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IMPROVING PEDIATRIC DRUG SAFETY: NEED FOR MORE EFFICIENT CLINICAL TRANSLATION OF PHARMACOVIGILANCE KNOWLEDGE

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ABSTRACT

There is urgency to improve the evaluation of pediatric drug safety in the pre-market and post-market phases of drug evaluation. The need to improve pharmacovigilance methods concerns not only new drugs but also existing drugs that have been used for many years in an off-label manner in children. Effective methods for early detection of adverse drug reactions (ADRs) and drug safety epidemiologic studies are a pressing need in pediatrics. Moreover, the nature and severity of an ADR as well as the extent to which the suspected drug is being used, will determine how quickly the information about risk needs to be made available to users and what would be the most appropriate method of communication. Based on our experience through the Genotype-specific Approaches to Therapy in Children study, an active ADR surveillance network of pediatric hospitals across Canada, we present five strategic elements that should be included in pharmacovigilance initiatives in pediatrics: active ADR surveillance; drug or ADR targeted pharmacovigilance; trained surveillance clinicians; case-control methodology and standardized procedures for recognition; reporting and evaluating drug-induced harm. In addition, linking pharmacovigilance with pharmacogenomics to find drug safety solutions is presented as a promising strategy for knowledge generation. Finally, we discuss the importance of an efficient translation of the pharmacovigilance knowledge into clinical practice to achieve safer drug therapy in children.

Keywords: *Pediatric drug safety; pharmacovigilance; surveillance; adverse drug reactions; knowledge translation; risk communication*

Lazarou's seminal work suggesting that more than 100,000 patients die each year in the United States from properly prescribed and utilized drug therapy[1] is suggestive of another "drug problem" that is often overlooked in health care delivery – that of adverse drug reactions (ADRs) which can be even more severe and more difficult to detect in children.

The paradox of modern drug development is that clinical trials provide evidence of efficacy and preliminary safety for a medication at standardized doses in carefully constructed, homogeneous populations, while individual patients are treated who often differ in their response to drug therapy, sometimes with devastating results. ADRs account for an alarming 7% of all hospital admissions[1,2], yet retrospective review of ADR reporting shows that less than 5% of ADRs are reported.[3,4] Systematic examination of medical outcomes from ADRs is clearly impossible if only 5% of the actual reactions are ever reported. Severe ADRs account for many drug withdrawals, and unfortunately, may not be recognized for years after a drug has been on the market. For example, pemoline, a central nervous system stimulant used mainly in children with attention deficit hyperactivity disorder (ADHD), was on the U.S. market for 30 years before withdrawal in 2005 due to reports of severe liver toxicity. Furthermore, at least 16 drugs have been withdrawn from the market because of ADRs since 1998.[5] Market withdrawal remains a blunt

instrument in preventing ADRs. In fact, many patients benefit from drugs for which a relative few patients suffer severe reactions. Without a means to identify those patients at risk for an ADR and to communicate the risk in a timely manner to health professionals and the public, the patients who would have benefited from these drugs are now denied these drugs if market withdrawal is the strategy of remediation.

Of particular concern is the alarming lack of understanding we have of ADRs in children augmented by the scarcity of comprehensive pediatric-specific programs aimed at identifying, treating, and preventing ADRs. There is a critical need to therefore improve pediatric drug safety evaluation both in the pre-market as well as during post-marketing phases of drug evaluation. The need to improve pharmacovigilance methods concerns not only new drugs but also existing drugs that have been used for many years in an off-label manner in pediatric care. Moreover, as soon as any risk is detected it needs to be effectively communicated to prescribers and patients followed by periodic updates of further studies being conducted to address the initially-identified safety concerns. The nature and severity of the ADR, and how widely the drug is being used can be key determinants of how quickly safety information should be made available to prescribers and monitors of drug therapy. These determinants can also inform the timeline for regulatory action and the most appropriate method of communication to health care professionals and patients.

