

- Ä Between July 1998 and April 2002, the FDA requested studies on 242 drugs, of which 53 were granted exclusivity
- Ä As of January 2003, 49 drugs have new labels
- Ä The FDA Modernization Act has stimulated pediatric clinical studies resulting in improved understanding of the pharmacokinetics of drugs prescribed in pediatric medicine, important dose changes, and improved safety for children taking certain drugs

JAMA 2003;290:905-11

Characteristics and indications of drug products with significant changes or findings- examples

Drug Product	Drug Class	Indication - Adults	Indication - Ped.	Adverse Events	PK/PD
Midazolam-HCl	Water-sol. benzodiazepine	Sedation, anxiolysis, amnesia	=	Congenital heart disease and pulmonary HT at risk	Start therapy at lower end and titrate up to avoid respiratory distress
Atovaquonet + proguanil HCl	Antimalarials	Prophylaxis and trtm of malaria	=	=	T1/2 shorter than in adults (1-2 d vs 2-3 d)
Etodolac	NSAID	OA and RA	Relief of signs and symptoms of JIA, 6-16 yrs. old	=	Vd and T1/2 different; higher dose per kg basis in younger children (X 2 the lower dose in adults)
Gabapentin	Anti-convulsant	Epilepsy	Adjunctive trtm of partial seizures in > 3 yrs old	Neuropsychiatric - hostility	Higher oral clearance by BW and increased dose needed in 3-5 yrs old

JAMA 2003;290:905-11

Decision about a Pediatric Development and/or Screening Program for a NCE

- É Prevalence of the disease (indication) in the pediatric population
- É Seriousness of the disease
- É Existing alternative treatments with risk and benefit profile
- É Potential unique pediatric indications for the NCE
- É Pediatric-specific endpoints for the indication or need to develop them
- É Age ranges of the population likely to be treated
- É Unique pediatric safety concerns with the NCE
- É Need for development of one or several pediatric formulation(s)
- É Potential for orphaning labeling

Informed Consent, Parental Permission, and Assent in Pediatric Practice

- Ä Parents have to give informed consent for their child to participate in a clinical trial
- Ä The child's wish must be respected – a reasoned refusal by a child to participate has to be accepted
- Ä Points required for valued informed consent:
 - É No financial inducement going beyond coverage of expenses and lost salary should be paid
 - É No pressure should be exerted on the families
 - É The families should be given sufficient time to consider trial participation
 - É All other general rules regarding informed consent

AAP, Committee on bioethics. Pediatrics 1995; 95: 314-317

Vulnerability of the Pediatric Population

- Ä The guidelines emphasize that patient recruitment must be free from inducements to either the parent(s) or the study participant
- Ä Planned reimbursements have to be approved by the responsible ethics committee
- Ä Pediatric studies require more and better trained personnel than adult studies
- Ä See the FDA recommendations 'Additional Safeguards for Children in Clinical Investigations of FDA-Regulated Products':
<http://www.fda.gov/cder/pediatric/index.htm>

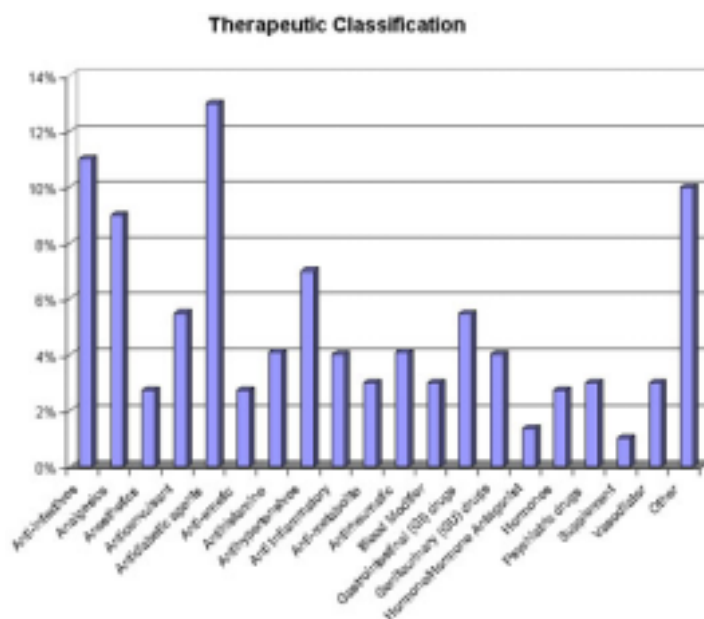
Use of placebo

The AAP guidelines list the following conditions where the use of placebo is ethically acceptable:

