

Report of Health Coalition Initiative/Action Research Workshop held on Tuesday 30th October 2001 at Wesley's Chapel, City Road, London EC1

**PAEDIATRIC PRESCRIBING
Children are not Little Adults**

There were over forty people from voluntary health and consumer organisations, the Department of Health, the pharmaceutical industry, professional organisations, parents, clinicians and researchers, attending this workshop.

This workshop was the first one where the HCI had collaborated with a member organisation: Action Research, a leading medical research charity which is enjoying its 50th anniversary in 2002 and is leading a campaign to raise awareness of the issue.

John Grounds, director of campaigns and communications at Action Research, chaired the event and opened the Workshop by introducing Action Research and its campaign. In his presentation, **A charity raising awareness and committed to research**, he highlighted the challenges, given the ethical, financial and complex issues involved.

John said that the campaign was gathering interest and support from various parties including researchers, MPs, politicians, the media and the Consumers' Association. He went on to explain that a partnership approach is needed to drive the issue forward and urged attendees to add their name to a statement already agreed by the speakers. (see end of report)

For 50 years Action Research has been funding research at the cutting edge of medicine and some of its major successes have focused on polio, rubella, folic acid, ultrasound and the hip replacement. As many as 150 projects are funded each year, which run from one to three years. They include premature birth, pregnancy complications, childhood diseases and disability, and conditions of ageing.

Action Research decided to launch the campaign, Drug Treatment in Children: Children Are Not Little Adults, mainly because it has a good track record of research in this area, and the issue has received little awareness.

Discussion points:

- *Pharmaceutical companies do not/not required to test specifically for children
- *40% of drugs given to children not specifically licensed for that purpose
- *65% of drugs used in treating new-born babies are unlicensed or licensed only for adults

John admitted that the issues are complex. But added that the main objectives for the Action Research campaign included:

- *Public, media and political awareness
- *Establish level of support within all interested parties

- *Guidelines on communication to doctors
- *Clearer prescription information
- *Review of USA and European initiatives
- *Requirement for appropriate testing

Parent **Art McConnell** spoke from the heart during the next presentation **Losing Lexie**. After explaining that his story was a 'very, very painful one', he went on to describe how Lexie was hit in the left eye by a ball during the school's sports day. A month after the incident Lexie was complaining of 'blurred' vision and she was referred to a consultant who prescribed an unusually high course of steroids (80mg a day) and antibiotics for an inflammatory condition in the left eye.

Within 24 hours, Lexie's face ballooned and over the coming weeks she developed terrible stomach pains and a rash. She was admitted to hospital where she was told she had chicken pox – caused by her immune system being destroyed by the medication.

Art said his daughter's condition worsened, and 'I could see she was dying'. Lexie lost consciousness and passed away. The end of Lexie's life was just the beginning of a long, painful battle for justice and Art concluded his presentation by saying his sad story was 'a clear illustration of why we are here today'.

Professor Al Aynsley-Green the National Director of Children's Healthcare Services used his presentation ***The Use of Medicines in Childhood - Seizing the Opportunity for Change***, to speak about the wider issues of healthcare for children. He said that the difficulties in prescribing for children reflected the much bigger issue about where children have been until now regarding policy.

The status of paediatric medicines is unsatisfactory and the field of medication in the neonate and child is complex. There is a need for specialist formulations of the highest quality and also for new clinical trials in the target populations. The use of unlicensed and off-label medicines in children is high although drug handling in children can differ significantly from adults (*Conroy et al Br.Med.J: 2000;320;79-82 and Conroy et al Arch.Dis.Child: 1999;80,F142-145*)

Even in 2001 the majority of new medicines are not licensed for use in children, and the use of many established drugs is not supported by comprehensive data on basic pharmacodynamics and pharmacokinetics in different groups of children. They are used on the basis of '*a respectable and responsible body of professional opinion*'. This does not mean that their use is unsafe.

This is a world wide problem, but the transformation of the standing, status and use of medicines in children in the USA offers lessons to be learned. The key components of the action were the political drive to recognise the importance of children, appropriate legislation, incentives for the

pharmaceutical industry, money to invest in the research infrastructure, the creation of Paediatric Pharmacology Research Units (PPRUs), better recruitment and training and a realistic and exciting career track.

