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Long-Term Consequences of Drugs on the Paediatric Cardiovascular System

Elizabeth Hausner, *Monica L. Fiszman*, *Joseph Hanig*, *Patricia Harlow*, *Gwen Zornberg* and *Solomon Sobel*

Food and Drug Administration, Silver Spring, Maryland, USA

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Abstract

Many pharmacological and toxicological actions of drugs in children cannot be fully predicted from adult clinical experience or from standard non-clinical toxicology studies. Numerous drugs have direct or indirect pharmacological effects on the heart and are prescribed for children of all ages. Toxicity or secondary effects may be immediate or delayed for years after drug exposure has ceased. Originally, the aim of this review was to compile information on the effect of specific drugs on the post-natal development of the cardiovascular system and to examine long-term follow-up of the use of cardio-active drugs in children. The limited database of published information caused the original question to evolve into an examination of the medical literature for three areas of information: (i) whether vulnerable developmental windows have been identified that reflect the substantial functional development that the cardiovascular system undergoes after birth; (ii) what is known about pharmacological perturbation of development; and (iii) what the likelihood is of drug exposure during childhood. We examined different scenarios for exposure including random, isolated exposure, conditions historically associated with adults, primary or secondary cardiac disease, psychiatric and neurological conditions, asthma, cancer and HIV. Except for random, isolated drug exposures, each category of possible exposure contained numerous drugs known to have either primary or secondary effects on the cardiovascular system or to influence factors associated with atherosclerosis. It is likely that a significant number of children will be prescribed drugs having either direct or indirect effects upon the immature cardiovascular system. A confounding

factor is the simultaneous use of over-the-counter medications and herbal or nutraceutical preparations that a patient, parent or guardian does not mention to a prescribing physician. Metabolism is also important in assessing drug effects in children. Differences in body water : body fat ratio, age-related gastrointestinal absorption, distribution, excretion, renal function and drug metabolizing capabilities make it possible for children to have a different metabolite profile for a drug compared with adults. There is little examination of drug effects on the interdependent processes of cardiac maturation and less examination of metabolite effects. It is difficult to identify delayed toxicities in children as these adverse events may take years to manifest with many patients lost to follow-up. Clearly this is an area of study where intermediate endpoints and surrogate markers would be of great benefit. Pharmacogenomics may be useful in providing markers of increased risk or susceptibility. A perspective must be kept in balancing the possibility of a problem with the very real benefits that many children experience from the use of these pharmaceuticals.

Many pharmacological and toxicological actions of drugs in children cannot be fully predicted from adult clinical experience or from standard non-clinical toxicology studies. There are societal, medical and regulatory reasons for heightened concern for the possibility of both acute and delayed (developmental) toxicity in the paediatric population. As a society, there is a stronger perception of the potential for developmental effects following childhood exposure to environmental chemicals than to prescription pharmaceuticals. Because environmental chemical exposures are understood to influence development and increase the risk of disease and dysfunction, several large, prospective trials are either planned or underway to better characterize the roles of these chemicals in the chronic conditions known as the 'new paediatric morbidity'. This includes asthma, childhood and young adult cancer, neurodevelopmental disorders, obesity, type 2 diabetes mellitus and some birth defects.[1,2] There is a growing awareness that pharmaceuticals – biologically active chemicals that are deliberately administered sometimes for prolonged periods of time – may also affect development. Despite this perception of a potential risk, there is little information about long-term post-natal effects of many commonly used drugs.

The magnitude of an adverse drug effect in the population is defined in part by the number of people affected in the group at risk over a given period of time. The ability to provide this information requires an awareness or recognition of the problem, a means of identifying an affected individual and good record keeping. It is almost impossible to find data for numbers of children with adverse cardiac development caused by prescription drugs. Does that mean that there is no problem? Toxicity may occur immediately or soon after exposure to a drug or may not be apparent for up to years after drug exposure has ceased. There are numerous drugs that have direct or indirect pharmacological actions on the heart and are prescribed for children of all ages. It is unclear whether the short- or long-term use of such drugs has long-term effects on cardiovascular development. This question must be kept in perspective – whether such a problem exists versus the very real benefits these medications provide for many children.

Development of the heart requires integration of functional development with changing body size, microvasculature,[3] protein isoforms,[4] receptors,[5-7] development of peripheral and central neural pathways,[8,9] the electrical activity of cardiac tissues, measured as the ECG,[10-12] and the maturation of the hypothalamic-pituitary-adrenal axis.[13] During the years when the components of the cardiovascular system are appearing, developing, changing and integrating, children are exposed to environmental chemicals, over-the-counter medications and prescription medications. The original intent of this article was to collate the existing data on the long-term effects of specific drugs when used in

children. As our search progressed, the paucity of published data directly related to this question caused our search to change. We examined the medical literature for three areas of information:

1. Whether vulnerable developmental windows have been identified that reflect the substantial functional development that the cardiovascular system undergoes after birth.
2. What is known about pharmacological perturbation of development.
3. What the likelihood is of drug exposure during childhood.

