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The European Society for Developmental Pharmacology (ESDP)*

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Abstract

The European Society for Developmental Pharmacology was founded in 1988. Since then it has met every two years. The society exists to promote the scientific study of medicines in the developing fetus, infant and child. The society has established the European Network for Drug Investigation in Children. The society and the network are involved in research as well as appropriate political action on behalf of children in relation to medicines.

Key words: Europe – Medicines – Children

ESDP Congresses

The first congress of the European Society for Developmental Pharmacology (ESDP) took place in Les Diablerets (Switzerland) in 1988 and five more congresses have taken place since then on a 'once every two years' basis (Table 1). Participants from 15 European countries, the United States, Canada, Australia and Japan have attended them. The Seventh Congress will take place in Jerusalem in 2001, having been delayed as a result of the unrest in the area.

ESDP congresses provide physicians and scientists interested in the effect of medicines on the developing fetus, infant and child with the opportunity to meet. Most participants are paediatricians with a specific interest in clinical pharmacology, but prominent clinical pharmacologists, obstetricians and non-clinical scientists participate as well. Basic developmental pharmacology, clinical paediatric pharmacology and licensing issues are topics covered at ESDP congresses (Table 2).

The backbone of the Society is the General Secretary. Professor Jean-Pierre Guignard promoted the formation of the Society and he was its General Secretary in the period 1986–1994. Professor Gerard Pons took that position in 1994 and he will complete his second term in the year 2000. Presidents of the Society have been Prof Fabio Sereni (1988–1990), Prof Lars Boreus (1990–1992), Prof Fiona Broughton-Pipkin (1992–1994), Prof Endre Sulyok (1994–1996), Prof Elisabeth Autret-Leca (1996–1998) and Prof Rafael Gorodischer (1998–2000).

Concerns of the Society

A common concern of ESDP members is the lack of sufficient scientific data on which to base drug therapy in children. For this reason this discipline is even today much more of an art than of a science. It is surprising, in view of the need for more data, that the field of paediatric clinical pharmacology has not been a popular one.

One possible reason for the lack of popularity of the specialty has been the lack of funds for the study

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Table 1. Congresses of the European Society for Developmental Pharmacology (ESDP)				
	Year	***Location***	***Country***	***President***
First	1988	Les Diablerets	Switzerland	J. P. Guignard
Second	1990	Tremezzo	Italy	F. Sereni
Third	1992	Borgholm	Sweden	L. Boreus
Fourth	1994	York	UK	F. Broughton-Pipkin
Fifth	1996	Pecs	Hungary	E. Sulyok
Sixth	1998	Ajaccio	France	E. Autret-Leca
Seventh	2001	Jerusalem	Israel	R. Gorodischer

Table 2. Papers presented at the last two congresses (Pecs and Ajaccio) of the European Society for Developmental Pharmacology (ESDP)		
	Free communications	**Invited lectures**
Basic	22	22
Clinical	57	10
Licensing	1	3
Total	80	35

of drugs in children. It has been the policy of many granting institutions that drug companies should pay for drug studies. However, in most cases the pharmaceutical industry felt that the expected profit resulting from the study of drugs in children did not justify investment. As a result of lack of funding, sufficient training programs have not been available.

It must be recognised that developmental and paediatric pharmacology is not considered by many a clearly defined specialty. Physicians treating children, and particularly paediatric subspecialists, often feel that they are experienced in the use of medicines and that they do not need the advice of another specialist in treating children.

The lack of paediatric studies has resulted in about 70% of prescription drugs having labelling limitations on their use in infants and children[1], and that about 70% of hospitalised children receive medications prescribed in an unlicensed or off-label manner[2]. This percentage is even greater in paediatric and neonatal intensive-care units[3,4]. In comparison to the use of approved drugs, prescription of unlicensed and off-label medications exposes children to greater risks[5]. It has been shown previously that the rate of adverse drug effects in neonatal intensive-care units is approximately 30%, and 15% of them are life-threatening[6].

