Using pharmacogenetics to understand adverse drug reactions in children

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Two patients undergo chemotherapy for osteosarcoma of the right proximal tibia. The patients are the same age, were diagnosed within two years of one another, and received identical chemotherapy regimens consisting of cisplatin, doxorubicin and methotrexate. Treatment was successful – both patients are alive and well. However, after only two cycles of chemotherapy, one patient developed bilateral hearing loss with a progressive decline in audiological function, while the other patient's hearing remained unimpaired. Ototoxicity is a well-characterized adverse drug reaction (ADR) to cisplatin, but why two patients who are so alike can experience profoundly different outcomes is perplexing. Heterogeneity of drug response is a common issue encountered in clinical practice.

ADRs
As exemplified in the case described above, drug therapy can result in undesirable adverse effects referred to as ADRs. ADRs range in severity, but can be permanently disabling or life-threatening. Children are at greater risk for ADRs due to a lack of formal testing of pharmaceuticals in paediatric populations. More than 75% of drugs have never been tested in children, and research that is conducted in children is based on small sample sizes (1). In the past, it was assumed that children respond to drugs in the same way as adults, as long as the dose is adjusted for a smaller body mass. However, because drug metabolizing enzymes, transporters and drug targets may undergo developmental changes as children age, this assumption may not be valid for all drugs and can impact the safety of medications in children (1). For some drugs, age-dependent metabolic differences are known, and dosing is adjusted to avoid dose-related toxicities. On the other hand, the underlying risk factors for many ADRs remain unknown, particularly for ADRs that are dose independent.

PHARMACOGENOMICS
Drug response is influenced not only by clinical and environmental factors, but also by a patient’s genetics. Genetic variation in drug metabolizing enzymes, drug transport systems and drug targets can lead to severe toxicity (2). Pharmacogenetics (also known as pharmacogenomics) is the area of research focused on the discovery of genetic variants that influence drug response, which can then be used to identify those at increased risk of experiencing an ADR. The terms pharmacogenomics and pharmacogenetics are often used interchangeably. Pharmacogenomics refers to the simultaneous study of many genes that may affect drug response, while pharmacogenetics refers to research focused on a few specific genetic variants.

The search for genetic biomarkers is commonly conducted using a case-control study design. DNA samples are collected from both cases (patients with ADRs) and controls (patients taking the same drug without ADRs), and the frequencies of genetic variants are compared between the two groups. Any genetic marker that is observed at a higher frequency in the cases compared with controls is a potential risk marker. The most commonly investigated genetic variants are single-nucleotide polymorphisms (SNPs). SNPs are alterations of a DNA sequence in which a single nucleotide is replaced by another nucleotide. Researchers may focus on SNPs in candidate genes or targeted metabolic pathways, or perform genome-wide association studies, in which more than one million SNPs can be investigated simultaneously. Strategies based on candidate SNPs, genes or pathways are the most classical approaches, but they require previous knowledge about the mechanisms underlying an ADR. In contrast, genome-wide association studies are more exploratory and can identify candidate SNPs that were not known to be involved in a particular ADR. Because of multiple comparisons of thousands of genes, a significant result requires an extremely low P value in these studies.

Following the identification of potential genetic markers, replication and validation of these findings in additional cohorts is crucial to confirm the association of a genetic marker with an ADR. This is especially important in genome-wide screenings because the large number of genetic variants investigated increases the possibility of chance findings. Once a pharmacogenetic marker is validated, it can be incorporated into a diagnostic test that can assist physicians in deciding which drug and which dose will be both safe and effective for a particular patient. In reference to the cisplatin case described previously, it is now known that variants in two genes, TPMT and COMT, are associated with cisplatin-induced hearing loss in children (3). More than 90% of children carrying at least one risk variant were shown to develop moderate to severe hearing loss. Testing for these variants before the start of therapy could identify children at increased risk of hearing loss and enable their therapy to be tailored accordingly.