Many of the articles we read noted a paucity of controlled clinical data for the first two questions. The databases searched included PubMed, Science Direct, MEDLINE and EMBASE. The terms used were combinations of 'pediatrics', 'development', 'juvenile', 'infant', 'neonate', 'child', 'young', 'adolescent', and 'cardio', 'heart', 'coronary', 'cardiovascular', or 'vascular'. Various permutations of these terms were modified with drugs or classes of drugs and/or modified with terms such as 'side effects', 'adverse', 'toxicity', 'toxicology', 'dead', 'development', 'maturation', 'growth', various specific diseases, 'pediatric cardiac toxicity', 'pediatric animal models', 'pediatric cardiac toxicity methods', 'drug', 'pharmaceutical', 'PK', 'pharmaco', 'metabolism', 'distribution', 'excretion', 'absorption', 'innervation', 'autonomic', 'sympathetic', 'parasympathetic', 'receptor', 'nervous system', 'regulation', 'electrical', 'ECG', 'arrhythmias', 'electrocardiogram', 'alpha adrenergic', 'beta adrenergic' and 'opioid'. Different animal species (pig, rat, dog, mouse and rabbit) were also combined with the different search terms. Time limits were not used in the original searches. Depending upon results, time limits were added to subsequent searches.

1. Scenarios to Consider

For a drug to produce an important change in cardiovascular development, a child must be exposed to a critical level of that chemical during a sensitive developmental window. The question thus arises of how likely it is that such exposure may eventually, or even transiently, compromise the physiological function or response of the heart.

1.1 Random, Isolated Exposure

A child may require treatment for an isolated or non-chronic health problem unrelated to the heart, for example, an ear, respiratory or skin infection. The agent or agents used may have some secondary, delayed or prolonged effects upon the heart. As a result of the short-term, random nature of the exposure, this is unlikely to be a situation of as high a toxicological concern as it might be, for example, in the context of organogenesis *in utero*. However, the possibility for undesired effects may be compounded by the use of over-the-counter medications and herbal or nutraceutical preparations that a patient, parent or guardian does not mention to a doctor.

1.2 Conditions Usually Associated with Adults

There is an increased incidence or recognition of conditions usually associated with adults occurring in children. Therefore, children may be treated with drugs that were designed for adults, where the drugs are known to target the heart or have secondary or adverse effects on a mature heart. For example, headache is one of the most common conditions of children and adolescents in industrialized countries, with a prevalence of 8–60%.[14] Migraine has been reported to occur in 3% of children aged 3–7 years, in 4–11% of children aged 7–11 years and in 8–23% of children aged 11–18 years.[15] The prevalence of tension-type headaches may be equal to or greater than that of migraines.[16] Treatments for an existing migraine headache include ibuprofen, paracetamol (acetaminophen) and sumatriptan nasal spray.[15] The triptans are used off-label for paediatric migraines.[17] Immediate adverse effects include taste disturbances and short-duration (10-minute) upper chest or neck 'pressure', asthenia, dizziness and dry mouth.[18] In many cases, the frequency of debilitating migraine headaches necessitates prophylactic treatment. One study showed the most commonly prescribed treatment to be the antidepressant amitriptyline (children aged ≥12 years) and the antihistamine cyproheptadine (children aged ≤12 years). Other drugs used for prophylaxis include propranolol, valproic acid, nimodipine, imipramine and topiramate.[19,20] While all these drugs have primary or secondary effects on the cardio-

vascular system, there is little information available on the long-term consequences, if any, of use in a child with an immature cardiovascular system.

1.3 Primary or Secondary Cardiovascular Disease

A child may have a cardiovascular condition that is either primary or secondary to another condition such as chronic renal disease. In addition to congenital cardiac conditions, an increasing number of children have the same risk factors for cardiovascular disease as adults, such as obesity, hypertension, smoking, diabetes and the metabolic syndrome.[21] In the US, the prevalence of overweight in children tripled from 1980 to 2000.[22] Correlated with childhood obesity are sequelae of hypertension, type 2 diabetes, dyslipidaemia, left ventricular (LV) hypertrophy, obstructive sleep apnoea and orthopaedic problems, typically viewed as conditions of adults.[23] Whether due to the increased incidence of obesity or independent of it, the recognition of hypertension in children is also increasing, from an estimated prevalence of 1% to more recent estimates of 5% in children 10–19 years of age.[24] Before the 1977 National Heart, Lung and Blood Institute Task Force on Blood Pressure Control in Children report, adult levels (>140/90 mmHg) were used to define hypertension in children and thus only severe hypertension was identified.[25] The 1977 task force concluded that asymptomatic primary hypertension was more common in children than previously thought. Hypertension in children now has a statistical definition: a child with repeated BP measurements between the 90th and 95th percentiles for gender, age and height is considered to have high normal BP (pre-hypertension) and those with BP measurements >95th percentiles on at least three occasions are considered hypertensive.[26] Children under 5 years of age must also be considered. For example, the incidence of hypertension in the neonate has been estimated to be from 0.2% to 2.6%.[27]