Things are beginning to happen in the UK and many new initiatives are beginning to address the wider health agenda affecting children. 'Sure Start' initiatives and programmes to reduce poverty levels will all contribute to improving children's health, and, combined with better advocacy for children, a developing government policy for children, and the recognition of the implications of the use of medicines in childhood will address the obstacles.

Children are different. They are NOT small adults, there are clear age stages: fetus, neonate, infant, pre-school, first school, adolescent, transition to adulthood. There are continuities across ages, but each has specific needs. They are also dependent on mothers, carers and families, and they are unable or are not allowed to speak for themselves. But they are now clearly recognised as people and also people who have human rights.

The Select Committee on Health in 1997 stated 'The current system with regard to testing and licensing of medicines for use by children is unacceptable'. It also urged action to ensure that 'children have timely access to safe and effective medicines which have accurate, scientifically justified prescribing information'.

The journey to this position has been long and there are libraries of reports and recommendations, many with scathing criticisms of previous policy. There has been an overall failure to see children as a client group, coupled with a tendency to ignore the human rights of the child. There has been a failure across the NHS to implement evidence based practice together with the dismantling of the loci of good practice. (*'Who is speaking for children and adolescents and for their health at the policy level?' Aynsley-Green, Barker, Burr, Macfarlane, Morgan, Sibert, Turner, Viner, Waterston and Hall BMJ 2000; 229-232*). All of this came to a head with the Bristol scandal.

The Report of the Public Inquiry into children's heart surgery at the Bristol Royal Infirmary 1984-1995 may well prove to be the most important document for British Medicine in 50 years. 48 pages; 2CDs 198 recommendations, 31 specifically for improving the care of children. *'The chapter on children was written with some anger'* - Ian Kennedy.

'Healthcare services for children are still, generally, fragmented and uncoordinated' Children have been treated as 'small adults who simply need smaller beds and smaller portions of food' (Editorial on the Bristol Inquiry. BMJ 2001;323:180_

'Children's services were described in the 1970s as a Cinderella service. Cinderella has never been to the ball. It's still a Cinderella service after 25 years. This can't be right.' (Ian Kennedy on the Bristol Inquiry BMJ 2001;323:183)

The key messages from Bristol: (Chapter 29)

The health care needs of babies and children... ***were too readily subordinated to the need to care for adult patients. There was no system to establish responsibility during the various phases of care. In the absence of effective planning, the particular needs of children were not effectively met***

Acknowledging the relative lack of concern for a group of highly vulnerable individuals leads to the question of who provides leadership for children's health care services and what has to change to create a culture where children are valued, that someone has a responsibility for children and that they are recognised as a client group with status, rights, a voice and expectations of service.

On 17th February 2001 the Secretary of State announced '*... these steps now enable us to launch a new national crusade to improve the health of our nation's children. ... I can announce today we will draw up new national standards for children's services ...*'

Government policy as a result has included initiatives at a macroeconomic level to tackle inequalities, neighbourhood renewal initiatives, investment in key mainstream services, and specific programmes such as the Children and Young People's Unit, Sure Start, Quality Protects, Connexions and Youth Justice, The Children's Taskforce and a NSF.

Professor Aynsley-Green identified what has to change to develop meaningful above and below partnerships. There has to be commitment, direction, standards, and resources from above, with an understanding of the levers for change and involvement and ownership from below - activation and motivation to harness the commitment of local movers and shakers; Above all children, young people and parents have to be involved.

A focus for all of this was the appointment of the National Clinical Director for Children with a remit

- To lead development of healthcare services for children
- Organise process
- Communicate
- Deliver the Children's NSF

The Children's Taskforce has 31 members, encompassing health, social care, education, management, voluntary and non-government organisations together with expertise from cross-government officials.