- ⌘ When there is no commonly accepted therapy for the condition and the NCE is the first one that may modify the course of the disease
- ⌘ When the commonly used therapy is of questionable efficacy
- ⌘ When the commonly used therapy carries a high frequency of undesirable side effects and the risks may be significantly greater than the benefits
- ⌘ When the placebo is used to identify incidence and severity of undesirable side effects produced by adding a new treatment to an established regimen
- ⌘ When the disease process is characterized by frequent, spontaneous exacerbations and remissions and the efficacy of the therapy has not been demonstrated

AAP, Committee on bioethics. Pediatrics 1995; 95: 314-317

Example of a consortium of Pediatric Centres: The Pediatric Pharmacology Research Units Network



www.ppru.org

Pediatric Clinical Research Networks

- Å **American Pediatric Pharmacology Research Unit Network (PPRU):**
<http://www.ppru.org>
- Å **European Network for Drug Investigation in Children (ENDIC) :**
<http://www.libraphar.co.uk/ppdt/abstracts/Anker.htm>
- Å **Source of information on rare diseases (European): Orphanet**
<http://orphanet.infobiogen.fr/>
- Å **NORD (National Organization for Rare Disorders):** <http://www.rarediseases.org/>
- Å **PRINTO (Pediatric Rheumatology International Network Trial Organization):**
<http://www.printo.it>
- Å **Pediatric Oncology resources (non exhaustive list):**
 - É **Europe:**
 - Å **SFOP:** <http://www.la-sfop.com/sfop/sfop.nsf/homepage>
 - Å **SIOP:** <http://www.siop.nl/welcome.htm>
 - Å **UKCCSG:** <http://www.ukccsg.org/>
 - Å **AIEOP:** <http://www.aieop.org/>
 - Å **GPOH:** <http://kki.charite.de/gpoh/>
 - Å **EORTC:** <http://www.eortc.be/>
 - É **North America:**
 - Å **COG:** <http://www.childrensoncologygroup.org/>
 - Å **NCI Pediatric Branch:** <http://www-dcs.nci.nih.gov/branches/pedonc/index.html>
 - Å **St Jude Hospital:** http://www.stjude.org/newhp/CancerCen_treatment.html

Pediatric Drug Priorities in Middle East and North Africa

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Jordan University Hospital and the
King Hussein Cancer Center
Amman, Jordan
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Age categories in drug testing in children

- Neonates- birth up to one month
- Infants- one month up to 2 years of age
- Children- 2 years up to 12 years
- Adolescents- 12 years up to 16 years
[final rule FR 64242]

The MENA region

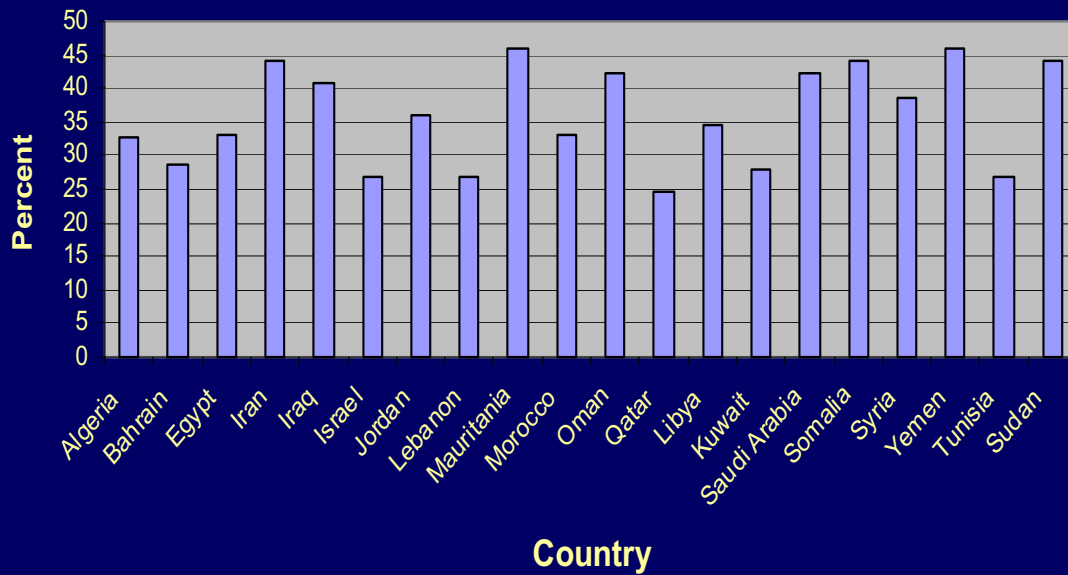
What is the Size of the consumer group in question?