A survey of North American paediatric nephrologists polled current practices in the management of paediatric hypertension. Of the 190 respondents, 47% and 37% chose ACE inhibitors (ACEIs) and calcium channel blockers (CCBs), respectively, as first-line treatment of primary hypertension. The use of diuretics and β-adrenergic receptor antagonists was also recorded. Angiotensin II type 1 receptor antagonists (angiotensin receptor blockers [ARBs]) were a minor second-line agent.[28] A more recent publication now indicates ACEIs, ARBs and CCBs as candidates for first-line therapy.[29]

The cardiac, vascular and organ receptors involved in BP regulation may not show the same level of sensitivity to an endogenous ligand or to a drug at different developmental ages. Differences in responsiveness may be due to differential maturation of receptor subtypes, signal transduction or effector proteins.[27]

Cell culture and experimental models of heart failure and hypertension have indicated involvement of the renin-angiotensin system and angiotensin II in the pathophysiology of cardiac hypertrophy and failure. Activation of the angiotensin II type 1 receptor mediates hypertrophy in both neonatal and terminally differentiated cardiac myocytes.[30] The heart increases in size firstly by cellular hyperplasia then by cellular hypertrophy.[31] The long-term effects of ACEIs and ARBs in decreasing hypertrophy of normal cardiac growth, in addition to pathological hypertrophy in cardiac disease, are not known.

1.4 Psychiatric and Neurological Conditions

The use of psychotropic medications in both the preschool population and in male and female populations under 20 years of age in general has increased significantly in the recent past,[32,33] as confirmed by a complete MEDLINE search of references from 1996 to the present. A number of psychiatric disorders, e.g. pervasive developmental disorders, are manifested and diagnosed within the first 3 years of life. Therefore, children may be treated at a very early age.[34] As the disorders tend to be chronic, children and adolescents may receive long-term treatment with psychotropic medications. Moreover, multiple medication use is common in the treatment of complex behavioural disorders that are refractory to therapeutic interventions. The rate of polypharmacy and the risk of adverse effects due to drug-drug interactions are increased further by unknown mechanisms when concurrent use of alternative nutraceuticals is employed. The alternative therapies include herbs, vitamins, nutritional supplements and chemicals such as chelating agents. These products carry their own unknown risks of adverse

drug reactions as well as contributing to amplified risks of pharmacological interactions.[35]

Drugs used for psychiatric disorders in children and adolescents include amfetamine mixed salts, modafinil, atomoxetine, risperidone, aripiprazole, lithium, valproate semisodium, carbamazepine, methylphenidate, clonidine, guanfacine, imipramine, clomipramine, desipramine, trazodone, venlaxafine, mirtazapine, lamotrigine, levetiracetam, haloperidol, chlorpromazine, fluphenazine, pimozide, thioridazine, trifluoperazine, tiotixene, olanzapine, quetiapine, ziprasidone, buspirone and amantadine.[36,37] All of these agents may have pharmacological effects upon the heart.

There has been a particular rise in the use of certain classes of psychiatric medications to treat some of the most serious symptoms such as psychosis, aggression and hyperactivity. For instance, the use of antipsychotic medications in children and adolescents is on the rise.[38] An examination in the US of trends in outpatient treatment of children and adolescents with antipsychotic drugs showed an increase in the absolute number of office-based visits from approximately 201 000 in 1993 to 1 224 000 in 2002, a 6-fold increase.[39] The rise in medication use may be due, at least in part, to a heightened awareness that psychiatric disorders may emerge in childhood or adolescence.[40] A recent analysis has demonstrated that outpatient visits with a diagnosis of bipolar disorder in individuals aged 19 years and younger have increased 40-fold from 25 per 100 000 in 1994–5 to 1003 per 100 000 in 2002–3. In contrast, the diagnosis of bipolar disorder rose 2-fold in the adult population over the identical time periods, increasing from 905 per 100 000 to 1679 per 100 000.[41] Furthermore, there is evidence of weight gain associated with antipsychotic drug use, as well as an increased risk of hyperlipidaemia, in adults given most antipsychotic medications.[42]

