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Hot Topic

Cytostatic drugs in infants: A review on pharmacokinetic data in infants

Hendrik van den Berg [a,b,*], John N. van den Anker [c,d,e], Jos H. Beijnen [f]

[a] Department of Pediatric Oncology, Emma Children Hospital – Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands
[b] Medicines Evaluation Board, The Hague, The Netherlands
[c] Division of Pediatric Clinical Pharmacology, Children's National Medical Center, Washington, DC, USA
[d] Departments of Pediatrics, Pharmacology, and Physiology, George Washington University School of Medicine and Health Sciences, Washington, DC, USA
[e] Department of Pediatrics, Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands
[f] The Netherlands Cancer Institute, Slotervaart Hospital, Amsterdam, The Netherlands

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ABSTRACT

Below a certain age protocols in pediatric oncology on cytostatic drug therapy advise use, of other parameters such as weight for dosing; this instead of the most conventional parameter, i.e. body surface area. In infants it is not uncommon that additional reductions are put on top of this for each cytostatic drugs to be administered. The rationale behind this is often lacking. Differences related to the ontogeny of absorption, distribution, metabolism and excretion are often not mentioned. Considering characteristics, such as lipophilia, ionization in relation to pH and size of the molecule and linking these characteristics with age related shifts in the gastrointestinal tract, composition of the body and renal function; predictions on pharmacokinetics (PK) in these infants can to a certain extent be made. More difficult are the shifts in activity of phase I and II enzymes, which are often not known for a specific product. In this review data on the ontogeny of relevant pharmacokinetic pathways in relation to the various cytostatic drugs and data from pharmacokinetic (PK) studies in infants are presented.

This review shows that the administration of cytostatic drugs in infants is often based on limited or even no data at all. Based on such a lack of evidence on treatment of infants with cancer; it should be mandatory that in each infant treated with cytostatic drugs pharmacokinetic data are collected. Compiling these data in a global database would enable evidence-based drug therapy in infants with malignancies, resulting in a more effective treatment with less toxicity in this vulnerable population.

Introduction

Adult cancer treatment is often based on the assumption that each individual person metabolizes cytostatic drugs with the same efficiency. Individual differences might however either result in increased toxicity or less efficacy. Increased toxicity is dealt with in a pragmatic way: dose reductions are often applied in the next courses. Increased metabolism resulting in an increased relapse rate is often not noted. Individual differences are, however, currently often linked to pharmacogenetic data.[1,2] These pharmacogenetic factors are in pediatric pharmacotherapy superimposed on developmental differences in relation to age, weight and body surface area. Especially in infancy substantial deviations in the pharmacokinetics (PK) of drugs are noted. Most pronounced are the PK changes during the first months of life. The response to the various drugs (pharmacodynamics) may be different in children with the same type of malignancy. However, in this review we will not focus on the pharmacodynamics of the cytostatic drugs.

Reports on the PK of cytostatic drugs administered to infants are very limited and often confined to a few studies and case reports in this age group; often only dealing with to adverse effects. Examples of cytostatic drugs are reports on the excessive neurotoxicity of vincristine, resulting in hypotonia, feeding difficulties and paralysis of respiratory muscles.[1–3] Unexpected side effects during chemotherapeutic treatment of Wilms' tumors have resulted in the recommendation to decrease the vincristine dosages to 50.[4] Still the situation on increased side-effects in infants has not been resolved.[5]

In many protocols and some textbooks the evidence for dose recommendations is less clear and sources often are not indicated.[6] In most protocols dose reductions are proposed in infants, either given as a percentage according to age or as calculations based on body weight instead of the body surface area. Since liver volume is correlated with body surface area and not to weight dosing according to body surface area would be more relevant for drugs with hepatic clearance only. However, the impact of ontogeny on

* Corresponding author. Address: Department of Paediatric Oncology, Emma Children Hospital Academic Medical Centre, University of Amsterdam, Room F8-242, P.O. Box 22700, 1100 DD Amsterdam, The Netherlands. Tel.: +31 20 5663050; fax: +31 20 6912231.
E-mail address: h.vandenberg@amc.uva.nl (H. van den Berg).

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the metabolic capacity is completely neglected this way.[7] Even in a specific protocol for infants with acute lymphoblastic leukemia (ALL) substantial dose reductions are mentioned irrespective of the drug involved.[8,9] The pharmacokinetic relevance of this is doubtful.[10,11] Although in pediatric oncology the age limit separating infancy from the toddler period is usually at 12 months, this review provides data on cytostatic drugs in children below the age of 2 years because these data are relevant and data in infants <1 year were often too scarce. Before discussing the various cytostatic drugs a summary is given on developmental changes relevant for the PK of cytostatic drugs.