The purpose of this paper is to discuss current pharmacovigilance methods which may have direct impact on the safe use of drugs in children. We propose some strategies to find pediatric drug safety solutions in a timely and efficient manner. Finally, we discuss the importance of an efficient translation of the pharmacovigilance knowledge into clinical practice to achieve safer drug therapy in children.

State of the Art in Pharmacovigilance

The World Health Organization (WHO) defines pharmacovigilance as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems.[6] After the use of thalidomide resulted in severe congenital abnormalities in children born to many women using this drug, awareness of the importance and need for improving drug safety has since grown around the world. Nevertheless, to achieve 'understanding' and 'prevention' of ADRs as final goals, there is still a need for optimizing the current pharmacovigilance methods and for translating more efficiently the pharmacovigilance knowledge to the clinical practice. A more recent example is the rofecoxib (Vioxx®) cardiovascular ADRs from which current pharmacovigilance and regulatory agencies have been strongly criticized. The Vioxx® withdrawal highlighted the needs and gaps in effective communication of drug safety and showed that from the point of view of public health, better understanding of the mechanisms which underlie ADRs, improving risk management and fostering well-informed benefit/risk prescribing decisions are the safety solutions that need to be promoted rather than removing medications from the market. In 2004, after a review of prescribing information about rofecoxib contained in the Canadian Compendium of Pharmaceuticals and Specialties, a group of academic scientists[7] reported that the product monograph did not adequately inform clinicians, and it provided insufficient information as to whether or not COX-2 selective NSAIDs increase myocardial infarction or total cardiovascular thrombotic events. Based on this example, it becomes evident that prescribers are challenged by the paucity of comprehensive resources and lack of time to find, extract and interpret all the relevant information of a drug before prescribing or making a therapeutic decision. This becomes more complicated for prescribers when the drug has been labeled with a special warning (“Black Box” warnings) because the benefit/risk equation is likely altered, but to an unknown extent. In the end, for patients benefiting from rofecoxib its withdrawal was certainly in detriment of their health particularly if they were then re-prescribed previously ineffective therapies.

Limitations of clinical trials regarding the inclusion of pregnant women and children are augmented by the fact that rare adverse effects, delayed effects or effects of long-term drug use are likely to fail to be detected during premarketing studies. However, it is unreasonable to assume that new drugs be approved for market only after all possible risks are known. Just as unreasonable would be a solution strategy that

drugs be withdrawn from the market after a first significant ADR is detected. Every stage of the drug's life cycle requires better pharmacovigilance practices to promote more well-informed prescribing and regulatory decisions.

In terms of pediatric drug use, concerns about drug safety are usually higher and the ´precautionary principle´ may be applied earlier to avoid any harm. Nevertheless, 75% of all medications in the US market are not labeled for pediatric use and only 6% of the drugs listed as the most frequently used in newborns and infants carry FDA-approved labeling for use in pediatric populations.[8] Multi-centre and multi-national pediatric drug safety initiatives are being launched only recently and there is still an obvious gap in the generation of information on most drugs on the market with regards to their effectiveness and safety in children.

The lack of inclusion of pediatric patients in phase III clinical trials has an ethical basis in drug development history, but should not be the rationale today to allow unlicensed drug use. At a minimum, we need to collect all evidence of drug effects in children to ensure the pediatric drug use dataset is more complete and provides a better understanding of drug outcomes. Moreover, evidence generation and clinical translation of drug safety knowledge needs to be global. While most of the world's children live in Asian, African and Latin American countries, most recognized pediatric pharmacology research units are located predominantly in high-income countries where the proportion of children is relatively low.[9] Safety initiatives should allow the transfer of knowledge of pediatric drug safety research from developed countries to the developing world.