In the treatment of attention-deficit hyperactivity disorder (ADHD), combination therapy is commonly employed to palliate symptoms such as impaired concentration while improving the ability to sleep. One example of a drug used commonly as adjunctive therapy in the treatment of ADHD is clonidine. Clonidine, an α_2-adrenergic receptor agonist indicated for use in the treatment of hypertension in adult patients, is used off-label to treat other paediatric neuropsychiatric conditions including chronic pain, Tourette's syndrome, substance withdrawal and post-anaesthetic agitation.[43-47] Clonidine and guanfacine, also an α_2-adrenergic receptor agonist, have been used increasingly as second-line medication for the treatment of symptoms of ADHD, particularly among adolescents with hyperactivity and aggressiveness.[47-49] Although the effect of clonidine on the palliation of symptoms of ADHD is not as robust as that of CNS stimulants, it is used frequently in combination with stimulants such as methylphenidate, amfetamine mixed salts or modafinil for ADHD co-occurring with tics, aggression or conduct disorder.[50] Studies performed in adults report a significant decrease in circulating catecholamines after a single dose of clonidine as well as a decreased sympathetic nerve outflow.[51] It remains to be established how these parameters are affected in the paediatric population and how a long-term blockade of the sympathetic tone may affect normal post-natal maturation of the cardiovascular system. To answer this question would require years of follow-up and extensive evaluation of all of the drugs used to treat the same disorder, such as ADHD.

The pharmacology of many psychotropic drugs has been described to include cardiovascular and autonomic side effects. For example, pharmacological effects of tricyclic antidepressants (TCAs) as a class have been identified. These include cardiac conduction effects, anti-cholinergic effects, and they have been shown to modulate α_1-, α_2- and β-adrenergic receptors, dopaminergic, serotonergic and histaminergic receptors. β-Adrenergic receptor abundance is consistently decreased by both TCAs and monoamine oxidase inhibitors.[52,53] The presence of metabolic and endocrine adverse effects remains controversial.[54]

Reports of sudden, unexpected death in paediatric patients taking certain psychotropic medications has raised awareness of the effects of these drugs upon the cardiac conduction system, particularly the corrected QT interval (QTc). Certain medications may also unmask underlying cardiac disorders.[55,56] Sudden death has been described in children receiving desipramine, as well as combined treatment with methylphenidate and clonidine, although a causal association has not been established.[57] Tachycardia

has also been reported secondary to a number of medications. While tachycardia does not always generate the same concern as QTc prolongation, it is an indication of an effect on the cardiovascular system. Whether the origin of the tachycardia is due to an effect on the atrioventricular node, autonomic tone and local neural or central neural pathways is not always known.

In addition to acute effects, reports from the forensic literature raise the question of cardiomyopathy, myocardial infarction/necrosis and heart failure following long-term use of amfetamines.[58] While much of this concern is derived from 'recreational' use of amfetamines, this may be a flag to examine the sequelae associated with prolonged therapeutic use.[59-62]

Several investigators have attempted to assess the long-term cardiovascular effects of several commonly used CNS stimulants. One group performed a pooled analysis of cardiovascular data from five clinical trials of atomoxetine.[63] A second group compared effects following 4 weeks of treatment with mixed amfetamine salts extended release versus 2 years of treatment.[64] The third group performed a meta-analysis of 13 studies of atomoxetine used for a 2-year period in children.[65] All three manuscripts reported increases in pulse and BP. One study noted decreases in the cardiac PR interval.[65] None of the changes cited was considered clinically significant; however, two considerations remain: (i) Are the findings of significance over a longer period of time such as 5, 10 or 20 years? (ii) Without standardization of dose administration and collection of cardiovascular data, has the full extent of the changes been described?

Epilepsy remains one of the neurological disorders of childhood and adolescence that can be life threatening if untreated. Seizures have been reported to occur in approximately 0.15–3.5% of newborns.[66] The incidence of childhood (2–12 years of age) epilepsy is estimated at 45/100 000 population.[67] Adolescent epilepsy has a prevalence of 1.5–2%. Some childhood syndromes may remit during adolescence, others may persist or begin during this developmental period. Hormonal activity has been suggested to be involved with seizure susceptibility although this possible relationship is incompletely understood.[68]

The age-specific syndromes for infancy, childhood and adolescence have unique pathogeneses, treatments and outcomes. One recent review divides childhood epilepsy into four main prognostic groups. The first group is the 'benign' epilepsies, which are not manifest after a few years and pharmacological treatment can often be avoided. The second group is the 'pharmacosensitive' epilepsies (30% of patients), in which seizure control is easily achieved by medication and spontaneous remission occurs in a few years. The third group, are the 'pharmacodependent' epilepsies (20% of patients), These are able to be controlled by drug treatment, but drug withdrawal is followed by relapse. In this group, treatment is expected to be lifelong. The refractory ('pharmacoresistant') epilepsies are the fourth group (13–17% of patients).[69] It is beyond the scope of this article to discuss all the permutations of treatment options for the variety of seizure syndromes. Drugs used for epilepsy, anticonvulsants, are used commonly in the stabilization of psychiatric conditions such as bipolar disorder. Those drugs used for epilepsy include benzodiazepines, levetiracetam, carbamazepine, ethosuximide, felbamate, gabapentin, lamotrigine, oxcarbazepine, phenobarbital, phenytoin, tiagabine, topiramate, valproic acid, vigabatrin and zonisamide.[69]

