A new paradigm for developing drugs in children: atomoxetine as a model

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Arch Dis Child 2005;90(Suppl 1):i13-i16. doi: 10.1136/adc.2004.059378

When prescribing drugs for children, it is fundamental to acknowledge that they are distinct from adults with a different physiology and metabolism. They are also still maturing. The development of drugs with a primarily paediatric indication thus requires the trialling of these drugs in a paediatric population to assess safety, tolerability, and efficacy as appropriately as possible. When designing and running a paediatric clinical trial, a number of complexities must be addressed to ensure a successful study, including practical considerations, ethical issues, and tailoring communication appropriately to study participants and parents. The drug development process for atomoxetine, a novel, non-stimulant treatment for attention deficit/hyperactivity disorder (ADHD), encompassed a preclinical programme, initial trials in healthy adults, and a proof of concept trial in adults with ADHD. Open label and placebo controlled studies in paediatric patients followed, thus establishing the drug's safety and efficacy in children with ADHD. Further trials have addressed, and continue to address, wider aspects of the atomoxetine response in a paediatric setting.

It is increasingly recognised that if a new chemical entity is being developed as a pharmaceutical treatment for a condition that affects children, extensive testing and trialling of this product in children as well as adults is required. Emerging legislation in the US attests to the importance of this (US Paediatric Research Equity Act, December 2003), and it will not be long before such advice and legislation is enforced in Europe. Recently, the Committee on Safety of Medicines (CSM) in the UK advised that the selective serotonin reuptake inhibitors (SSRIs) class of agents should not be used to treat major depressive disorders in children,^{1,2} partly because of the paucity of reliable data on their use in paediatric patients. An exception was, however, made for fluoxetine. Following a comprehensive and rigorous clinical trials programme in children and adolescents, the CSM believes that fluoxetine has a favourable risk:benefit ratio in this population.³⁻⁵

DIFFERENCES BETWEEN CHILDREN AND ADULTS

Those of us working in the field of paediatrics will be familiar with the maxim "children are not small adults" and will be comfortable with the fact that we should not treat them as such within

a medical context. There are numerous ways in which children and adults differ that might make it inappropriate to administer to a child a drug that has only been tested comprehensively in an adult population. A child has a different physiology to that of an adult. Furthermore, the way one communicates with a child is different, and children are still developing physically, neurologically, socially, and emotionally.

Children's differing physiology might affect the way drugs are absorbed, distributed, metabolised, and excreted. For example, gut maturation progresses as a child gets older—gut transit time tends to be shorter and acid secretion in the stomach has a different profile. This has an impact on how well a drug is absorbed. In addition, the hepatic cytochrome P450 enzyme systems that metabolise drugs tend to work more slowly in young children (generally less than 2 years of age)—a fact that recently came to light with the example of cisapride, a medication that was frequently prescribed for gastro-oesophageal reflux. Cisapride is metabolised by the cytochrome P450 3A4 pathway. Thus, when it was given to certain susceptible babies with slow metabolic function, the resulting higher plasma levels induced QT prolongation and cardiac events.

There could also be important differences in the acute side effect profile. For example, the heart rate of a newborn baby would be normal at 140 beats per minute and this decreases progressively into adulthood to approximately 70 beats per minute. If the side effect of a particular drug has an effect on heart rate, then it is important to assess this appropriately in differing age groups.

Perhaps more importantly, children are still *developing*. They are growing physically (height and weight) as well as developing neurologically and cognitively. Children are still maturing in terms of reproductive physiology and in a broader context developing socially and functionally as human beings in society. We need to ensure that any drug that is to be administered to a child, particularly for a prolonged period of time, does not have any detrimental consequences on development. However, the assessment of longer term adverse events is difficult and expensive.

Child healthcare itself is changing. Healthcare technology and its applications to clinical practice are advancing. Babies born several months prematurely are surviving, whereas in the recent past that would have been unthinkable.

