Therapeutic Drug Monitoring in Pediatric Practice: A Critical Appraisal

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ABSTRACT

The criteria for drug monitoring in children are almost similar as applicable in adults, though certain factors need to be taken into consideration. The dramatic pace of change in other areas of clinical therapeutics has not reflected significantly in the specialty of pediatrics, accounting for the poor development of therapeutic drug monitoring in children. Major drug interactions in the pediatric population have been revealed. CYP3A4 hepatic microsomal enzyme plays a major role in these drug interactions. The continuing education and awareness of these interactions among healthcare practitioners is critical in optimizing effectiveness and minimizing toxicity. Therapeutic drug monitoring is primarily indicated for drugs with narrow therapeutic margin; though certain category of patients may still manifest evidence of toxicity, despite drug concentration being within the therapeutic range. The use of pharmacodynamic data in synergy with therapeutic drug monitoring represents the most viable approach to individualized therapy. Pediatrics is at the epicenter of the emerging discoveries in the field of genomic medicine. The relevance of therapeutic drug monitoring as a global therapeutic index encompassing pharmacokinetics, pharmacodynamics, pharmacogenomics and drug interactions can never be overemphasized. In conclusion, the prospects of clinical pharmacogenomics as therapeutic drug monitoring for the future in pediatric practice is quite promising.

Key words: Appraisal, Clinical pharmacogenomics, Drug disposition, Drug interaction, pharmacodynamics, Pharmacokinetics, Therapeutic drug monitoring.

INTRODUCTION

Therapeutic drug monitoring can be defined as measurement of drug concentrations in biologic matrix with a view to assessing correlation with patient's clinical condition and the need for dose adjustment. The criteria for drug monitoring in children are almost the same as applicable in adults, though certain factors should be taken into consideration[1]. It has been shown that children aged 9 years and below receive approximately 12% of all drugs prescribed in the United State of America alone[2]. Pharmacokinetic and pharmacodynamic behaviour differ significantly in the pediatric age group compared to the normal adult population. Parental compliance in administering drugs at the appropriate time interval may further accentuate patient non-compliance in the pediatric population. The dramatic pace of change in other areas of therapeutics has not reflected in the specialty of pediatrics accounting for the poor development of therapeutic drug monitoring in children[3]. It is therefore, no wonder that infant, toddlers and children being denied access to benefits of modern drug therapy are referred to as "therapeutic orphans". This paper examines the fundamental issues

underlying therapeutic drug monitoring in pediatric practice with a view to optimizing patient care.

MATERIALS AND METHODS

An advanced search of literature using pubmed central, medline and embase was carried out with a view of accessing peer reviewed full journal articles, abstracts, reviews, comments, letters to editors, project reports, dissertations, theses and books relevant to the subject matter.. The keywords used in the search were as follows: appraisal, drug disposition, drug interaction, pharmacodynamics, pharmacogenetics, pharmacogenomics, pharmacokinetics and therapeutic drug monitoring.

Drug interactions

Drug interactions generally refer to effects of concomitant administration of a drug with other drugs (drug-drug interaction) as well as drugs with food (food-drug interaction) or other substances which results to a clinically measurable modification in either magnitude or duration of action of the index drug. Changes in drug disposition brought about by a particular drug can alter the pharmacokinetics of another drug. The clinical consequences of these interactions may manifest as sub-therapeutic effect due to reduced serum drug concentration or increased adverse effects due to elevated level of serum drug concentration. This clearly underscores the need for drug monitoring to ensure that requisite target concentration is achieved.

Drug-Drug Interaction

A significant number of adverse events in hospitalized patients as evidenced by epidemiologic studies is accounted for by drug-drug interactions[4,5]. A study revealed variety of major drug interactions in the pediatric population, highlighting cases of first significance rate interaction with rapid onset[6]. Electrolyte changes particularly potassium loss induced by loop diuretics results to hypokalemia potentiating digoxin toxicity. Moreover, at low serum potassium level, tubular secretion of digoxin is inhibited, further increasing digoxin serum concentration and prolonging its elimination half-life with consequent risk of cardiac arrhythmia. Concomitant administration of the non-sedating antihistamine terfenadine with macrolide antibiotics should be avoided due to risk of cardiotoxicity. There

is need for caution in the co-administration of loop diuretics and aminoglycoside antibiotics due to synergistic potentiation of oxotoxicity; although dose-dependent toxicity may still manifest in the course of administering drugs individually[7]. Predictable drug interaction occurs during concomitant administration of azole antifungals such as ketoconazole, itraconazole, voriconazole with barbiturates leading to their increased metabolism and sub-therapeutic serum concentration mediated by induction of microsomal liver enzymes by barbiturates. Other classes of drugs in which increased metabolism is reported following concomitant administration with barbiturates include: beta-adrenoceptor blockers, calcium channel blockers, antidepressants and corticosteroids. Rifampin is a strong inducer of hepatic microsomal drug metabolizing enzyme and co-administration with drugs such as dexamethasone, theophylline, paracetamol and tolbutamide will result to increased metabolism and reduced therapeutic effects of these drugs. Increase in the metabolism of paracetamol induced by rifampin results to accumulation of metabolites which are hepatotoxic[8].