Ratio of the population < 15 years of age

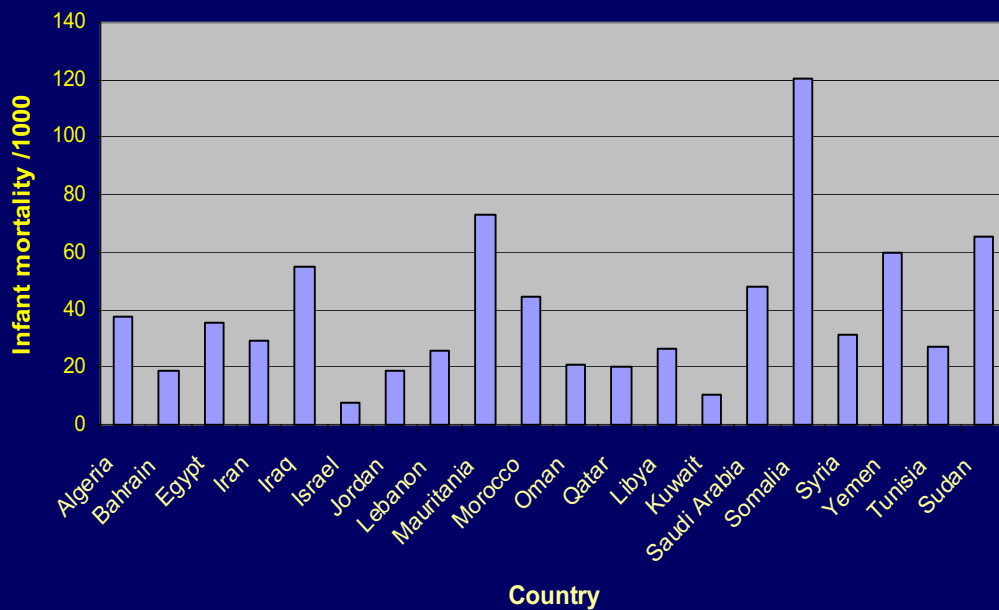
Classification of the economic status of MENA countries

Low income	Low middle income	High middle income	High income
Mauritania	Algeria	Lebanon	Israel
Somalia	Egypt	Libya	Kuwait
Sudan	Iran	Oman	Qatar
Yemen	Iraq	Saudi Arabia	UAE
	Jordan+PNA		
	Morocco		
	Syria		
	Tunis		

Percent of the population < 15 yrs



Infant mortality rate in the MENA countries



Pediatric Drug Priorities in Children in the MENA region

- Drug classes
 - Anti-infective
 - Vaccines
 - Other cardiovascular, neurological and antihypertensive
 - Nutritional supplements
 - Antidiarrheals
 - Ant asthmatics, bronchodilators, inhalers etc
 - Chemotherapeutic agents
 - Other

Pediatric Drug Priorities in Children in the MENA region

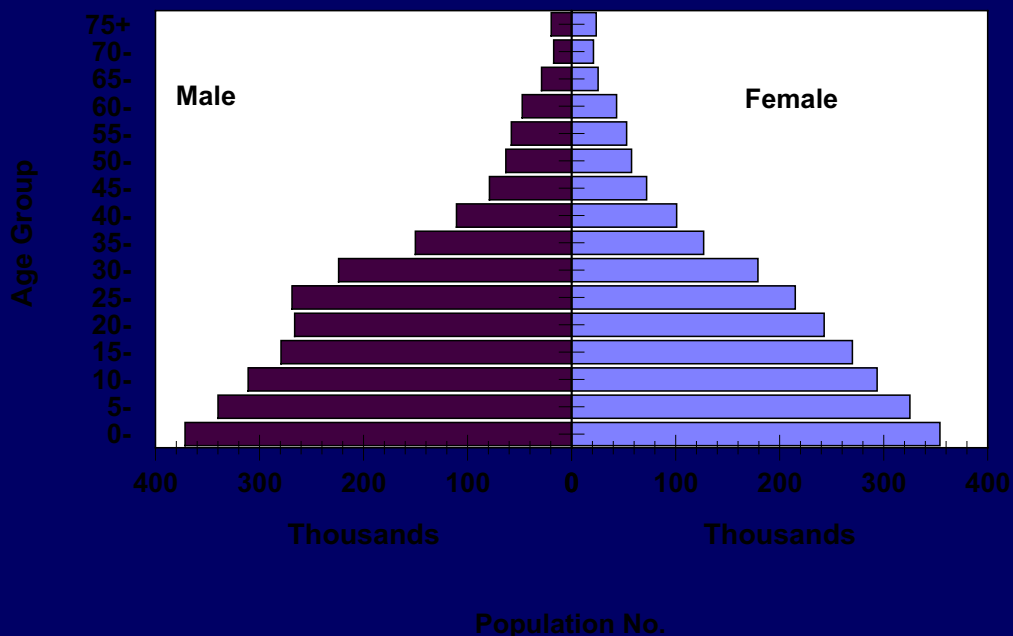
- Issues
 - What are the Most commonly prescribed drugs?
 - How are the existent drugs being used?
 - What are the existent monitoring mechanisms of drug use in the MENA regions?
 - What are the regulations and guidelines about introduction of new drugs?
 - What are the existent regulations and guidelines about the testing of drugs in children in the MENA region?

