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Optimising the use of medicines to reduce acute kidney injury in children and babies

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ABSTRACT

The majority of medications in children are administered in an unlicensed or off-label manner. Paediatricians are obliged to prescribe using the limited evidence available. The 2007 EU regulation on the use of paediatric drugs means pharmaceutical companies are now obliged to (and receive incentives for) contributing to paediatric drug data and carrying out paediatric clinical trials. This is important, as the efficacy and adverse effect profiles of medicines vary across childhood. Additionally, there are significant age-related changes in the pharmacodynamic and pharmacokinetic activity of many drugs. This may be related to physiological (differential expressions of cytochrome P450 enzymes or variable glomerular filtration rates at different ages for example) and psychological (increasing autonomy and risk perception in teenage years) changes.

Increasing numbers of children are surviving life-threatening childhood conditions due to medical advances. This means there is an increasing population who are at risk of the consequences of the long-term, early exposure to nephrotoxic agents. The kidney is an organ that is particularly vulnerable to damage as a consequence of drugs. Drug-induced acute kidney injury (AKI) episodes in children and babies are principally due to non-steroidal anti-inflammatory drugs, antibiotics or chemotherapeutic agents. The renal tubules are vulnerable to injury because of their concentrating ability and high-energy hypoxic environment.

This review focuses on drug-induced AKI and the methods to minimise its effect, including general management plus the role of child-specific pharmacokinetic data, the use of pharmacogenomics and early detection of AKI using urinary biomarkers and electronic triggers.

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Abbreviations: AKI, acute kidney injury; TIN, tubulointerstitial nephritis; EU, European Union; CF, cystic fibrosis; CKD, chronic kidney disease; GFR, glomerular filtration rate; NSAIDs, non-steroidal anti-inflammatory drugs; COX inhibitors, cyclooxygenase inhibitors.

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1. Introduction

The majority of prescribed medications in children are administered in an "off-label" or unlicensed manner. This means that they are prescribed for either an unapproved indication, age group, formulation or dosage due to a lack of regulatory approval to meet the acceptable standards of efficacy, safety and quality (Frattarelli et al., 2014). Paediatricians therefore prescribe most medicines using the best available evidence in the best interests of their patients. The reason for medications having to be prescribed in this manner is due to the lack of evidence to inform regulatory bodies, as previously there were no financial incentives to undertake the necessary studies.

The pharmaceutical industry is no longer permitted to develop new medicines for use in adults only. In 2007 the European (EU) Union introduced a new regulation concerning medicinal products that are indicated for use in paediatric populations (Hawcutt & Smyth, 2008). Parallel legislation exists in the US (Turner, Catapano, Hirschfeld, & Giaquinto, 2014). The EU Paediatric Drug Regulation aims to encourage more high quality ethically sound research in children and adolescents to promote the achievement of marketing authorisation in a greater number of medicines. This was achieved through the introduction of Paediatric Investigation Plans (PIPs), offering substantial funding incentives to the pharmaceutical industry for contributing to paediatric pharmacology research (van Riet-Nales et al., 2014). Pharmaceutical companies who now complete a PIP can be rewarded with a six-month extension to the patent of their product. Furthermore so called 'orphan drugs', those that have been developed to treat a rare condition in children, are now rewarded with two years market exclusivity, and any off patent drug designed for children will get an eight-year data and ten-year market exclusivity for that indication (Paci & Vassal, 2012). Since the introduction of these EU incentives, there has been an increase in the proportion of clinical trials that include children (Turner et al., 2014).

Child-specific data is very important. Children are distinct from adults and even differ across infancy and childhood as they are undergoing extensive physiological and psychological changes during growth and development. In children the bioavailability, volume of distribution, metabolism and clearance of drugs differs from adults. Differences exist in gastric pH, intestinal emptying and bile and pancreatic acids in children together with increased total body water and alterations in membrane permeability affecting drug distribution (Fernandez et al., 2011). The hepatic blood flow and metabolising enzymes are decreased with implications for drug metabolism; excretion is affected by the immature glomerular filtration, renal tubular secretion and tubular reabsorption of children, especially babies. These changes are particularly true in the younger population such as the neonate (de Wildt, Tibboel, & Leeder, 2014), during critical illness or in children with co-morbidities (Liborio, Branco, & Torres de Melo Bezerra, 2014). In a similar manner to adults, drug interactions and genetic variations may also exist. Using adult data to directly guide the use of drugs in children therefore has its limitations, and it is for this reason that they deserve dedicated pharmacological research using a translational approach (Fig. 1).