Food-Drug Interactions

Food-drug interaction is the effect produced when certain foods or beverages are taken concomitantly with drugs. Food-drug interactions alter the pharmacokinetics or pharmacodynamics of a drug or nutritional element. Regrettably, consensus toward specific drug–nutrient interactions, standardized management approaches and properly designed studies on the epidemiology of food-drug interactions are still lacking. The continuing education and awareness of these interactions among healthcare practitioners is critical in optimizing effectiveness and minimizing toxicity[9]. Altered bioavailability of a drug such as complex formation with metal ion, partitioning in dietary fat or adsorption of drug in insoluble dietary component may occur due to direct interaction of food with a drug. The microsomal hepatic drug metabolizing enzymes particularly CYP3A4 play a key role in food-drug interaction[10]. Elevated serum concentration of certain drugs by more than five-fold following ingestion of grape fruit has been reported and linked to enzymatic inhibition of selective microsomal drug metabolizing enzymes[11]. Grapefruit juice has no effect on drug pharmacokinetic parameters after intravenous administration but causes significant

rise in drug bioavailability after ingestion, suggesting that it has no effect on liver CYP3A4 but significantly inhibits intestinal CYP3A4[12,13].

Bergamothin is the major furanocoumarin found in grape fruit responsible for drug interaction, exhibiting both concentration and time-dependent *in vitro* inactivation of cytochrome P450 microsomal enzymes; furthermore, its metabolite also inhibits CYP1B1 and CYP3A4[14,15].

Drug interaction with grapefruit juice is influenced by the time of ingestion. It has been reported that 12 hours after intake of grapefruit juice, the bioavailability of lovastatin doubled[16], though a clinically significant interaction did not occur after an interval of 24 hours[17]. A study revealed that grapefruit juice did not have any significant effect on maximal plasma concentration of digoxin, a substrate of P-glycoprotein[18]. Orange juice significantly reduced area under the curve, AUC of celiprolol by 83% and the mean peak plasma concentration by 89%[19]. The AUC of felodipine was increased by sour orange to 76% compared to 93% by grapefruit juice[20].

Drugs routinely monitored

Therapeutic drug monitoring is primarily indicated for drugs with narrow therapeutic margin in which the serum drug concentration that results to adverse effect is quite close to the concentration required to achieve beneficial therapeutic effect. It is pertinent to note, however, that certain patients may still exhibit adverse effects, even in situation where drug concentration is within therapeutic margin due to variations in individual pharmacokinetic and pharmacodynamic indices.
Digoxin is a cardiac glycoside derived from *Digitalis lanata*. Digitalis can be accurately monitored using HPLC combined with tandem mass spectrometry. Digoxin immunoassays have the advantage of rapid turnaround time and automation, but subject to interference by endogenous digoxin-like immunoreactive substances (DLIS) due to their structural similarity. Digoxin may accumulate in smaller amounts in immature infants due to diminution in total body fat seen in preterms. Digoxin is weakly protein bound as compared to DLIS which are strongly protein bound, hence free drug concentration measurement of digoxin is preferable in order to eliminate interference. A study indicated

that toxic effects of digoxin appear at concentrations from 1.2ng/mL, whereas the therapeutic effects occurred within concentration range of 0.5 to 0.9 ng/mL[21]. A study reported poor correlation between DLIS concentration and patient age, total bilirubin and serum creatinine level[22]. Moreover, concentrations of DLIS in maternal blood may be significantly decreased relative to cord blood.