They will develop a strategy for engaging children and young people and carers, and they will link with regional taskforces,

The Children's NSF Mission is to *Improve the lives and health of children and young people through the delivery of appropriate, integrated, effective, and needs-led services*

The Principles

- Child and family centred
- Voice of children and young people
- Achievement of well-being, health and full potential for ALL children
- Support in adversity, disability and ill health
- Needs led services, evidence based delivery
- Appropriate settings of care
- Partnership with social care and education
- Context of life's chronology

LIFE chronology

- pre-conception, pregnancy and childbirth
- neonate
- infant
- pre-school child
- school age child - primary and secondary
- adolescence
- transition to adulthood

The Four Threads: health, social care, education and environment

- Needs assessment by chronology for health and well being, and for support in illness and adversity
- Services required
- Settings of care
- Organisational structures; new ways of working
- Targets
- Performance assessment and management

The NSF Expert Working Groups

- maternity
- children who require acute/hospital services
- child and adolescent mental health and emotional well being
- children with disabilities and long term problems
- vulnerable children
- what every child needs for health and well being
- + information R&D/Evidence, Workforce

these do not necessarily pre-determine the final structure of the NSF.

KEY issues:

- managing expectation - short vs long term
- reality of what reasonably can be achieved
- communication and ownership
- building on what's good already
- managing resources more effectively
- structure of services
- workforce - roles, training and capacity
- shifting the balance of power

- what has been happening in the UK in paediatric pharmacology, therapeutics and pharmacy - a very great deal!
- advocacy for children
- government policy for children
- use of medicines in childhood

KEY developments:

- RCPCH - Medicines for Children
- National Paediatric Drug Information Centre
- Academic Centre in Derby/Nottingham
- Committee on the Safety of Medicines
- British Forum for the use of medicines in childhood
- RCP/RCPCH Intercollegiate Training Committee
- two national training posts
- The NHS National Paediatric Pharmacology Research Network (NPPRN)
- Centre for Paediatric Pharmacy

THE NHS National Paediatric Pharmacology Research Network

- A managed network linking 8 partner institutions, UK wide
- A NPPRN Co-ordinating Centre
- A Strategy Board
- A Funders Forum

AIMS: To improve patient care and the use of medicines in children by:

- building research capacity
- improving the quality of research in all dimensions
- improving the performance of clinical trials
- seeking collaboration and partnerships between the NHS, Universities and Industry
- improving public awareness

The Centre for Paediatric Pharmacy Research: The Partners:

- Great Ormond Street Hospital for Children
- The Institute of Child Health
- The School of Pharmacy
- The pharmaceutical industry
- Children, parents and families

Components of ACTION

- political drive for importance of children
- legislation
- incentives for the pharmaceutical industry
- money to invest in research infrastructure
- creation of PPRUs
- recruitment and training
- a realistic and exciting career-track

Professor Aynsley-Green summarised his presentation by saying that there had been considerable progress within the last 4 years through a cultural transformation in recognising the importance of children. Children are now on the political horizon, there is a commitment to improving the use of medicines in childhood, and advocacy has been effective. This is an outstanding opportunity to match the excellence of the British pharma industry with pre-eminence in paediatric research and clinical practice.

Dr. Richard Tiner, Medical Director of the ABPI *spoke about Current Obstacles and the Way Forward*. A promising idea, which is still in its infancy, is the idea of transferable exclusivity. He noted that 46% of medicines given to children in general paediatric wards in Western Europe are unlicensed or off-label (*Conroy et al BMJ8/1/00*)

Dr Tiner outlined the activities of the pharmaceutical industry and regulatory authorities at the moment all drugs have patient information leaflets and there is an electronic medicines compendium (www.emc.vhn.net). In the US there has been an initiative to incentivise the pharma industry to do a lot more work with children through the extension of patent rights for 6 months.

The pharma industry and regulatory authorities in Japan, Europe and the USA have developed an initiative (ICH E11) to look at the Clinical Investigation of Medicinal Products in the Paediatric Population. It is the goal of this guidance to encourage and facilitate timely paediatric medicinal product development internationally. If work has not been done to this standard then the chances of getting a license is small.

Some general principles were outlined that paediatric patients should be given medicines that have been appropriately evaluated for their use. And that drug development programmes should include the paediatric population when it is anticipated that there will be paediatric use.

However, this raises some important issues:

- Data on the appropriate use of medicinal products in the paediatric population should be generated unless the use of a specific medicinal product in paediatric patients is clearly inappropriate.
- Justification for the timing and the approach to the clinical programme needs to be clearly addressed with the regulatory authorities at an early stage and then periodically during the development process. This clearly enhances the need for companies and regulators to work together.
- An immediate question is the sort of formulations which will be needed for use by children. There is a need for paediatric formulations that permit accurate dosing and enhance patient compliance.
- Several formulations such as liquids, suspensions and chewable tablets, may be needed or desirable for paediatric patients of different ages.