Pediatric Drug Priorities in Children in the MENA region

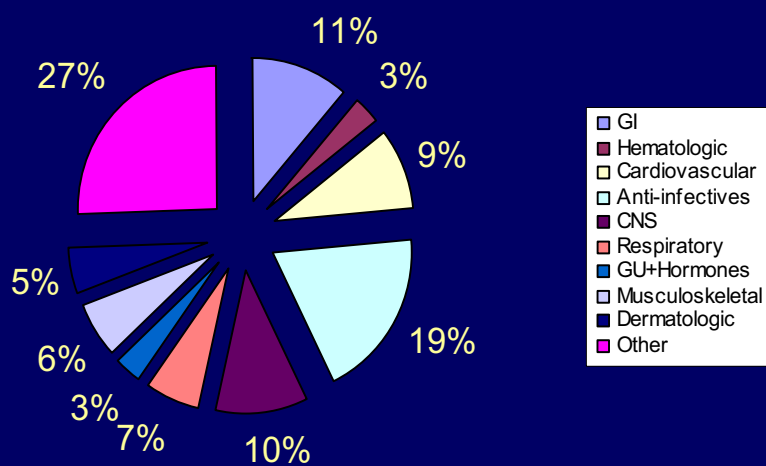
What are the Most commonly prescribed drugs?



Figure (2) Age distribution of Jordan population 2000



Expenditure on Therapeutics, Jordan 2001



Pediatric Drug Priorities in Children in the MENA region

- In Jordan antibiotics are the most widely used drugs in both adults and children
- In children antibiotics constitute more than 30% of the prescribed drugs
- The same is applicable in other countries though actual studies are lacking

Pediatric Drug Priorities in Children in the MENA region

- Increasing drug resistance in hospitals.
- MRSA now > 50% of isolates. (JUH>55%)
- Gm- increasingly resistant. Multiply resistant pseudomonas aeruginosa is seen in some cancer patients. ESBL outbreaks in some ICUs
- Inappropriate (abuse) use of antibiotics.

Pediatric Drug Priorities in Children in the MENA region

- Solution.. Antibiotic stewardship program
 - Educational effort directed at physicians
 - Indication of the drug
 - Proper duration of therapy
 - Usage of proper dose
 - Use the narrowest spectrum possible
 - Guidelines for the treatment of common syndromes so as to minimize inappropriate use

Pediatric Drug Priorities in Children in the MENA region

How are the existent drugs being used?

Pediatric Drug Priorities in Children in the MENA region

- Drug use data is scarce in most MENA countries.
- Cost benefit and cost efficacy of old and newly introduced drugs, vaccines?
- Level of expertise in drug use?
- Number of the drugs in current use not studied specifically for pediatric indication?

Pediatric Drug Priorities in Children in the MENA region

What are the monitoring mechanisms for
drug use?

Pediatric Drug Priorities in Children in the MENA region

- Monitoring mechanisms are thus far wanting.
- Must Monitor adverse events
- Monitor cost benefit and cost efficacy especially in regards to new and expensive agents.

Pediatric Drug Priorities in Children in the MENA region

- Solution
 - Introduce effective mechanisms to monitor drug use.
 - Awareness campaign to increase reporting of adverse events and evaluate performance of drugs.
 - Encourage and Perform studies about already licensed drugs which are currently being used in children without the proper labeling for that indication.

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What are the regulations and guidelines about
introduction of new drugs?