As for many nongenetic predictive biomarkers, a pharmacogenetic marker cannot guarantee that a patient will or will not experience an ADR. Instead, it can warn a physician about potential complications and help them to make a more informed decision about what therapy would be best for their patient. When determining how this genetic information should be used in clinical practice, factors that need to be considered are the availability of equally effective alternative drugs, the severity and implications of the ADR itself, and the risks associated with altering a therapy regimen that has been shown to be effective. In the example of cisplatin, carboplatin may be used as an alternative drug for some tumours in carriers of genetic risk variants. For other patients, no
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equally effective alternative drug is available. Therefore, we need to determine whether otoprotective drugs could be used to prevent hearing loss in patients with a high genetic risk, or whether a different dosing scheme could prevent ototoxicity in these patients without compromising therapeutic effectiveness. In all patients with risk variants, increasing the frequency of audiograms could help to detect hearing loss earlier and reduce the debilitating consequences of this ADR.

Most pharmacogenetic markers have been discovered in adult patients, and it is unknown whether they have the same predictive value in children. Because developmental changes can affect the impact of genetics on drug response, it is inaccurate to rely solely on results from adult pharmacogenetic studies for therapeutic decision-making in children. This is evident in the case of the anticoagulant warfarin. In adults, it is well documented that polymorphisms in two genes, CYP2C9 and VKORC1, have a significant effect on warfarin dosing, and that variants in these genes can result in life-threatening bleeding or thromboembolism. However, a recent paediatric study on warfarin pharmacogenetics did not produce the same results (4). This study found that age had more impact on warfarin dosing in children than VKORC1 or CYP2C9 genotypes, suggesting a reduced importance of these gene variants for warfarin dosing compared with adults. Therefore, pharmacogenetic studies that focus exclusively on children are of the utmost importance to understand how genetics influence paediatric drug response and to determine which children are at increased risk of experiencing an ADR.

ADR SURVEILLANCE

In Canada, health care professionals voluntarily report ADRs to Health Canada, generating alarm signals for potential drug safety risks. However, this passive reporting system possesses many flaws, with the most notable being insufficient reporting of ADRs. It is estimated that 95% of ADRs go unreported, and those that are reported lack important details regarding dose and time of onset of the suspected reaction (5). Active ADR surveillance is one possible solution to this problem because it enables enrollment of a large number of patients while also collecting high-quality reports. An example of this type of surveillance system is The Canadian Pharmacogenomics Network for Drug Safety (CPNDS). The CPNDS is a unique, nationwide active ADR surveillance network with dedicated surveillance clinicians, located in 13 paediatric hospitals across Canada, who are specifically trained to identify and report ADRs in children (6). This targeted approach to ADR reporting has proven to be very successful in the past, with the CPNDS identifying genetic factors causing cisplatin-induced hearing loss (3) and codeine-induced neonatal opioid toxicity (7).

USING PHARMACOGENETICS IN CLINICAL PRACTICE

Increased awareness of pharmacogenetic effects is vital for reducing the occurrence of ADRs. In 2009, the CPNDS reported an association between a CYP2D6 gene duplication and neonatal central nervous system depression following codeine exposure while breastfeeding (7). Before this study, codeine was considered to be compatible with breastfeeding by the American Academy of Pediatrics (8). The CPNDS is working with health authorities to increase our understanding of this fatal, yet avoidable ADR.

For appropriate use of genetic information, improved guidance for physicians is needed. Clinical practice guidelines and other decision tools that explain when a genetic test should be performed and how therapy regimens should be adjusted based on the results must be developed. A survey among primary care physicians in the United States found that while 76% had received some training in clinical genetics, only 4% felt confident counselling patients about genetic testing (9). Thus, whether the promise of pharmacogenetics and personalized medicine can be fulfilled depends not only on discovery and validation of genetic markers, but also on training of physicians and development of evidence-based guidelines that will facilitate the use of genetic knowledge in clinical settings.

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