Abbreviations: CSM, Committee on Safety of Medicines; FDA, Food and Drug Administration; MHRA, Medicines and Healthcare Regulatory Agency; NCE, new chemical entity.

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Immunisation and improvements in sanitation have lead to a decrease in the incidence of infectious illnesses. Chronic problems, however, are increasing in prevalence. There is increasing recognition of behavioural disorders and their negative longer term consequences for the individual and society. In addition, parental expectation with regard to child healthcare is changing and there is an increasing need to take their (and the child's) viewpoints into consideration when making treatment decisions.

DRUG DEVELOPMENT PROCESS FOR ATOMOXETINE: OVERVIEW

When developing a new chemical entity (NCE) for a child, the balance between acceptable risk and perceived benefit needs careful consideration with specific attention on the following areas:

- Is the disease life threatening?
- Are effective treatments readily available?
- What are the short term side effects of the NCE?
- What are the longer term side effects (relating to developmental concerns regarding growth, neurology, and so on)?
- What will the duration of treatment be?

The drug development and licensing process is complex (table 1). It typically takes 10 years and costs approximately £500 million to take an NCE from its discovery in the laboratory, to the market where it will benefit patients.

Atomoxetine is a novel, non-stimulant treatment for attention deficit/hyperactivity disorder (ADHD). It was approved by the US Food and Drug Administration (FDA) in November 2002 and has recently (May 2004) been granted a license by the UK Medicines and Healthcare Regulatory Agency (MHRA) for the treatment of ADHD in children, adolescents, and adults. Atomoxetine is a selective inhibitor of the presynaptic noradrenaline transporter with minimal affinity for other receptors or transporters.⁶ It has gone through a development process that has extensively tested efficacy and safety in paediatric patients. Atomoxetine is unique as a psychopharmacological product, in that the majority of the testing has been in children rather than

adults. At the time the drug was approved by the MHRA, approximately 5000 children and 600 adults had received atomoxetine as part of a clinical trial. As part of the preclinical animal study programme for atomoxetine, juvenile animal experiments were performed to assess developmental toxicology as comprehensively as possible. These were done primarily in rats and beagles. Young rats were administered atomoxetine daily (from day 10 to day 84—early postnatal age through to adulthood) in three separate studies, designed to assess general toxicity, growth, organ maturation, reproductive development, and neurobehavioural development. During atomoxetine treatment, the rats matured physically and behaviourally with normal bone growth, no major organ toxicity, and normal reproductive function (although there was a slight, clinically irrelevant delay in the onset of sexual maturation). Juvenile beagle dogs were administered atomoxetine from the age of 8 weeks to 12 weeks to compare general toxicology in this young population to previous findings in adult dogs. There were no neurological or persistent ophthalmological findings, no effect on body weight gain, no major organ toxicity, and no electrocardiographic abnormalities attributable to atomoxetine.⁷

To what degree the preclinical developmental animal studies can be extrapolated to humans is yet to be ascertained as there is a limited database in young animal models and there are currently no standardised criteria for doing such experiments. It is becoming increasingly accepted though, that juvenile animal developmental models are important in developing NCEs for use in children.

Following on from the animal studies, phase I studies, looking at safety and the pharmacokinetic profile, are performed in healthy volunteers (that is, they do not have the condition that the compound is targeting). FDA ethical guidelines do not allow the administration of an experimental medicine to a healthy child as it offers no direct benefit to the child in question.⁸ In the case of atomoxetine, its selectivity and specificity for the presynaptic noradrenaline transporter, along with data regarding the efficacy of desipramine in children with ADHD⁹ (another compound which binds to this receptor, although not as specifically or selectively as atomoxetine), led to interest in its development as a treatment for ADHD. After initial safety and pharmacokinetic data were established in healthy adults, a proof of concept study in adults with ADHD was performed. A proof of concept (or "proof of principle") study is one performed during the exploratory phase of a molecule's development. It is designed to determine early on whether or not a candidate compound would be suitable for further development towards licensing. Selecting which molecules progress towards licensing (and thus have significant investment into their clinical trial programmes) are key decisions that need to be made, recognising that the majority of novel substances that enter phase I will not reach the marketplace. In the case of atomoxetine, the proof of concept study assessed the hypothesis that such a noradrenergic agent might be an attractive therapeutic option for adult patients with ADHD. It comprised a double blind, placebo controlled, crossover study of 22 adults with ADHD and demonstrated significant reduction in ADHD symptoms.¹⁰