Introduction of new already licensed drugs in Jordan

- Must provide evidence of use in specified disease indication.
- Licensed drugs must be used in country of origin for the same indication.
- Drugs are tested locally for chemical composition and specification.
- Rely heavily on regulatory agencies from country of origin, FDA etc in order to license drug use in Jordan.
- Pediatric use decided by treating physician.
- Similar guidelines are also used in other countries

What are the existent regulations and guidelines about the **testing** of new drugs in adults/children in the MENA region which have not yet been licensed?

Thus far not well advanced

Jordan Mosaic from Madaba



The Jordan Guidelines for New not yet licensed Drugs

- First published in January 2nd 2001
- Not approved in the final form
- NO pediatric component

The Jordan Guidelines for Drug Trials

- Drug trials are divided into two groups
 - Therapeutic clinical trials
These are clinical studies conducted on sick patients.
 - Non therapeutic trials
These are conducted on normal volunteers with the aim of studying pharmacokinetics , bioavailability

The Jordan Guidelines for Drug Trials

- Studies cannot be conducted without obtaining the necessary license to do so after approval of the therapeutics committee of the ministry of health and the minister of health

The Jordan Guidelines for Drug Trials

- Drug trials have to be conducted in hospitals that are equipped to handle emergencies and that have a licensed medical laboratory
- Written Informed consent must be obtained before any drug trials are conducted.
- A committee [IRB] which is composed of at least 5 members and includes both males and females, and has a representative of the civil society and a legal advisor as well as experts.

The Jordan Guidelines for Drug Trials

- IRBs must approve trials on humans using already licensed drugs
- The MINISTER of health must approve trials conducted on humans if the drug is not yet licensed.
- The MOH higher committee must approve the IRBs

The Jordan Guidelines for Drug Trials

- Penalty including imprisonment or payment is mandated if the guidelines, the supervisory functions or lack of reporting of adverse events has committed by an individual investigator.
- Penalty to Institutions that are not adherent to the guidelines is monetary.

Drug usage in children

- Children are considered “therapeutic orphans” when it comes to drug development.
- Less than 25% of licensed drugs include pediatric information in the USA.
- Thus far in Jordan we allow only the use of already licensed compounds from original manufacturer.
- Regulations about conducting drug trials are still not a law in Jordan

Issues in Drug Trials

- Must define better the functions of IRBs.
- ?? Credentialing of IRB members.
- ?? Possibilities of Conflict of interest issues must be raised.
- Balance between patient rights and genuine investigation into useful drug modalities must be addressed.
- Some diseases are more prevalent in our area
Our patients should be the primary targets of such trials if we are to be the beneficiaries.

Diseases that are relatively more common in some of the MENA region countries

- Hepatitis C
- Rotavirus
- Hepatitis b
- Diarrhoeal disease including parasites.
- Respiratory illness.
- Neonatal sepsis.
- Tuberculosis.
- Malaria
- ? Genetic diseases

Conclusions

- Drug therapy in the MENA region should be more thoroughly studied
- Cost efficacy and cost benefit analysis should be applied in order to define the role of new and more expensive agents.
- Regulations and guidelines about drug trials must be introduced in order to allow the study of drugs in our population.

Conclusions

- Research capacity, oversight capacity with review of processes and bioethical components should be addressed before embarking on drug trials in our region.
- Serious consideration to investigate drugs that are more prevalent in our area should be addressed.
- Pediatric component should be studied on a selective basis. Special guidelines should be set in children even if guidelines for adults were adopted.

Oryx at the Shomari reserve





TESTING NEW AND OLD DRUGS IN CHILDREN: THE PRINTO PERSPECTIVE

Nicola Ruperto, MD, MPH

IRCCS G. Gaslini, Genova, ITALY for the

Paediatric **R**heumatology **I**nternational **T**rials **O**rganisation
PRINTO



Outline of the talk

- Introduction about the difficulties in performing clinical trials in children
- The example of the “**P**aediatric **R**heumatology **I**nternational **T**rials **O**rganisation” (**PRINTO**)



Pediatric drugs

- ⇒ Drug safety and efficacy are seldom evaluated in children
- ⇒ More than 50% of all drugs prescribed in pediatric practice (and up to 90% in some pediatric subspecialties) are used either “unlicensed” or “off label”



The need of controlled trials in children

- ⇒ Children are not “small adults”: the pharmacokinetic and the toxicity of a drug may differ considerably
- ⇒ Childhood diseases may be different from their adult counterpart (e.g. chronic arthritis)



Summary of problems for trials

- ⇒ Rarity of the paediatric diseases
- ⇒ Financial problems
- ⇒ Other specific problems:
 - Methods to assess the outcome
 - Paediatric formulations
 - Ethical problems

Ruperto & Martini for PRINTO: BMJ 2000; 320: 1210-1

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Rarity of the paediatric diseases

- ⇒ most of the paediatric diseases are rare diseases (so called orphan diseases)

Possible solution....