The spontaneous or voluntary reporting system is a pharmacovigilance method which is usually presented as a method with sufficient advantages to warrant widespread use: effective for safety signal generation, wide population-based coverage, continuous, rapid and inexpensive. Nevertheless, it should not be the only method used in pharmacovigilance, particularly pediatric pharmacovigilance. These systems are designed for the detection of signals for new, rare and serious ADRs. However, they rely on voluntary reporting by healthcare professionals or consumers and are thus characterized by low levels of reporting and negligible clinical utility since most reports have insufficient clinical data from which to derive conclusions. Most critically, these spontaneous surveillance systems are focused on regulatory affairs and are not designed to provide clinicians and parents with much needed evidence necessary to support safer medication use. The WHO Collaborating Centre for International Drug Monitoring recommends the implementation of a voluntary reporting system as the first step in starting pharmacovigilance activities in any country.[10] Unfortunately, many countries rely only on this system promoting the accumulation of pharmacovigilance reports globally as the key drug safety development strategy, but without having any direct or immediate impact on drug safety for their populations. This phenomenon is more common in countries where pharmacovigilance is seen as a bureaucratic process and where no appropriate regulatory framework is created and fostered in order to support national pharmacovigilance efforts to improve drug safety for local populations. Unfortunately these countries are usually where the majority of the children of the world live and where research in pediatric drug safety is poor or nonexistent. The world's database maintained by the Uppsala Monitoring Centre (UMC) called Vigibase, contains all the individual case reports (ICRS) of suspected ADRs that each participating country provides. In the most recent reporting period (2005 - 2010), the countries with the highest numbers of correct and active ICRS in the Vigibase per 1 million inhabitants and year are: New Zealand, United States, Switzerland, Ireland and The Netherlands.[11] With the exception of Cuba, which is the only country listed within the top 20 countries that is not classified as a high-income economy country, no African or Latin American representation is present. This scarcity of information on ADRs worldwide will have serious consequences for the healthcare of children as well as of adults given the known morbidity and mortality from ADRs.

Knowledge Generation Strategies in Pediatric Pharmacovigilance

Developing effective methods for early detection of ADRs in pharmacoepidemiologic studies is a pressing need in pediatrics. Recently, Etwel et al.[12] proposed a method for the early identification of rare but serious ADRs using the case of

pemoline. After its introduction in the US in 1975 and until 1995, there were only three reported cases of pemoline-associated fulminant liver failure.[13] After the publication of the third case by Berkovitch et al. in 1995[13] additional cases of liver failure associated with pemoline began to be reported worldwide. Based on these three cases only, authors calculated at that time a relative risk of 45.3 for children receiving pemoline and developing fatal liver failure. Thirteen years later, the FDA database contained 30 cases and additional 11 peer review reports were available from the literature.[12] Using this information together with information regarding the rate of idiopathic acute liver failure (ALF) and the annual number of children treated with pemoline in the US, the relative risk of pemoline-associated ALF was calculated. The authors found that as early as 1978, a significant signal existed indicating risk associated with pemoline use. Pemoline was removed from the market in 1999 (Canada) and 2005 (USA). This example shows that it is not only important that more cases of specific ADRs are reported, either to the national surveillance systems or communicated through peer-review journals, but also to link them with data from health service systems and population-based statistics to determine both health outcomes and defined denominators of population drug use. This strategy will allow us to better understand the benefit/risk profile of drugs used in pediatrics, identify risks earlier and make better prescribing and monitoring decisions based on more accurate information.

The need for more and better-designed drug safety studies becomes evident in the case of chemotherapy for children with cancer. In 2007, Paolucci et al.[14] reported a total of 43 drugs, 16 patented and 27 off-patent, which should be considered priority for pharmacokinetics, long-term safety, efficacy and age-appropriate studies in children. As the authors pointed out, most of the drugs used in childhood cancer are off-label and should therefore fall under the definition of 'investigational medicinal products' requiring full pharmacovigilance strategies, even when pediatric oncologists may have longitudinal experience with these agents in practice. Nevertheless, since most of these drugs are off-patent to date, there are no industrial partners interested in registering a pediatric indication which could lead to the conduct of the studies needed and then to appropriate labeling changes.[14]

Survival of childhood cancer patients has been estimated to be approximately 75%.[15,16] However, the case of childhood cancer exemplifies very well the impact of lifelong health consequences that might result from ADRs. Even today, when more children are surviving cancer because of the increasing effectiveness of chemotherapeutic agents, a high percentage of survivors have to live with chronic or late-occurring health effects (e.g., heart disease, lung disease or hearing loss). The conduct of studies of late or long-term effects of cancer drugs in children is therefore critically important to improve the safe use of drugs.