- For injectable formulations, appropriate drug concentrations should be developed to allow accurate and safe administration of the dose.
- The toxicity of some excipients may vary across paediatric age groups and between paediatric and adult populations e.g. benzyl alcohol is toxic in the preterm neonate, and for paediatric patients there is a huge difference between 1ml and 0.9ml.

Pharmacokinetics:

- Dosing recommendations for most paediatric medicines are usually mg/kg up to a maximum adult dose. Dosing based on mg/square metre body surface area might be preferred. However, clinical experience indicates that measuring height or length is difficult and calculation errors of body surface area are common.
- Low blood volume.

Safety:

- It is important for practitioners to pass back information on accidental overdose/ingestion.

Post-marketing information:

- It is important in some cases for long-term follow-up studies to be undertaken to determine effects of certain medications on growth and development of children, this will take several years and can be expensive.

Defining age classification is important:

- The neonate
- pre-term new born infants
- term new-born infants (0-27 days)
- infants and toddlers (28 days to 23 months)
- children (2 - 11 years) may need a larger dose than adults per body size
- adolescents (12 to 16-18 years)

Issues about consent and assent to treatment are also major issues not only in treatment, but will also be in research participation.

Consent is usually given by a parent or guardian on behalf of the child and the child will assent to the treatment on its own behalf. As a rule, around the world, a paediatric subject is legally unable to provide informed consent, although older children are often able to be quite pro-active .

Issues around consent in neonatal RCTs (*S Mason and P Allmark. The Lancet. Vol356 Dec 16 2000 pg 2045*)

200 parents views were sought:

- *'We were so shocked, we signed without knowing much'*
- 18 parents said that they were not given an information sheet

- 30 (21%) were unaware of the possibility of withdrawing
- 5 asked for consent after trial had begun, (this would be regarded as misconduct under the GMC Code of Conduct Guidance)
- Several unaware of role of REC

Clinician views

- 7/107 did not use an information sheet
- 66 (62%) thought that parents should be given full information
- some reported limiting disclosure about risks in order to obtain consent
- 3 did not obtain consent for the trial
- 50/107 felt that requirement to obtain informed consent sometimes prevents useful neonatal research
- 102 (95%) had received no formal training in obtaining informed consent

The pharma industry is increasingly taking the view that they must act to ensure that high standards pertain in obtaining appropriate consent for participation in RCTs of children from their parents and/or guardians.

In order to minimise distress protocols and investigations should be designed specifically for the paediatric population and not simply re-worked from adult protocols.

Dr Tiner said that the EU Health Council Resolution of December 2000 called on the Commission to develop incentives and other measures for paediatric research for new and existing medicines as soon as possible, but this could be a very slow process.

The EU Clinical Trials Directive published in May 2001 (2001.20/EC) is worth looking at for most recent guidance. At the same time the pharmaceutical industry through EFPIA (European Federation of Pharmaceutical Industry Associations) set up the EFPIA Paediatric Task Force. At the end of November 2001 a paper was sent to all industry CEOs about a proposal to the EU about how to incentivise industry to develop paediatric medicine development by transferring exclusivity to academic institutions to do the work and then sell it on to the manufacturers. There are major problems for industry about medicines which are off patent as generic companies will just piggy back the work without paying for the research.

If these initiatives do take off there could be huge development in paediatric medicine and then the issues to face will be whether or not the UK will be able to provide enough high quality centres for paediatric clinical trials? Whether the EU will provide adequate incentives to industry to develop paediatric medicines? And will ways be found to support research on older products?

The pharmaceutical industry is committed to developing paediatric medicines and has demonstrated this through setting up the Children's NSF Working Group, through the creation of the Multidisciplinary Working Group, and in promoting paediatric clinical pharmacology. Two companies are directly funding paediatric initiatives GlaxoSmithKline at Great Ormond Street and

MSD at Aberdeen, and industry has put in two million pounds to training clinical pharmacologists.