....need of large networks to collect in a short period of time an adequate number of patients with reliable scientific information



Financial problems

- ⇒ Small market, and therefore small interest because of small revenues for the pharmaceutical industry that demand a relatively short enrolment period for their studies

Possible solution....

- ⇒ Large networks
- ⇒ Other source of funding: ex. European Union
- ⇒ Legislative intervention: FDA, EMEA,



European Commission

Better Medicines for Children

Proposed regulatory actions on paediatric medicinal products

(February 28, 2002)



....European Commission

- ⇒ The EC wishes that the EMEA will adopt measures to address the lack of suitably adapted medicinal products for children including the "pediatric rule"
- ⇒ The EC also wishes the creation of a Pan-European network of clinical excellence for performance of paediatric studies

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Other specific paediatric problems

- ⇒ Specific methods to assess the outcome (what is disease activity, what is damage, how to define response to therapy)
- ⇒ Paediatric formulations: liquid formulation, single dose
- ⇒ Ethical problems:
 - Problem of consent (by proxy, by the child?)
 - use of active drugs instead of placebo



Pediatric Rheumatic diseases (PRD)

- ⇒ Juvenile Idiopathic Arthritis (JIA)
- ⇒ Juvenile Systemic Lupus Erythematosus
- ⇒ Juvenile Dermatomyositis
- ⇒ Juvenile Scleroderma and juvenile Systemic Sclerosis
- ⇒etc.



First controlled studies in JIA

- ⇒ Ineffective:
 - Penicillamine and hydroxychloroquine:
 - » *Brewer et al. N Engl J Med*
 - Auranofin
 - » *Giannini et al. Arthritis Rheum 1990*
- ⇒ Effective:
 - Methotrexate in low dose
 - » *Giannini et al: N Engl J Med 1992*

Studies conducted in USA-USSR by the Pediatric Rheumatology Collaborative Study Group (PRCSG)



PRD common problems

- ⇒ PRD are rare conditions with
 - substantial morbidity
 - consequence on quality of life (pain still present in 30% of the JIA patients after 15 years)
 - monetary costs
 - Current available drugs, and new drugs, used in new dosages, new route of administration
 - **Safety and efficacy data small and unreliable**

Ruperto et al J Rheumatol, 1997

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Paediatric **R**heumatology **I**nternational **T**rials
Organisation (**PRINTO**)

Italy, May 1996

PRINTO purposes

- General aims:
 - “...to foster, facilitate, and conduct high quality research in the field of paediatric rheumatology...” from the PRINTO bylaws
- Specific aims:
 - To find effective new treatment for childhood rheumatic diseases



www.printo.it



PRINTO Organisation Chart



PRINTO Membership

- ⇒ National co-ordinators: 44 countries
- ⇒ Centres: 150
- ⇒ Members: 217
- ⇒ Mailing list: 600 physicians

PRINTO National Co-ordinators



Argentina C De Cunto	Georgia K Pagava	Poland AM Romicka
Australia KJ Murray	Germany HI Huppertz	Portugal JA Melo-Gomes
Austria C Huemer	Greece F Kanakoudi-T	Russia I Nikishina
Belgium R Joos	Hungary Z Balogh	Saudi Arabia S AlMayouf
Brasil C Machado	India A. Aggarwal	Slovakia R Vesely
Bulgaria D Mihaylova	Israel Y Uziel	Slovenia T Avcin
Chile M Miranda	Italy A Martini	South Africa M Roux
Costa Rica O Porras	Korea South SC Bae	Spain J De Inocencio
Croatia M Harjacek	Latvia I Rumba	Sweden B Andersson-G
Cuba C Coto Hermosila	Lithuania V. Panaviene	Switzerland M Hofer
Czech Rep P Dolezalova	Luxembourg Berthet F	Turkey H Ozdogan
Denmark S Nielsen	Mexico R Burgos-Vargas	Tunisia R El Menza
Finland P Lahdenne	the Netherlands W Kuis	Un Kingdom P Woo
France AM Prieur	New Zealand S Rudge	Yugoslavia G Susic
Egypt Y El Miedany	Norway B Flato	

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Issues to be addressed:

- ⇒ *provide facilities for clinical trials*
- ⇒ provide specific tools to assess drug efficacy
- ⇒ study already marketed drugs
- ⇒ study new drugs