Specific clinical indications for monitoring of anticonvulsant therapy in pediatric patients include determinantion of baseline effective concentrations, evaluating cases of toxicity, lack of efficacy and non-compliance. It has since been shown that dosing of anticonvulsant drugs based solely on mg/kg body weight was not effective[23,24]. A study reported that despite drug concentration below optimal therapeutic interval established at the time, a number of epileptic patients undergoing treatment remained seizure free[25]. Measurement of free phenytoin levels in suspected cases of toxicity where total serum phenytoin is within the optimal therapeutic range may be necessary as phenytoin is highly protein bond (90%). Carbamazepine is one of the most commonly used anticonvulsants approved for children over six years. Immunoassay method widely used for measuring carbamazepine concentration in blood, is subject to interferences due to cross-reactivity with carbamazepine metabolites and other structurally similar compounds[26]. Phenobarbital is a sedative hypnotic effective in the treatment of epilepsy with the exception of absence seizures, though not currently recommended as first or second line drug for seizure control in children. Toxic effects including alteration in level of consciousness, shallow breathing, bradycardia and renal failure occur with overdose. Cross-reactive interferences with amobarbital, butobarbital, secobarbital and phenytoin have been reported following phenobarbital immunoassay[27].
Increased incidence of toxicity occurs in asthmatic children at theophylline plasma concentration above 20mcg/mL. Serum concentration 10 to 20 mcg/mL is effective in relieving asthmatic attack in children. CYP1A2 microsomal enzyme is responsible for metabolism of theophylline which is reported to be faster in females compared to males. A study has shown that steady state serum concentration of theophylline was reduced by 24.5% while the theophylline clearance increased by 51.1% in children exposed to passive smoking[28]. A twofold

reduction in half life of theophylline was reported in smokers relative to non-smokers[29].

Increased risk of otoxicity and nephrotoxicity seen in aminoglycosides such as gentamicin and tobramycin is associated with sustained peak concentration above 12-15µg/ml and/or trough levels exceeding 2mcg/ml. The clearance of aminoglycosides is increased in children as compared to adults; and patients with fever exhibited lower plasma concenetration and shorter half-life[30]. Glomerular filtration rate (GFR) on which clearance of aminoglycoside depends is drastically lowered in neonates particularly premature newborns. Prolonged half-life of aminoglycosides in neonates may be accounted for by the increase in volume of distribution,V_d of aminoglycosides in neonates. Hence, increase in V_d and reduced clearance of gentamicin have been observed in neonates[31]. Vancomycin which is excreted in urine unchanged is frequently monitored due to its low therapeutic index, complicating therapy with combined risk of ototoxicity and nephrotoxicity[32]. Monitoring of trough and peak concentrations of vancomycin and their ranges is quoted in literature[33]. However, a conservative range of 20-40µg/mL for peak concentration and 5–15µg/mL for the trough is recommended for infants[34]. Trough concentrations above 30ng/mL and 80 to 100ng/mL may be associated with increased risk of nephrotoxicity and ototoxicity respectively. The decrease in clearance of most beta lactam antibiotics is as a result of reduced renal clearance in neonates[35].

The lack of adequate viral suppression in the absence of therapeutic drug monitoring of anti-retroviral drugs has been shown by various studies. The incidence of inter-patient variability and drug-drug interactions in pediatric population is one of the major indications for therapeutic drug monitoring of antiretroviral drugs. Available evidence is suggestive that both non-nucleoside reverse transcriptase inhibitors, NNRTIs such as nevirapine, delavirdine, efavirenz and protease inhibitors, PI such as saquinavir, indinavir, atazanavir, lopinavir, ritonavir, neltinavir are good candidates for therapeutic drug monitoring; while nucleoside reverse transcriptase inhibitors, NRTIs such as zidovudine, lamivudine, stavudine, zalcitabine and didanosine are not. The simultaneous measurement of any combination of antiretroviral drugs using tandem mass spectrometry has facilitated assessment of both compliance and optimization of dosage regimens in children[36,37].

Future propects

The vast genetically determined variations in drug response makes even more difficult the search for optimized pharmacotherapy[38]. The use of pharmacodynamic data in synergy with therapeutic drug monitoring represents the most viable approach to individualized therapy. The identification of genotype as aid to therapeutic drug monitoring is a very promising prospect[39]. Notwithstanding, knowledge of measurement of serum drug concentration followed by appropriate adjustment, still remains inevitable as awareness of metabolizer status may not be sufficient to allow for prediction of serum drug concentration measurement. The drastic reduction in the cost of genotyping and more importantly next generation sequencing techniques, following the successful completion of the Human Genome Project have led to insights into gene regulation and complex interplay of factors responsible for normal development. The emerging fields of clinical pharmacogenomics and practice of personalized medicine are among the most tangible outcome of the Human Genome Project[40-42]. Pharmacogenomic biomarkers are useful adjuncts to facilitate practice of personalized medicine. Pediatrics is at the epicenter of the emerging discoveries in the field of genomic medicine. Notwithstanding the daunting challenges of translating genomic knowledge into improved patient care, pediatricians and their patients are favourably disposed towards benefiting maximally from this genomic revolution[43].

In conclusion, the relevance of therapeutic drug monitoring in pediatrics encompassing pharmacokinetics, pharmacodynamics, pharmacogenomics, drug interactions, selection of appropriate drugs and techniques for monitoring can never be overemphasized. The prospects of clinical pharmacogenomics as therapeutic drug monitoring for the future in pediatric practice is quite promising.

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