In terms of detecting risk in a timely and effective manner, the use of data-mining and other automated methods for signal generation from pharmacovigilance databases has shown to have important limitations in terms of comprehensive exploration of multiple sources of confounding.[17] Further research is needed in order to optimize automated signal generation since the communication of false-positive signals of suspected causality to pediatricians can lead to inappropriate modifications of their clinical practice.

An obvious challenge in drug safety knowledge generation in pediatrics is the need of data collection from multiple medical centres. The creation of networks linking pediatric centres through pharmacovigilance databases is of vital importance. This will allow the increase of sample size for any study, which is especially important for the detection of rare ADRs or for drug safety surveillance in orphan disease pediatric subgroups. New advances in gene technologies hold great promise in understanding drug response heterogeneity. The linking of pharmacogenomic and pharmacovigilance information may be very helpful in identifying potential drug safety solutions. Achieving sufficient statistical power to distinguish a real ADR-biomarker association from stochastic noise is crucial. Based on our experience through the Genotype-specific Approaches to Therapy in Children study, an active ADR surveillance network of pediatric hospitals established in 2005 across Canada[18,19], we present here five strategic elements that we

consider should be included in pharmacovigilance initiatives in pediatrics.

1. Pediatric Active ADR Surveillance

An active surveillance approach is desirable in pediatric pharmacovigilance studies to generate knowledge promptly and to enhance the estimation of true risk in clinical practice. Due to underreporting within voluntary surveillance systems and to the limitations of clinical trials in children, large-scale epidemiological evaluation of ADR reporting through active surveillance, may be the only reliable and consistent source of information on the benefit-risk profile of drugs used in pediatrics. Mandatory reporting does not seem to solve the problem of underreporting. For example, in Italy, an active monitoring system of ADRs in children was developed through a network of family pediatricians. After 1 year of operation, this network raised the rate of 4 ADRs per 100,000 children reported to the mandatory Italian system to an incidence of 15.1 reported ADRs per 1000 children.[20] The Canadian GATC surveillance model also proved to be more effective than the voluntary ADR national surveillance system given that in the first 6 months of operation, 3 cases of ibuprofen-induced Stevens-Johnson syndrome were identified, while over 32 years the Health Canada surveillance database contained only 4 reports for the same drug-ADR combination.[18] Hence, increased reporting and more thorough data collection processes are two outcomes that are likely to occur if active surveillance systems are put in place.[21,22]

Active surveillance systems should be seen as a logical follow-up as well as a complementary strategy to voluntary reporting systems. These systems can help to overcome underreporting and when supported by standardized methodology, they can augment and optimize the detection of ADRs, which is the first step of the pharmacovigilance process. More and better reporting must be encouraged among health professionals but also among patients, since reporting by patients often provides more detailed descriptions of how ADRs affect patients´ quality of life.[23] In fact, patient reporting in spontaneous reporting systems has shown to be feasible and to contribute significantly, both in quantity and quality, to the reporting of ADRs.[24,25]

While performing pharmacovigilance studies, difficulty obtaining follow-up information on reported cases has been listed as one of the limitations of voluntary post-market reporting.[26] The active surveillance approach permits updates and reassessment of the information initially collected (e.g., clinical description of ADR severity and diagnostic studies performed) thus assisting more thorough analyses through the inclusion of additional information later deemed essential in risk assessment. For example, risk factors other than the drug later found relevant such as tests used to accurately diagnosis a specific ADR or follow-up clinical description of ADR outcome in patients.