While epilepsy itself may be associated with underlying endocrine and metabolic disorders, different antiepileptic drugs have been associated with effects on bodyweight, serum insulin levels and lipid profile.[70-75] Abnormalities of all of these are factors associated with an elevated risk of coronary artery disease. One investigator concluded that increased low-density lipoprotein-cholesterol and decreased apolipoprotein A1 seen in children receiving long-term, antiepileptic drug treatment could plausibly create a higher risk of atherogenesis than in healthy control children.[76] Concurrent medical conditions must also be considered: conditions that may occur concurrently with epilepsy include depressive disorder, ADHD, autism spectrum disorders, anxiety disorders and migraine. Sankar[77] has reviewed safety and efficacy considerations for management of paediatric epilepsy. Combinations of medications recommended for co-morbid conditions present additional possibilities for cardiovascular complications.

1.5 Asthma

The US Centers for Disease Control and Prevention reports asthma as one of the most common chronic medical conditions of children.[78,79] In 2001, it was estimated that 6.3 million Americans under the age of 18 years had asthma. The asthma-related hospitalization rate is highest for children aged 0–4 years.[80] For young children, the word 'asthma' may be used to encompass episodic and reversible obstructive airway disease characterized by wheeze, cough and breathlessness. Multiple aetiologies may produce these symptoms. The majority of the infants who wheeze are symptom free by the age of 6 years and do not need anti-inflammatory drug maintenance.[81] Treatment for wheezing and atopy may begin in infancy, out of concern for loss of pulmonary function. Wheezing and asthma are usually treated with inhaled glucocorticoids, β_2-adrenergic receptor agonists, anticholinergic drugs, leukotriene receptor antagonists and, on occasion, systemic glucocorticoids, cough suppressants and antibacterials.[81] The long-term effects of early intervention are not well described for the disease progression or for secondary effects. There are conflicting reports over the sequelae to the use of β-adrenergic receptor agonists[82] and glucocorticoids.[83] There are conflicting reports about inhaled glucocorticoids decreasing linear growth in the paediatric population.[84] To address these concerns, the US FDA issued a paper concerning the labelling of intranasal and inhaled glucocorticoids noting that growth velocity may be decreased even in the absence of hypothalamic-pituitary-adrenal axis suppression. The potential for 'catch-up' growth after discontinuation of treatment was described as 'not well studied'. The ultimate recommendation is for a weighing of potential risk to clinical benefit.[85] The situation is similar to the question of cardiac toxicity: there are questions requiring long-term follow-up. As the answers may never be available, the clinical benefit must be weighed against potential risk.

Since glucocorticoids potentiate catecholamines due to their extraneuronal noradrenaline (norepinephrine) uptake blocking properties,[86] there were also concerns about inhaled glucocorticoids being potentially dangerous to the heart when combined with β-adrenergic receptor agonists. However, some studies have indicated that salmeterol, a long-acting β_2-adrenergic receptor agonist, has a safety profile comparable to placebo even when combined with high-dose inhaled glucocorticoids.[87,88]

1.6 Cancer

New therapies turn certain types of cancer into a chronic condition, increasing the importance of long-term drug effects. Increasing numbers of childhood cancer patients are surviving for more extended periods. Studies in the UK showed 5-year survival for children with malignancies to be approximately 25% in the 1960s and almost 75% in the 1990s.[89] By the year 2010, approximately 1 in every 250 adults aged 20–45 years in the US may be a survivor of malignant disease in childhood or adolescence.[90] For long-term health and survival, cardiac growth needs to match somatic growth. One follow-up study of young (median age 22.8 years) survivors at a median of 13.5 years after treatment completion showed 58% of the 290 people studied had at least one chronic medical problem; endocrine, cardiac and pulmonary problems were the most common.[89]