An Action Research funded project was at the heart of Professor James McElnay's talk. The Professor of Pharmacy Practice at Queen's University, Belfast gave a detailed presentation called ***Provision of evidence base for optimising dosage of unlicensed drugs in children***. He introduced his talk by explaining that on February 27 1997 a House of Commons Select Committee expressed deep concern about this situation and huge media exposure ensued, which opened up the area of unlicensed drug use in children.

Alarming, many drugs used for the diseases of childhood have only been licensed for use in older children and adults. In the absence of clear dosing guidance for infants/young children physicians are forced to estimate doses from adult values, based on the child's weight or surface area. Children are not simply small adults and the medicines they receive may have different beneficial and adverse effect profiles. Multiple drug sampling over a prolonged period is the usual way by which evidence is gathered to construct dosing guidelines for adults. This intensive testing involves a relatively few subjects; however, due to its invasive nature it is usually considered unethical in infants and young children.

A multidisciplinary research group has been established at Queen's University Belfast to address the issue of the lack of pharmacokinetic and pharmacodynamic data for drugs used outside their license in infants and children. The group was established through funding from Action Research and has over the last year been extended to include researchers from Alder Hey Hospital, Liverpool.

Professor McElnay said there were two important areas for research: pharmacokinetics – how a drug is absorbed in the body, metabolised and distributed for example; and pharmacodynamics – what the drug does to the body, side-effect profiles etc.. We have to be aware of both aspects when devising drugs for children, he said.

The research programme uses the technique of sparse data analysis. This is a novel approach which involves obtaining small numbers of blood samples from infants and children who are already receiving an adult medicine in their routine treatment.

For each drug investigated, parental (and where applicable child) consent is gained.

Simultaneous to the blood sampling, the child is monitored by a trained research nurse to assess the beneficial (and adverse) effects being experienced. The latter for example, in the case of a non-steroidal anti-inflammatory drug, can involve the administration of a pain questionnaire, evaluation of routine clinical laboratory data and assessment of post-operative bleeding.

A custom-designed study database is then produced.

By using a couple of examples of drugs tested (diclofenac and Indomethacin), Professor McElnay presented the methodology used by the research team and outlined the infrastructure which has been established to perform this type of investigation.

He stressed that the project could help us understand the potentials of both **overdosing** and **underdosing** in patients, and will hopefully lead to the development of some evidence-based guidelines for children.

Drugs being investigated include:

- Diclofenac (0-12y)post-op analgesia
- Captopril (0—12y): heart failure
- Enalapril (0-12y): hypertension
- Cisapride (0-12y)GORD;stress ulceration
- Cisapride /ranitidine combinations
- Ranitidine (0-7y):GORD;stress ulceration
- Codeine (0-1y; rectal - all ages): post-op pain
- Paracetamol (0-3 months) fever/pain post-op
- Spironolactone (0-12y): heart failure
- Midazolam (oral 0-12y; all routes 0-7y): day clinic procedures
- Indomethacin: patent ductus arteriosus

Professor Imti Choonara Professor in Child Health at the Academic Division of Child Health, University of Nottingham highlighted ***the need for evidence based information and European action***

It is widely accepted within medicine that clinical practice should be evidence based. Unfortunately for many conditions in children there is limited evidence available regarding the most appropriate medicine to use, the dose, frequency or duration of treatment (*Choonara I, Nunn AJ. Should the treatment of children be evidence-based? Paed Perinatal Drug Therapy 1999;3:2-3*) Such information is usually obtained from clinical trials that are carried out by the pharmaceutical company who wish to obtain a product license for their new medicine.

Studies in Europe and the UK have shown that significant numbers of children both in hospital and out of hospital receive medicines that are either unlicensed or used in an off-label manner (*Turner S, Longworth A, Nunn AJ, Choonara I. Unlicensed drug use on paediatric wards. BMJ 1998;316:342-345*) (*Conroy S, Choonara I, Impicciatore P et al. Survey of unlicensed and off-label drug use in paediatric wards in European countries. BMJ 2000;320:79-82*)

Off-label use is when a medicine is used at a different dose or frequency, in a different age group, or for a different indication than that recommended by the

manufacturers (Turner S, Nunn AJ, Choonara I. *Unlicensed drug use in children in the U.K. Paed Perinatal Drug Therapy 1997; 1:152-55*)