Finally, active surveillance strategies operating within institutional, national and international pharmacovigilance programs can serve three important purposes: further investigation and strengthening of signals generated by voluntary reporting systems; explore specific drug safety concerns and interests of health professionals within the institutions or geographical regions; and finally, establish collaborations with regulatory agencies to be responsive to drug safety or public health emergency situations (e.g. intensive safety surveillance of antiviral drugs during an influenza outbreak).

2. Targeted Safety Surveillance

To date, the large number of drugs used to treat pediatric conditions both for licensed or unlicensed uses makes the proper investigation of ADRs a titanic mission. Single pharmacovigilance centers or multicentre networks both face the challenge of limited available resources and the need for a more focused and targeted approach to address drug safety issues. Centers and networks work within larger health care institutions, and therefore require a focused mandate of improving health care for patients within that system. The larger goal of population health is laudable, but not very practical or fundable within the health care delivery framework. Traditional spontaneous reporting systems are typically not designed to target specific drugs or actively interact with clinicians in order to explore

their concerns and safety needs. On the contrary, drug-problem targeted pharmacovigilance systems can be kept abreast of new drug safety concerns as they become known to front-line clinicians. They can be responsive to new information and should be able to adjust their data collection program as necessary.

The prioritization of drugs to be studied under a targeted safety surveillance study will depend on the specific interests and needs of an institution or region, but will also be influenced by the resources and time required to conduct such studies. Drugs could be added to the target list when new to the market, and specific drug-ADR combinations for which a signal was generated through voluntary surveillance systems are some factors that could drive the activities of a targeted system.

In addition, targeting specific drugs may assist in more effective and rigorous study designs and better characterization of ADR cases. This could also improve data collection and reduce many potential confounding factors in ADR determination. In the end, this focused approach will assist for a more accurate estimation of the risk for specific drugs.

For drugs with mechanisms of action that may be causative of specific ADRs (e.g. rofecoxib), targeted surveillance programs could be implemented to monitor drug safety in the early post-marketing period. Specifically in pediatrics, more studies are needed that explore ADR incidence for different age groups as well as the risk of ADRs related to the unlicensed and off-label use of drugs in children.[27] Whereas licensed drugs are monitored by spontaneous reporting, epidemiological surveys or surveillance systems, there is currently no similar process for monitoring and collecting information on ADRs caused by unlicensed and off-label drug use both in the hospital and in primary care.[27]

Targeting drugs used in pregnant women is also a pressing need in pharmacovigilance in order to gain more knowledge about safety and outcomes of drug exposed pregnancies. Teratology information services (TIS) have been demonstrated to be useful for performing exposed cohort studies and gathering information predominantly on insufficiently tested or potentially risk-prone drugs.[28] TIS document the exposed pregnancy through the risk inquiry approach and are able to ascertain cases in a prospective manner. Prospective enrollment of controls is also possible in order to conduct case-control studies. The communication infrastructure of TIS also makes it possible to collect information about pregnancy outcomes through questionnaires or phone calls at a later stage, usually with high rates of response from patients. This routine interaction with patients and health professionals requires that TIS personnel communicate risk in an appropriate way, but it also makes TIS a target of effective knowledge translation strategies for drug safety. Programs and networks like the European Network of Teratology Information Services (ENTIS)[28] and the Motherisk Program in Canada[29] are important for generating drug safety knowledge in pregnancy and for detection of signals of suspected causality.

Other possible areas to target pharmacovigilance systems´ efforts are the conduction of comparative studies for new pediatric products and for pediatric drugs expected to be used in a long-term basis. Drug safety concerns in pediatric oncology and neurology can also be successfully addressed if pharmacovigilance centres join resources with disease-centered networks.

Finally, for pharmacovigilance programs linked with pharmacogenomic studies to achieve efficient knowledge translation to clinical practice, targeted genetic biomarker discovery and predictive testing for specific drugs are at this time the only potentially cost-effective strategies.