Doxorubicin, a very effective chemotherapeutic agent for childhood neoplasias, is associated with both acute (during treatment or during the first year after its completion) and delayed cardiac toxicity, such as continued myocardiocyte loss, myocardial fibrosis and failure of myocardial growth. Acute effects include dysrrhythmias, myopericarditis and LV failure. The delayed toxicity of decreased LV function may appear years after conclusion of treatment with the incidence of severe echocardiographic abnormalities increasing with duration of follow-up[90] and doses ≥279 mg/m^2.[91] Cardiac toxicity has also been associated with other agents such as cyclophosphamide, fluorouracil, amsacrine, ifosfamide, cytarabine, paclitaxel, cisplatin, busulfan and mitomycin. Cardiac effects with these agents are usually seen within days to weeks of completion of dose administration. Cisplatin toxicity may occur up to 18 months following completion of dose administration.[92,93] One study of patients with Hodgkin's lymphoma showed an increased relative risk of cardiac death following radiation therapy that was highest for those under 20 years of age at the time of

treatment and a decreased risk with increasing age at treatment. A point made in a review of adolescent Hodgkin's lymphoma is the significant evolution of treatment regimens over the past 10–20 years. Therefore, studies comparing long-term outcomes may be examining outdated regimens.[94]

1.7 HIV Infection

Approximately 2.3 million children aged <15 years worldwide are infected with the HIV virus. Most live in Southeast Asia and sub-Saharan Africa.[95] As improvements in therapy have led to an increase in survival, the effects of chronic HIV infection on different organ systems have become better recognized in both children and adults. The virus itself can cause cardiac and metabolic changes.[96,97] Autopsies and retrospective analyses estimate that cardiac lesions may be present in 25–75% of AIDS patients.[98] How this compares to an age-matched control cohort is unclear.

The most common manifestations of HIV in the cardiovascular system include pericardial effusion, myocarditis, dilated cardiomyopathy, endocarditis, pulmonary hypertension, cardiac neoplasms, drug-related cardiotoxicity, highly active antiretroviral therapy (HAART)-associated metabolic complications and coronary artery disease.[99] Echocardiographic findings in HIV-infected children include LV dysfunction, increased LV mass, myocarditis and pleural effusion. In a prospective, multicentre study of 205 HIV-positive, vertically infected children, the 5-year cumulative incidence for LV end diastolic dilatation was 21.7% while heart failure and/or use of cardiac medications was 28.8%.[100]

The multiple drugs used for controlling the primary infection and subsequent opportunistic infections may result in adverse effects from individual agents, adverse drug interactions and unknown long-term drug toxicities that result from the interactions. Antiretrovirals may slow the viral damage to the heart but still make their own contributions to cardiac myocyte disruption. Metabolic complications associated with HAART include lipodystrophy, dyslipidaemia, insulin resistance, hyperlactataemia, osteopenia and growth failure. The maldistribution of fat, dyslipidaemia and insulin resistance may predispose to future cardiovascular disease and type 2 diabetes, although data on long-term consequences in children are not available. It should also be considered that many patients may have underlying diseases or metabolic conditions that the drugs will either unmask or exacerbate.[101] The levels of plasma cholesterol found in a study of Swiss HIV-infected children treated with protease inhibitors were similar to lipid levels in children with heterozygous familial hyperlipidaemia. Patients with heterozygous familial hyperlipidaemia usually develop heart disease after the third decade of life. The increased relative risk of coronary artery disease for children with HIV is probably minimal until they reach adulthood.[102] While the long-term effects of antiretroviral drugs are now being characterized, it must be remembered that the benefits clearly outweigh the potential adverse effects.

2. Pharmacokinetic and Metabolic Considerations

Adult clinical data do not necessarily provide an accurate picture of paediatric pharmacokinetics or metabolic profile. Acute age-related differences in medication sensitivity may be maturational or genetically based differences in metabolism or pharmacokinetics. The overall differences of children versus adults can be seen in terms of body water : body fat ratio, age-related gastrointestinal absorption, distribution, excretion, renal function and drug-metabolizing enzyme development.[103-105] Adult levels in each of these categories are reached at different times with all possible permutations. While cytochrome P450 enzyme levels are below adult levels through to 6 months of age, there are *in vivo* data to suggest that the activity levels in children reach and even surpass adult levels, possibly due to a larger liver mass per bodyweight.[106] It is also possible for children to have a different metabolite profile for a given drug compared with adults, as exemplified by paracetamol. From neonates up to the age of approximately 9 years, paracetamol sulphate is the major metabolite, whereas after 9 years of age, the glucuronide is the main metabolite. In this case, the qualitative difference in metabolites does not pose a safety risk. The same metabolites may also have different rates of clearance in different age groups, as demonstrated with morphine. Morphine-6-glucuronide is a more potent analgesic than morphine. The immature glucuronosyl trans-

ferase system that exists early in post-natal life may contribute to a prolonged pharmacological effect and therefore an increased risk of adverse reactions to morphine in infants.[107] While the metabolite profile in adults and laboratory animal species may be well studied and the activity of major metabolites characterized, the same can not always be said for the metabolite profile in children. There is little knowledge of drug effects on the interdependent processes of cardiac maturation and even less knowledge of metabolite effects.