Following on from the proof of concept studies in adults, a small open label safety study was completed in children which found that the drug was also safe and effective in this population.^{11 12} Comparing these sets of safety and pharmacokinetic data made it possible to extrapolate some of the adult findings to children—for example, regarding dosing on a weight based regime.

After the initial studies in children were completed, and as knowledge of the safety, efficacy, and pharmacology of

Table 1 Stages of drug development

Drug development stages	Description
Drug discovery	Laboratory based development of a new chemical entity (NCE); generally a molecule designed or discovered to bind to a specific receptor
Preclinical animal experiments	Application of the NCE to animal models to ascertain a level of safety before administration to human subjects
Phase I studies	Administration of the NCE to small numbers of healthy human adult volunteers under carefully supervised conditions, predominantly to determine safety and pharmacokinetic profiles
Phase II studies	Administration of NCE to small numbers of human adults (often with the disease) to ascertain efficacy
Phase IIIa/b studies	Larger clinical studies, often multicentre and international to further define efficacy and safety, with the ultimate aim of satisfying regulatory agency requirements
Phase IV studies	Studies performed after a marketing authorisation has been granted, designed to answer clinical questions about the NCE (for example, safety and efficacy in comorbid conditions)
Post marketing surveillance	Collection of adverse event data (usually to assess rarer side effects and idiosyncratic reactions)

Figure 1 Outline of the development programme for atomoxetine.

atomoxetine increased, a proof of concept, placebo controlled study was performed in children aged 7–12 years; this was then repeated to confirm the positive finding,¹³ and the clinical trial programme in children and adolescents subsequently evolved. A placebo controlled, dose ranging study followed to identify the most suitable dose for maximal efficacy on core ADHD symptoms.¹⁴ Further placebo controlled studies were then performed to optimise dosing options,^{15–16} specifically looking at a once daily dose.¹⁷ The clinical trial programme then progressed to characterise effectiveness, wider aspects of the atomoxetine response, and specific clinical questions including effects on relapse prevention,¹⁸ executive functioning,¹⁹ and specific comorbidities.²⁰

It is increasingly recognised that functional outcomes are important in the management of any chronic illness. This is particularly so in children, where quality of life in different settings (for example, home, school) and self esteem can be compromised, resulting in detrimental effects on social development and academic progress. A further complication of a child's chronic illness is the stresses it can cause within the family unit; several atomoxetine studies addressed these "broader" effects.^{14–21}

At the end of the acute monitoring and assessment period of the clinical trial programme, everyone who had taken part in a trial of atomoxetine was given the option of entering a long term (five year) open label study where they would continue receiving atomoxetine. There were two main reasons for this. Firstly, it was felt that if a patient received a beneficial response from atomoxetine, then it would be

unethical to stop treatment while the drug was still awaiting licensing approval (which could have taken months to years in some circumstances). Secondly, all patients entering the long term, open label phase were continually monitored for safety—this allowed for continuing collection of the longer term safety data.^{22–24}

An overview of the development programme for atomoxetine has been outlined in figure 1.

CONCLUSION

Although there are a number of complicating practical and ethical factors that need to be addressed, it is becoming increasingly important to perform pharmaceutical research in children if a drug is to be used in this population. Atomoxetine has been developed with a paediatric population in mind, and represents a positive model for drug development in children that can be applied to other therapeutic areas.

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