3. Case-control Methodology

The majority of pharmacovigilance databases in the world are populated only by reports of ADR cases. The lack of data on control patients matched for age, gender but most importantly for suspected drugs, prevents the confirmation of signals of suspected causality and the identification of risk factors other than the drug. Among the current ADR surveillance methods, case-control studies make the validation and assessment of drug-ADR associations possible.[30]

Thus, the combination of these studies with an active surveillance approach would be useful for signal strengthening and risk factor identification. Matching cases as accurately as possible with controls is not an easy task mainly

when cases exhibit polypharmacy at the time when the ADR occurred. Sample size for performing association studies may be small at single institutions and therefore multicentre data collection is essential.

Levi et al. used case-control methodology (ratio of cases to controls 1:3) to assess medication risk factors of Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) in children.[31] The study was carried out by pooling data from the databases of two multicentre studies, SCAR and EuroSCAR. Cases and controls were matched for age, gender and country/region. The use of this methodology allowed authors to confirm anti-infective sulfonamides, phenobarbital, carbamazepine and lamotrigine as drugs strongly associated with SJS/TEN in children and to find acetaminophen use as a potential risk factor for SJS/TEN. This study had sufficient statistical power to identify a high relative risk of the ADR for drugs rarely used by controls, and to identify risk factors with weaker associations when the control exposure prevalence was relatively high. This example shows that to establish a significant association between an ADR and drug use, comparative cases and controls are needed. Moreover, to estimate risk more accurately and to improve the understanding of ADRs in children, all possible risk factors need to be identified as clearly as possible (e.g. age, gender, concomitant drugs or genetic variants) using case-control methods.

4. Trained Surveillance Clinicians

Current pharmacovigilance systems require experienced surveillance clinicians who are trained to accurately recognize, document, and collect critical drug safety data. Hasford et al.[32] reported that German physicians do not report ADRs for three reasons: the ADR is already well known (75.6%), the ADR is too trivial to report (71.1%), and because of uncertainty concerning definite causality (66.3%). Some authors suggest that lack of time due to workload of health professionals rather than expertise and ability to diagnose a possible ADR are responsible for the poor quality of information gained from spontaneous reports.[33] However, in Germany where ADR reporting is mandatory, 25% of physicians have never diagnosed an ADR at least once in the past, almost 20% admit to being unaware of the existence of a national reporting scheme, and approximately 30% noted they knew neither how to report nor the respective official regulations of conduct.[32] These antecedents make obvious the need for surveillance clinicians located in major health centers whose principal, even sole responsibility is the identification, documentation and reporting of ADRs.[21] Payment to physicians has shown to increase reporting rates[23] but this type of incentive cause a burden on the cost of the pharmacovigilance activities, which could be managed more effectively by paying trained clinicians in each institution to merely dedicate their activities to drug safety surveillance.

Likewise, trained clinicians are useful when safety signals may be confounded by factors related to pharmacoepidemiology. Expertise in clinical pharmacology and therapeutics can be helpful in advising about potential biases when generating signals of suspected causality. Grégoire et al.[17] demonstrated how a first signal of an association between angiotensin receptor blocker (ARB) use and hypoglycaemia disappeared after stratification on antidiabetic drug use, suggesting confounding by indication. In fact, a decreased risk of hypoglycaemia was found from the reporting of hypoglycaemia in patients taking antidiabetic agents and ARBs. This demonstrates the need for improving signal generation methods but also how important expertise and training are when assessing potential risks of drug use.

5. Standardized Methodology

Accurate and detailed clinical data are critical factors in the discovery of ADR-associated biomarkers. Relevant clinical ADR data needs to be collected in a standardized way to assist the complex process of evaluating possible confounding factors, such as disease state, interacting drugs, and clinical judgment by the ADR surveillance clinicians. Furthermore, the establishment of ADR surveillance networks requires the use of customized databases where data must be entered in a consistent manner for further analysis. International harmonization of terms used in pharmacovigilance must be strengthened as well. Communication in

pharmacovigilance must be clear and consistent otherwise the conceptual frameworks necessary for process improvement are overshadowed.[34] For more efficient clinical translation of drug safety knowledge gained, communication between all stakeholders must be efficient as well.