Specific peculiarities of children that influence drug action derive from functional and anatomical changes that take place with increasing age. Changes in body water and fat content in protein binding, in liver and kidney function, and in relative sizes take place during the child's growth and development. The concept that 'children are not small adults' applies, as in many other fields, and also with regard to drug kinetics and effect. Awareness of this peculiarity became public domain with the thalidomide tragedy, an example of unusual drug effect. The experience with thalidomide, and also in relation to a host of other therapeutic tragedies and severe side-effects, were important milestones in the history of paediatric drug therapy – in particular the death of 107 children following the use of a sulphanilamide elixir[7], the chloramphenicol-induced grey-baby syndrome in neonates[8], the sulphonamide-induced kernicterus[9], and the tetracycline-induced teeth discoloration and enamel changes[10].

We have learned over the years that specific conditions seen in children require specific drug therapies. For most of them we use medications designed for other purposes in adults. For instance, the non-steroidal anti-inflammatory drug indomethacin is often used in neonates not for inflammatory conditions, but for the non-surgical closure of a heart condition – the ductus arteriosus; this drug is also used in infants and children in the treatment of Bartter syndrome. Theophylline is used in neonates not for the treatment of asthma, but for the prevention of apnoea of prematurity. Two other centrally acting stimulants – caffeine and doxapram – have practically no use today outside neonatology, where they are used in the prevention of apnoea. It was found that the adrenergic agonist methylphenidate is useful in the treatment of children with attention-deficit–hyperactivity disorder. An exception to the rule is surfactant, a drug specifically designed for the management of a paediatric condition – the respiratory distress syndrome (hyaline membrane disease). We lack effective therapies for common paediatric illnesses, such as bronchiolitis.

In contrast to children, adults have usually more than one approved drug for any given condition. For instance, over 30 drugs are available for the treatment of cardiac arrhythmias[11], but only one of them (digoxin) is approved for paediatric use[12]. It may be argued that antiarrhythmic agents have not been properly studied in children because abnormalities in cardiac rhythm are rare events in paediatrics. But

even in the case of poisonings – a common paediatric condition – only 40% of the recommended antidotes are labelled for children[13].

We also lack sufficient data for most drugs given to the pregnant and lactating mother on their effect on the fetus and the nursing infant[14].

Formulations

Another area of special interest is the issue of paediatric formulations. The lack of paediatric formulations often leads to the unlicensed use of many drugs (for instance, the pharmacist crushes tablets to prepare suspensions). We do not know how much and how fast the drug is absorbed, and how stable are these extemporaneous formulations.

The lack of paediatric formulations may lead to medication errors. When computing the dose for an infant, or when diluting the stock solution of the drug, the decimal point may be misplaced, and then the child receives either ten times more, or ten times less, medication[15]. This may result in lack of efficiency, or toxicity, resulting in the death of the infant[16]. Also, owing to the small volumes of medicines given intravenously to small infants, some of the drug does not reach the patient but remains in the tubing; solutions on how to overcome this difficulty have been formulated[17], but it remains a formulation obstacle. No doubt, there is an urgent need to have special paediatric formulations for many drugs.

A related issue is that of the drug diluent and vehicle. The report of renal failure and death of children following the administration of an elixir of sulphanilamide in 1937[7] was not attributed to the antibacterial agent itself, but to its diluent, diethylene glycol. This tragedy was a landmark in the legislation of licensing and labelling of medications in the USA, which affected the rest of the industrialised world. It could be thought that such a significant event would prevent further similar tragedies. However, 50 years later reports appeared of toxicity of another solvent – propylene glycol – in young infants[18,19], and a therapeutic tragedy with 38 reported deaths of low-birth-weight infants owing to the polysorbate vehicle of 'E-Ferol', a vitamin E preparation[20]. None of these formulations had been studied in children prior to routine use.

Clinical Trials

The lack of economic incentive has been a reason for the lack of paediatric drug studies. Another important reason has been the need for special ethical guidelines for carrying out clinical trials in children. Guidelines have recently been developed in the USA, in Europe and in other countries. This is paradoxical because the history of clinical trials in children dates back over two millenia. The Book of Daniel in the Old Testament gives us an example of a very early clinical trial[21] – after conquering Jerusalem, the Babylonian King Nabuchadnezzar ordered a chief servant to bring to him the brightest and most beautiful youngsters of Judea in order to raise them in his palace. The King asked his servant to give them royal food to eat and wine to drink. Daniel, who was among those youngsters, refused to eat the royal food and to have wine. He convinced the King's envoy to perform a 'clinical trial' – to feed him and three of his friends only legumes and water, and to give the royal food to the other children. At the end of 10 days the servant would compare results. As it turned out, Daniel and his friends looked better nourished than the children fed the royal food and wine.