International Coordinating Center

- ⇒ Located in Genoa c/o the IRCCS G. Gaslini
- ⇒ Equipped with knowledge and facilities (6 people) to conceive, conduct and analyze clinical trials
- ⇒ Financed by the European Union (4 grants as of today)

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Issues to be addressed:

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- ⇒ study new drugs



PRCSG-PRINTO criteria

⇒ ACR 30 Pediatric criteria

Giannini EH, Ruperto N, Ravelli A, Lovell DJ, Martini A.
Arthritis Rheum. 40; 1202-9: 1997

⇒ Accepted by the FDA for all regulatory trials in JIA



ACR 30 pediatric criteria

JIA Core set variables:

- 1) physician global assessment of disease activity
- 2) parent/patient assessment of overall well-being
- 3) functional ability
- 4) number of joints with active arthritis
- 5) number of joints with limited range of motion
- 6) ESR or C reactive protein

At least 30% improvement from baseline in 3 of any 6 variables, with no more than one of the remaining variables worsening by >30%



Problem left

- ⇒ Validation of the core set in a clinical trial
- ⇒ Need of standardized and internationally available measures for functional assessment in JIA (and health related quality of life assessment for the other PRD)

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I PRINTO EU grant (BMH4-983531)

Quality of life project in JIA: cross-cultural adaptation and validation of 2 health related quality of life instruments:

- The Childhood Health Assessment Questionnaire (CHAQ)
- The Child Health Questionnaire (CHQ)



- The project started with the 12 countries founders of PRINTO (and therefore 12 languages) and.....

CHAQ and CHQ

Translation and cross-cultural adaptation of CHAQ and CHQ in 32 languages with 6,443 patients collected

(Argentina, Austria, Belgium, Brasil, Bulgaria, Chile, Croatia, Czech Republic, Denmark, Finland, France, Georgia, Germany, Greece, Hungary, Israel, Italy, Korea, Latvia, Mexico, Netherlands, Norway, Portugal, Poland, Russia, Slovakia, Spain, Sweden, Switzerland, Turkey, United Kingdom, Yugoslavia)





What did we learn?

- ⇒ Large networks need
 - to take into account the languages barriers (possible solution: PRINTO national coordinators) and
 - To take into account the different socio-economic realities of the participating countries

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What about...

- ⇒ Juvenile systemic lupus erythematosus (JSLE)

- ⇒ Juvenile dermatomyositis (JDM)



II PRINTO EU GRANT (QLG1-2000-00514)

Disease activity and disease damage core
sets of outcome measures and definition
of improvement for JSLE and JDM

Ruperto et al Rheumatology 2003



Enrollment

- ⇒ **852 patients collected from 42 countries:**
 - JSLE 557 patients
 - JDM 295 patients

- ⇒ **2 consensus conferences**



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Issues to be addressed:

- ⇒ provide facilities for clinical trials
- ⇒ provide specific tools to assess drug efficacy
- ⇒ study already marketed drugs
- ⇒ study new drugs

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MTX in JIA

Giannini EH, Brewer EJ, Kuzmina N et al: N Engl J Med 1992,29,1043-9

A randomized double blind placebo controlled trial shows the efficacy of low dose MTX (10 mg/m²) once a week in JIA

But what about children who do not respond to this dosage?.....



..the need of evidence base medicine

- ⇒ Anecdotal report on higher dose MTX
- ⇒ 1996: International survey to select the most important trial(s) to be performed
(Lovell, Prieur, Woo, Martini. Arthritis & Rheum 1996)
- ⇒ 1998: European Union grant no BMH4 983531 CA



I PRINTO EU grant (BMH4-983531)

To assess the efficacy and safety of parenteral MTX in **INTERMEDIATE** versus **HIGHER** doses in children with polyarticular course JIA who failed on **standard dose** MTX