Adjusting dose only on the basis of pharmacokinetics implies that adults and children are developmentally similar and ignores differences in dynamics of response. As an example, developmentally associated changes in myocardial Na-K-ATPase have been described in dogs, guinea pigs, rats and humans.[108,109] In humans, the mean value of Na-K-ATPase found for 0–6 months of age was 1.6-fold of the mean value found for the age range 6 months to 8 years. The total amount of Na-K-ATPase was approximately 30 nmol within the first 3 years and 80 nmol at age 8 years.[109] Age-related differences in cardiac glycoside toxicity and sensitivity may be related both to age-dependent changes in volume of distribution, changes in myocardial mass with growth and also to changes in myocardial Na-K-pump concentration. Doses of digoxin are adjusted for premature neonates, term neonates and infants/children. Methods for extrapolation from adult dosages are frequently inaccurate.[110]

To further complicate the monitoring, digoxin-like immunoreactive substances (DLIS) have been identified in the serum of neonates even in cases where neither the mother nor the child received digoxin during gestation. While the concentration of these DLIS are reported to peak within a few days of birth and decline thereafter, DLIS have been found in the serum of children up to 6 years of age.[111] Digoxin hepatic metabolism only accounts for about 16% of its elimination and is not dependent on the cytochrome P450 system.[112] Renal clearance is the main elimination pathway for digoxin in humans[113] and is correlated with the glomerular filtration rate. Most (57–80%) digoxin is excreted unchanged by glomerular filtration without significant reabsorption by the renal tubule, while up to 28% is eliminated by non-renal routes.[114] However, digoxin is also secreted via P-glycoprotein (P-gp) located on the luminal membranes of the renal proximal tubules.[115,116] In mice, changes in digoxin clearance rates with age were correlated with P-gp expression in the kidney,[117] suggesting that human infants and toddlers are likely to have higher renal clearance of P-gp substrates. The higher clearance in these children is the result of both early achievement of the adult level of P-gp expression in the kidney as well as increases in the glomerular filtration rate to levels above those of an adult.[118] Information on long-term follow up of cardiac growth and function following digoxin treatment was not found.

Like digoxin, the clearance of carvedilol is more rapid in paediatric patients than in adults,[119] and this may have contributed to a finding of no significant improvement in clinical heart failure outcomes in children and adolescents with symptomatic systolic heart failure.[120] The authors of this study propose a differential effect of carvedilol in children and adolescents based on ventricular morphology. However, differences may also be based on yet unknown developmental effects on receptor coupling and sub-cellular signalling.[121,122]

3. Non-Clinical Assessment of Developmental Cardiac Toxicity

The embryology and peri-natal changes of the heart have been highly detailed primarily through animal and *in vitro* studies.[123-125] Changes after the peri-natal period are less well described. Much of this information is also derived from animal studies. While some human data are available, the sample sizes are typically small and sampling bias must be considered when assessing how applicable the information is to the general population.

Extrapolating animal data to humans assumes similarity of processes and developmental stages. Birth is not a timepoint when all species are at a similar degree of anatomic, functional and behavioural development.[126] As one example, there are differences in the degree of cardiac innervation at birth among commonly used laboratory animal species.[127] This particular difference may alter the timing of the overall maturation process due to the role of sympathetic innervation in coordinating several developmental steps. There is no one animal

species that serves as the complete surrogate model for human cardiovascular development.

In the non-clinical safety assessment for a drug in development, an immature cardiovascular system is routinely encountered in Segment III reproductive toxicology studies, where rat pups may be exposed to a drug late in gestation and during lactation. The assessment of the pups at the end of the study is through growth, external landmarks of development and tests of learning and behaviour. Clinical chemistry and haematology are not routinely studied. Even though exposure to a drug occurs after the major gross anatomical development of the heart and great vessels is complete, premature decedents are examined only for gross anatomical defects. Functional assessment of the cardiovascular system is rarely if ever performed. Thus, there are significant gaps in the understanding of developmental effects of most new therapeutic agents when they are in the clinical trial phase.

4. Legislation Pertaining to Paediatric Studies

Paediatric care involves both label and off-label use of drugs, sometimes based upon clinical lore without controlled trials. Several regulatory actions have been taken by the FDA to encourage clinical research on the effects of pharmaceuticals in children.

The relevant legislation is in several Acts including:

- FDAMA (Food and Drug Administration Modernisation Act of 1997, Public Law No. 105–115, 111 Stat. 2296) and the subsequent Pediatric Rule of 1998 (21CFR201.23).
- BPCA (Best Pharmaceuticals for Children Act of 2002, Public Law No. 107–109, 115 Stat. 1408).
- PREA (Pediatric Research Equity Act of 2003, Public Law No. 108–155, section 505B21USC355B).