Off-label use is a far greater problem than the use of unlicensed medicines, both in the UK and throughout Europe. One study has suggested there may be a greater risk of drug toxicity following the use of medicines in an off-label manner (Turner S, Nunn AJ, Fielding K, Choonara I. *Adverse drug reactions to unlicensed and off-label drugs on paediatric wards; a prospective study. Acta Paediatr 1999;88:965-968*)

Initiatives in North America have seen a major increase in the study of medicines in children. Concern has, however, been raised that the medicines being studied in American children are those where there is the greatest potential for profit rather than those where there is greatest clinical need (Jong GW, Van den Anker J, Choonara I. *FDAMA's written request list: medicines for children. Lancet 2001;357:398*)

It is important that in Europe we learn from the American experience and ensure that financial incentives are targeted at those medicines of greatest need.

Professor James Leonard, Professor of Paediatric Metabolic Disease at the Institute of Child Health University College, London talked about **orphan drugs which form a heterogeneous group, each one having particular problems**. Orphan drugs can be divided simply into two categories - off label and orphan drugs. He concentrated in his talk on his field of interest and on medicines used to treat metabolic disorders.

The conditions are generally rare or very rare so that there has, until recently, been little interest from the pharmaceutical industry. The use of the medicines in metabolic disorders has been based on an understanding of the biochemistry and the medicines themselves not infrequently had, to be obtained from unusual sources such as laboratory suppliers. Inevitably therefore they have not been subject to the same rigorous testing that would have been necessary for a licensed product. However, the benefits appear to outweigh the potential risks.

Professor Leonard said that the situation was improving, but that collaborative projects are essential. The pharmaceutical industry is developing products but different problems are now emerging; for example delays in the introduction of new medicines whilst studies are completed, and the cost of medicines.

Professor Leonard outlined a strategy for the future

- 1 Accept that the current situation is inevitable and develop special funding arrangements to cover the cost
2. Refuse to accept it and find alternatives
3. Develop statutory body to oversee all issues

In summary Professor Leonard said that children should have medicines that are safe and effective, however, the difficulties need to be recognised, and Workshops such as this are an innovative way of bringing together the relevant players to work towards a solution.

Discussion points

The need for more clinical paediatric pharmacologists and more funding for these posts and questions around who should be funding them

The opportunities for funding research training fellows in helping encourage career paths in these areas

Ensuring there are appropriate people sitting on the peer review panels of funding bodies such as charities, who are aware of the types of issues discussed, the whole dynamics of childhood diseases and the difference between patient and off patent drugs for example

The need to spread the word much wider and keep the profile high, for example keeping up the pressure on The Lancet and the BMJ to publish relevant articles

There were positive words about transferring patent exclusivity and the opportunities it might bring

There was agreement that there were plenty of issues arising from the Workshop, and it was hoped that participating organisations and individuals would work together to ensure children receive the appropriate and safe treatments and medicines they deserve and need.

In the time being, many of the speakers were willing to kindly add their name to the following joint statement:

JOINT STATEMENT

Drug Treatment in Children (Children Are Not Little Adults)

We recognise that the majority of drugs used in the medical treatment of children in hospital are not specifically tested for that purpose. We are also aware of recent figures estimating that two thirds of children in hospital and 90 per cent of sick newborn infants receive medicines prescribed in an unlicensed or off label manner.

However, there is wide recognition that the medical, legislative, financial and ethical issues surrounding paediatric prescribing are extremely complex.

Any solution requires the participation of pharmaceutical companies, general practitioners, hospital doctors, medical researchers, patient representatives, politicians and medical charities.

We recognise the importance of finding a solution which is in the interests of all concerned, particularly children receiving drug treatment and make a commitment to working in conjunction with all interested parties to achieve this.

Agreed by:

*John Grounds, Director of Campaigns and Communications at Action Research

*Dr Richard Tiner, Medical Director of the Association of British Pharmaceutical Industry (ABPI)

*Professor James McElroy, Professor of Pharmacy Practice at Queen's University of Belfast

*Professor Imti Choonara, Professor in Child Health at the Academic Division of Child Health, University of Nottingham

*Professor James Leonard, Professor of Paediatric Metabolic Disease at the Institute of Child Health

*Art McConnell, a father who lost his daughter to an adverse reaction to steroids

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