Linking Pharmacovigilance with Pharmacogenomics

As a final topic of drug safety knowledge generation strategies is the developing science of pharmacogenomics. By linking pharmacovigilance activities with pharmacogenomic determination, there is a higher probability of finding drug safety solutions. Clearly, we are moving into the 'safety-omics' era.

Although many factors influence the effect of medications (e.g., age, organ function, drug interactions), genetic factors account for a significant proportion of drug response variability[35] and contribute to half of all ADRs.[36-39] Thus, pharmacogenomics may increase our understanding of the effect that fluctuating gene expression and physiological maturation have on drug response and of age-related factors in disease and treatment outcomes.[40] From a purely genetic viewpoint, many severe ADRs likely represent a type of genetic disease, but one with a specific and known environmental component, the drug. Thus the genetic analysis of ADRs is a promising approach to eventually diagnose and prevent the occurrence of serious ADRs. Interpretable and meaningful pharmacogenomics data is dependent upon accurate characterization of phenotypes. This is why the integration of active and targeted surveillance, trained surveillance clinicians, case-control methodology, standardized reporting and rigorous data analysis procedures are crucial to identify genetic markers for safer drug therapy. Although pharmacogenomics may affect the size of patient groups that may become therapeutically orphaned, there is a clear legislative commitment in many countries to maintain pediatric testing as a priority. Pharmacogenomic testing is therefore likely to become standard and eventually mandatory.[40] Nevertheless, the current clinical utility of a pharmacovigilance program that incorporates pharmacogenetic information is extremely limited.[41] Reasons for this include the small number of genetic biomarkers already confirmed and validated for clinical use, the scarcity of genotyping technology and financial resources in most of healthcare institutions, and the limited degree of understanding and knowledge of most prescribers regarding application of pharmacogenomic data within clinical practice.

There are other concerns developing along with the rapidly advancing and increasingly less expensive genetic technology. If advances in pharmacogenomic research are funded independent of advances in risk communication and knowledge translation research, there may be significant failure in adapting and responding to the needs of those for whom pharmacogenomics was intended to benefit: the patient, the pharmacist and the physician. A challenging impact of pharmacogenomics on appropriate translation of drug safety knowledge was recently emphasized by Howland.[41] In medical centers where prescribers were more aware of the influence of genetic variation on drug metabolizing enzymes as complicating factors of drug therapy, clinicians were preferentially selecting drugs not metabolized by CYP2D6 if severe adverse effects were believed to be likely.[41] Based on the current status of pharmacogenomics knowledge, this modification in clinical practice therapeutics is the result of overly simplistic knowledge of the clinical pharmacology underlying ADRs and is therefore inappropriate.

Need for More Effective Knowledge Translation

Effective drug safety knowledge translation means effective communication of risk to all the clinicians involved in the drug use process (i.e., physicians, pharmacists, nurses), patients and caregivers. Effective communication dictates that information must be provided in a way that is useful to the intended recipients.[33]

An example of failure in risk communication involves isotretinoin. From a non-interventional population-based study of women exposed to isotretinoin, Bérard et al. found a rate of pregnancy four times greater and a greater rate of elective abortions (84%) than in previous reports.[42] Predictors of becoming pregnant and receiving an elective abortion after first-trimester isotretinoin exposure were lower socio-economic level and high use of healthcare services (MD visits, ED visits and hospitalizations). Concomitant oral contraceptive use in conjunction

with isotretinoin to prevent pregnancy was not universal. This study demonstrated that guidelines used to increase awareness of isotretinoin teratogenicity had no significant impact on pregnancy rates over time. Even when a serious ADR like teratogenicity is well known and easily identified, the associated risk of harm cannot be minimized.[42,43] Given the known teratogenic effects of isotretinoin, even one pregnancy should be viewed as a failure of pregnancy preventing programmes.[44]