In addition to differences in drug handling in children, the consequences of childhood drug exposure on organs including the kidney may only become apparent once the child grows into an adult. Due to advances in medical management, many children are now surviving previously life-threatening conditions: for example, the survival rate of extreme prematurity (those infants born <27 weeks gestation) has improved from 62% to 81% over the past 20 years (Bode et al., 2009), and death from multi-organ failure has halved (Joffe, Anton, & Burkholder, 2011). Survival rates from childhood leukaemia have dramatically improved from 28% in 1968 to current rates of 81% (in 2005) and 0.1% of all adults are now survivors of childhood cancer (Basta, James, Gomez-Pozo, Craft, & McNally, 2011; Mariotto et al., 2009). This pattern is seen in chronic disease states too: the life expectancy of patients with cystic fibrosis (CF) is now around 40 years of age (Harness-Brumley, Elliott, Rosenbluth, Raghavan, & Jain, 2014). With this increased survival long-term renal morbidity associated with treatment in childhood is now being identified in adults. For prematurity, childhood cancer and cystic fibrosis chronic kidney disease (CKD) in later life is now recognised (Mulder et al., 2013; Quon, Mayer-Hamblett, Aitken, Smyth, & Goss, 2011; Rodriguez-Soriano, Aguirre, Oliveros, & Vallo, 2005); furthermore, adult patients with CF have an annual prevalence of CKD of over 2%. In each of these patient groups the CKD risk is directly related to the earlier exposure of nephrotoxic agents and perhaps even acute kidney injury (AKI) episodes. Previous studies demonstrate that even with normal baseline renal function, a single AKI episode increases the risk of CKD by up to 1.9–13 times (dependent on the definition of severity used) when compared to a matched non-AKI population, even after a short follow up period (Belayev & Palevsky, 2014). Although it should be noted that the findings described in all of these studies are merely proposed causal associations.

Thus, it is important to note that as a consequence of medical advances, where intensive treatment with antibiotics improves outcomes and acute organ injury can be managed, and as life expectancy rises, the burden of CKD due to nephrotoxic drug exposure causing AKI in childhood is likely to increase. This increasing risk emphasises the importance of preventing AKI through a person-centred approach to ensure patients obtain the best possible outcome from their medicines in a safe and effective way. This is termed medicines optimisation (NICE, 2015). The aim of this review is to illustrate and discuss ways in which the use of nephrotoxic medications in children could be optimised in order to reduce AKI episodes and subsequently minimise the long-term risk of CKD.

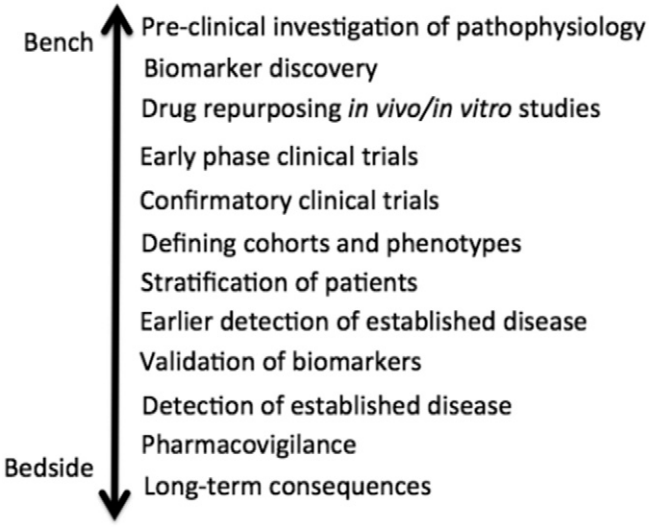

Fig. 1. The translational pathway (from 'bench' to 'bedside' and back again) illustrating the clinical and research requirements in order to reduce drug-induced kidney injury.