As we see it, the field of paediatric drug therapy has tremendous potential for study. In the world there are about 1.8 billion children under the age of 15 years and the number of children under 15 years in European countries is about 140 million[22]. This indicates that many children are in need of medicines, and that there should be a profitable market for many paediatric drugs and paediatric drug formulations, particularly for common illnesses.

Achievements Abroad

Only the USA has introduced an obligation on pharmaceutical companies to submit data for children. In 1994, the FDA was unsuccessful in asking holders of marketing authorisations for drugs marketed in the USA to collect and submit existing data to provide a record of their administration to children. In 1997, a series of measures was taken that combined regulatory requirements and financial incentives. These measures took effect in April 1999 and the data must be made available as from January 2001. These measures include regulatory requirements and financial incentives.

The American Government has also recognised that this is an area where research is limited and have therefore committed major funding from the US National Institutes of Health to encourage both clinical trials in children and an increase in scientific knowledge on the differences in drug metabolism and mechanisms of action in this age group. A network of 13 drug investigation centres – the Pediatric Pharmacology Research Unit network, has been created[23].

Recent European Political Moves and Decisions

A European report on the clinical investigation of medicinal products in children has been published and came into effect in September 1997. To date

this guidance has had little effect on the study of medicines in children.

European representatives have participated in the International Conference of Harmonization (ICH-E11) together with American and Japanese delegates. The text should be adopted in November 2000 and is composed of guidelines aiming at worldwide harmonisation of drug evaluation in children, particularly defining age groups to be studied, fostering the development of paediatric drug formulations and categorising different types of drug development in children.

The French Minister of Health (Mme Martine Aubry) recently made the decision to take advantage of the French Presidency of the European Community to propose a text on drug evaluation in children to the European Parliament. Mme Annie Wolf has been appointed to co-ordinate the preparation of this text. She was responsible for preparing the text for the European Orphan Drug Act.

A draft memorandum on paediatric drugs has been prepared by the European Presidency. This draft states that, in the absence of regulatory requirements, there is insignificant development of drugs for children and insufficient paediatric formulations exist. In order to encourage the development of paediatric drugs, regulatory requirements should be accompanied by financial incentives.

The European Network for Drug Investigation in Children (ENDIC)

The issue of drug licensing has been getting progressively greater attention at ESDP congresses. A special session was devoted to this subject at the Ajaccio 1998 Congress, and a workshop will be held at the Jerusalem 2001 Congress with the participation of American and European speakers, representing the American Pediatric Pharmacology Research Unit Network, the European Network for Drug Investigation in Children and Industry, and the US Food and Drug Administration.

The formation of ENDIC (a working group within the ESDP) in 1998 reflects this increasing interest in the issue of licensing[24]. The purpose of this European network is to promote all aspects of drug research and evaluation in children, particularly supporting specific paediatric labelling of drugs and the development of specific drug formulations for different age groups. The network is composed of eleven European centres in Finland, France, Germany, Israel, Italy, the Netherlands, Sweden, Switzerland and the UK. It aims at unifying research expertise throughout Europe in the field of paediatric drug therapy and creating an environment where drug evaluation in children can be conducted according to international harmonised guidelines and good clinical and laboratory practices.

ENDIC published a position paper in the *Lancet* entitled Closing the Gap in Drug Therapy[25], and members representing five European Union countries carried out a survey of unlicensed and off-label drug use in paediatric wards, which was published in the *British Medical Journal*[2]. Recognising the need for political action, ENDIC also sent a letter to all members of the European Parliament and national Ministers of Health, entitled *Medicines for Children*[26].

A network of drug investigation centres throughout Europe should be supported by public funds. This network will be able to

- Perform randomised multicentre clinical trials to provide adequate labelling of drugs used in children and to foster new drug application. The network should facilitate patient recruitment and linkage with other networks.
- Provide translational scientific data which focus on developmental pharmacology.
- Provide an excellent teaching and training environment in paediatric pharmacology.

There is no justifiable reason for children to be second class citizens, to remain therapeutic orphans and not have the same rights as adults with regard to the use of medicines. There is room for optimism, but much work is required to produce the indispensable conditions to close this gap.

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