A large amount of pharmacovigilance data is available but dispersed throughout research papers in the literature.[33] About 30% of the world literature on adverse drug reactions is in the form of single anecdotal or case series reports.[34] Some of these reports must be considered possible associations only that are not necessarily elevated to the status of signals of suspected causality, requiring further research.[34] Moreover, inconsistencies in the use of the pharmacovigilance terminology restrict the utility of systematic reviews and meta-analyses. Further, most practitioners do not have easy access to all relevant journals. Drug risk messaging to clinicians that are not linked with preventative strategies are unlikely to decrease risk and be translated into 'real world' medical practice.

The transmission of the right message, through the right media, to the right audience is the major challenge of risk communication strategies. Johann-Liang et al. reported that after 5 years of implementation of the US Best Pharmaceuticals for Children Act (BPCA) in 2002, the number of pediatric adverse events reported to the FDA for children remained steady, while those for adults increased.[26] This phenomenon could be due to differences in drug use between adults and children, the presence of more comorbidities in adults, or increased polypharmacy in adults with a consequent increase in more ADRs.[26] However, off-label use and under-recognition of ADRs by caregivers may also be important causes of underreporting in children. Due to communication limitations, pediatric patients are less likely to be able to express response to medications with the same clarity as adult patients.[22] Physicians may not know how to look for a particular ADR, when it is more likely to occur along the course of treatment, nor how to diagnose and manage reactions.[33] Very specific drug safety information that pertains to individual therapeutic agents, guidelines for ADR management, and suggested therapeutic modifications need to be clearly detailed in pharmaceutical product information.

Finally, advantages of patient engagement in pharmacovigilance activities should not be underestimated. A two-way communication process can be satisfactorily established between pharmacovigilance centers and patients or parents, in order to increase drug safety knowledge and to both inform and counsel patients and families. Furthermore, all types of pharmacovigilance centers should have a duty to inform patients and physicians of specific drug risks, playing a more active advisory and educational role.[45]

Concluding Remarks

Children often cannot verbally express their own drug therapy experiences. As a result, newborns, infants and children who require medication for acute, chronic and life saving treatment are at risk of a variety of ADRs ranging from ineffective treatment and minor ADRs to severe morbidity and death.[36,46] It is for these reasons that children worldwide are described as "therapeutic orphans" and are placed at an increased risk of therapeutic failure, while ADRs continue to cause unnecessary disability and death. The lack of many appropriate pediatric formulations, exposure through maternal prenatal drug use and breast milk, along with off-label use, all increase the risk of ADRs in children.

There is a pressing need for an evidence-based drug treatment approach that seeks to minimize life-threatening and permanently-disabling ADRs caused by drug toxicity in children.[36] The lack of information on pediatric drug safety and effectiveness, combined with inadequate mechanisms for monitoring and assessing ADRs results in a high-risk situation for children requiring pharmaceutical treatment.

Physicians must base therapeutic choices for these vulnerable populations on scant or incomplete information, while parental consent to therapies is often based on information that is inadequate to assess the risk such therapies pose to their child. As stated in the Erice Manifesto[47] the science of pharmacovigilance – monitoring and evaluating drug safety issues and

communicating them effectively – is a vital activity of worldwide significance in the safeguarding of patient welfare and public health. So far, pediatric needs in terms of pharmacovigilance have not been properly addressed. We strongly encourage the establishment of pediatric drug safety networks worldwide (within healthcare institutions as well as regional, national and international networks) to better use the scarce resources and the adoption of more proactive drug safety evaluation initiatives to solve drug safety problems for children in a timely manner.

Conflict of Interest

Authors declare no conflict of interest. Trade names were used only as means of product identification and does not imply endorsement.

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