Under the FDAMA, section 11, manufacturers can obtain 6 months of additional marketing exclusivity for certain drugs if they conduct paediatric clinical studies as specified in a written request issued by the FDA. Sponsors may receive exclusivity even if the results of the trial are not statistically significant. As of March 2007, 568 paediatric studies have been completed since 1998 with many labelling changes as a result of information produced by these studies. Further information may be found at the following website: www.fda.gov/cder/paediatric/lablechange.htm.

The provisions for the study of paediatric drugs under the FDAMA applied to drugs under patent only and for which manufacturers had an economic incentive (exclusivity). There remained a considerable number of widely used ‘off-patent’ drugs that were not studied for various aspects of their activity in children. This led to the enactment of the BPCA in 2002, which, in addition to re-authorizing the exclusivity provisions of the FDAMA, provided a mechanism for studying ‘off-patent’ drugs. This Act gives authority to the US National Institutes of Health (NIH) for drug development activities that fall into three general categories:

- identification of drugs needing study;
- written requests from the FDA to the manufacturers to conduct paediatric studies deemed necessary;
- referral of the drug to the NIH to conduct necessary testing should the sponsor decline to do so. The BPCA provides for a fund to be available for such testing.

With the enactment of the PREA in 2003, the FDA has had the opportunity to exert considerable influence on the conduct of clinical studies in the paediatric age group. Not only does the approval of a new molecular entity through the New Drug Application process require paediatric studies (or a carefully argued reason for waivers from such studies), but also any change in formulation, mode of administration or dosage of a previously approved drug leads to a requirement for paediatric clinical studies. This is most noteworthy in the area of suitability petitions for generic drugs where changes in the proposed generic drug may precipitate a requirement for a paediatric study under the PREA. Both the BPCA and the PREA were due to expire on 30 September 2007 but have been extended in Title IV (PREA) and Title V (BPCA) of the House of Representatives bill H.R. 3580.

These measures have had some success in encouraging a more data-driven understanding of how drugs work in the paediatric population. However, clearly questions still remain.

5. Future Trends and Needs for Additional Research

In preparing this article, the literature was searched for information on paediatric cardiovascular development. The original intent was to collate the existing data on the long-term effects of specific drugs when used in children. However, while there has been much research about different aspects of the post-natal cardiovascular system, long-term follow-up to drug use was extremely rare in the literature. It was also very difficult to identify developmental windows that might be especially sensitive to pharmacological perturbation. Nowhere did we find a comprehensive synthesis or integration of the changes involved in cardiovascular maturation. Nor did the material that exists in the scientific literature permit an adequate characterization of post-natal development. Global gene and protein expression data were also missing from the literature at the time of writing.

There is an increasing body of literature regarding molecular and cellular aspects of cardiac toxicants. Most of this work involves mature rodent hearts, cell culture or *in vitro* techniques. There are few prospective clinical trials in children with long-term follow-up. Less is described regarding sex-related or ethnic differences in cardiac growth and development. An understanding of the normal processes of cardiovascular maturation is necessary for identifying abnormal processes.

Functional assessment of the cardiovascular system with comparison to an appropriate cohort may be a useful measure in paediatric trials, but this kind of evaluation is rarely seen. The endpoints typically used in adult clinical trials, i.e. death, myocardial infarction and stroke, are rarely seen in the paediatric population. It has also been recognized that true clinical endpoints do not occur in proximity to the surrogate marker being used.[128] It is not clear how to identify delayed toxicities in addition to acute effects. As seen with doxorubicin, delayed toxicities may take years to manifest, with many patients lost to follow-up. This is clearly an area where intermediate or surrogate endpoints are necessary. Pharmacogenomics may be useful in providing markers of increased risk or susceptibility.

6. Conclusions

We asked whether prescription drugs could alter paediatric cardiovascular development and what the likelihood of exposure to prescription drugs is. There are emerging health and social issues that have resulted in an increased number of children receiving medications of all classes for serious medical needs. Diseases typically associated with adults are now appearing in younger populations and require treatment. There is no question that many children are deriving significant health benefits from many of the medicines in use. After examining the current medical literature, our conclusion is that a significant number of children will be exposed to one or more known cardioactive medications during the period of cardiovascular development. It is unclear how best to monitor for short- and long-term adverse consequences. Clearly, the administration of drugs to individuals with developmentally immature organ systems must be recognized as a legitimate issue that needs to be addressed and resolved in some fashion prior to widespread administration of potentially valuable therapeutic agents to paediatric populations. The lack of data for long-term outcomes of treatment impedes understanding of this problem. The availability of relevant data could either put the issue to rest or lead to an understanding of how to prevent the problem. As in all things, a balance must be kept between concern over possible long-term risk and the very real immediate benefits of a given treatment.

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Correspondence: Dr *Elizabeth Hausner*, Food and Drug Administration, Office of Drug Evaluation I, CDER, Division of Cardiovascular and Renal Drug Products, 5901-B Ammendale Road, Beltsville, MD 20705-1266, USA.