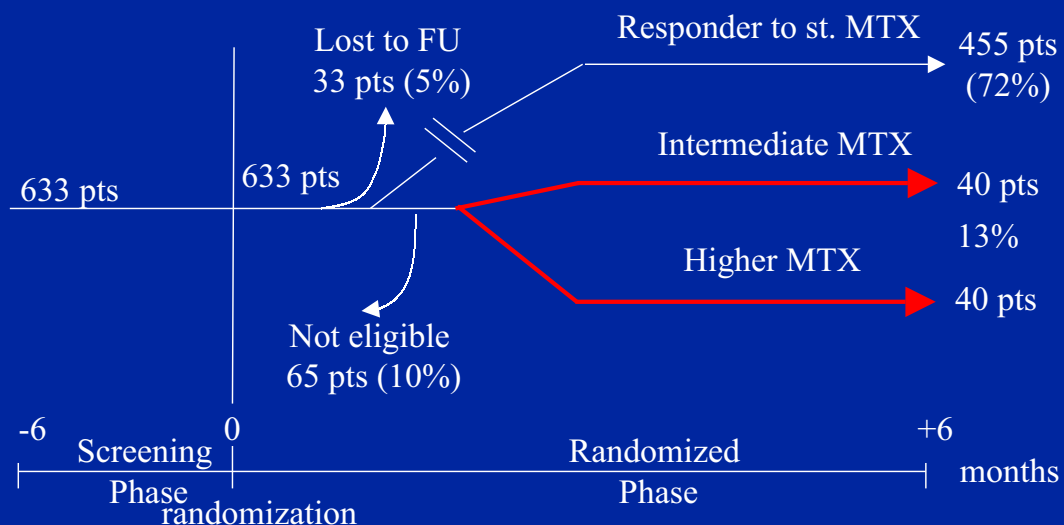


Study design

- ⇒ 2 phases:
 - Screening (6 months duration)
 - Randomized (6 months duration)
- ⇒ Randomized, open label, multinational
- ⇒ “Standard of care” trial:
 - insurance, medication, visits, and laboratory paid by the usual method of cost reimbursement in each country
 - essential data collection via fax (data from routine follow-up)

Flow diagram

Ethics Committee approval: 63 centres in 20 countries (4 refused)





What did we learn?

- ⇒ **Scientifically:** The plateau of efficacy of MTX in JIA patients is reached with the parenteral administration of intermediate dose (higher doses not helpful)...EVIDENCE BASED MEDICINE!!
- ⇒ **Ethically:** Ethics committees and national regulatory agencies refused trial in children (4 countries denied participation)
- ⇒ **Politically:** Big trials can be done **WITHOUT** the help of pharmaceutical companies



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Issues to be addressed:

- ⇒ provide facilities for clinical trials
- ⇒ provide specific tools to assess drug efficacy
- ⇒ study already marketed drugs
- ⇒ **study new drugs**



...after the FDA paediatric rule

- ⇒ Biologic agents
 - Etanercept
 - Infliximab
 - Adalimumab
 - CTL4Ig
- ⇒ 3 trials with Non-steroidal anti inflammatory drugs
- ⇒ 1 phase IV study on cyclosporine
- ⇒ More to come.....

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What did we learn?

- ⇒ Before the FDA paediatric rule industries were not interested in performing drug studies in children



What PRINTO offer to sponsors?

- Design of the study
- Design of the protocol
- Design of the case report forms
- Selection of centres
- Data collection
- Monitoring of side effects
- Data analysis
- Data report



III PRINTO EU grant (2001/RD/10003)

European information network on PRD
directed to families

Web site: up to date information about

- PRD (consensus statements for families)
- Map of paediatric rheumatology centres
- Map of associations to help families

PROJECT IN COLLABORATION WITH PRES

www.pediatric-rheumatology.printo.it



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IV PRINTO EU grant (II-0246 2003/2006)

Paediatric Rheumatology INternational Trials
Organisation (PRINTO) fellowship

- 24 scholarships available for Latin American recipients to come to Europe
- 4 scholarships available for European recipients to go to Latin America
- Participating countries
 - » Latin America: Argentina, Brasil, Chile, Costa Rica, Cuba and Mexico.
 - » Europe: Italy, France, Netherlands, Sweden, United Kingdom



How to apply for a clinical trial

- Request to the PRINTO Chairman
 - abstract of the project
 - preliminary protocol
 - source of funding
- Protocol discussion by the PRINTO Advisory Council
- Feasibility survey among potential participants
- Trial implementation



PRINTO results

- May 1996: foundation in Pavia, Italy
- August 1996: MTX protocol discussion
- June 1997: first grant from the EU
- March 1999: second grant from the EU
- June 2001: third grant from the EU
- February 2003: fourth grant from the EU
- Joint collaboration with PRC SG, pharmaceutical industries



Conclusions

- ⇒ What we need to study drugs in children?
 - Large international networks
 - Appropriate instruments to evaluate drug efficacy
 - Adequate legislation

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Pediatric Rule

- ⇒ FDA final rule 1998 (effective December 2000)
 - Paediatric studies required for new & marketed drugs and biological products
 - Drug studies for which there may be a “meaningful therapeutic benefit” or substantial number of patients
 - Six month extension of marketing exclusivity for completing paediatric studies requested by FDA