Absorption

The majority of cytostatic drugs are administered intravenously to infants. In a few patients oral administration is used. These infants mainly suffer from leukemia and are treated with 6-mercaptopurine and methotrexate during the maintenance phase of their treatment. Since there are currently no pharmaceutical formulations for oral use in infants marketed, extemporaneous formulations are standard of care. The quality of these extemporaneous formulations is not secured and in case of tablets used as a starting point, the matrix of excipients and the breaking strength are essential variables.[12] Developmental factors important for the oral use are gastric acid production, pepsin secretion, and gastric emptying. Secretion of both gastric acid and pepsin are strongly decreased in infancy. In addition this secretion is influenced by enteral feeding.[13,14] For phenobarbital it has been shown that higher dosages are needed. For cytostatic drugs there are no data available.[15] As a result of this low acid and pepsin secretion increased absorption related to state of ionization of weak acids (such as methotrexate), is to be expected. Gastrointestinal motility is decreased in infancy and gastric emptying is initially decreased.[16,17] Since both methotrexate and 6-mercaptopurine (being the most often administered orally administered drugs) are water soluble, changes in biliary function and biliary composition are less important in infants with a malignant disease.[18,19] In general it is assumed that intestinal surface is reduced in early childhood, despite the fact that if using anthropometric data, the intestinal surface exceeds adult values.[20,21] Differences in intestinal bacterial flora can be of major influence on pharmacokinetics (PK).[22] As a result the formation of the methotrexate metabolite, DAMPA, which is produced by bacterial enzymes from methotrexate will be influenced by the kind of feeding. The drug-metabolizing enzyme function of the intestinal wall in infants differs substantially from adults. Epoxide hydrolase and glutathione peroxidase show little age dependency in contrast to CYP1A1, which expression was shown to increase with age.[23] In contrast, young infants have a significant expression of CYP3A4 and P-gp m-RNA.[24] But activity may be, despite expression, significantly different. As such the intestinal CYP3A4 activity was shown to increase during childhood.[25] It should be mentioned that both data on expression and drug-specificity of enzymes cannot be extrapolated from the liver to the intestine. In most infants with a malignancy abnormal gastro-intestinal absorption will not be recognized, since only a very limited number of drugs are administered orally. In at least one of the most frequently used drugs, 6-mercaptopurine, adverse reactions based on unexpectedly low leukocyte counts will often be explained by TPMT polymorphism and not by deviations in absorption.

Distribution

For oral as well as parenteral medication several issues related to drug distribution have to be considered; i.e. differences in body composition such as total body water, extracellular water and body fat, and altered binding to various plasma and tissue proteins. Lipid soluble drugs have relatively larger distribution volumes in infants as compared to older children due to the relatively higher amount of fat. But also for water-soluble drugs larger distribution volumes can be noted due to the larger extracellular water component. Inter-individual variation is common. Body composition changes during development. Total water, especially extracellular water, decreases during childhood. In the first months after birth total body fat increases, at later ages a relative decrease occurs. The affinity of plasma protein is different depending on the type of plasma proteins. The most important plasma protein is albumin. Drug binding, both increased as well as decreased, differs for several drugs, due to differences in fetal versus non-fetal albumin characteristics. Not only albumin influences plasma binding. Other plasma constituents do influence drug binding as well. Examples are plasma globulins and glycoproteins, which are generally decreased and free fatty acids which are commonly increased. Higher binding as well as decreased binding was demonstrated for various drugs. No data exist for cytostatic drugs.[11,26,27]

Metabolism

Although metabolism occurs in several tissues, the liver is probably the most important site for drug metabolism of cytostatic drugs.

Liver volume and hepatic blood flow determine the amount of drug that can be metabolized. Younger children have a relative high liver volume, and liver volume has a close relation with body surface area and hepatic blood flow.[21] Microsomal protein content is about two-third of the maximal concentration, which is reached at an average age of 30 years.[28] There is an increased intrinsic cytochrome P450 activity, however it is doubtful if that accounts for the increased clearance of most P450 drug substrates in children.[29] Phase I and II reactions are still in a process of maturation. In childhood and especially in neonates and infants the expression and activity of both phase I and phase II enzymes differs in many aspects. In this respect, the above mentioned discrepancy in the intestinal wall on expression of m-RNA and activity of CYP3A4 may be present in the liver as well. A point of caution is the interpretation of absolute activity in the body on basis of determination of samples. Although it was shown that liver volume was a parameter correlated with pharmacokinetics.[30] Allometric scaling showed that the maximal activity of UGT1A4 was only reached at the age of 18.9 years, instead of reaching it at the age of 1.4 years. This underscores the importance to take several factors into account.[31]

Considering the developmental variations in activity of drug metabolizing enzymes there is a major difference in drugs that need a metabolic step prior to getting cytostatic activity versus those drugs, where the parent drug is active as such. In pro-drugs a slower rate of metabolic activation will lead to lower blood levels of the active drug and extension of the period during which the active metabolite is present in the body. On the other hand developmental changes in elimination have consequences as well. If elimination (hepatic or renal) is diminished this will lead to higher blood concentrations and prolongation of the availability of the active metabolite/drug. In case elimination of the prodrug is normal, blood levels of the active drug tend to be lower. However, this might be reversed in case the metabolic step from pro-drug to active metabolite occurs at a slower rate. The final result might be that very low concentrations of active drug are present for a more prolonged interval. Since toxicity and efficacy can be related to either peak concentrations or duration of exposure or both, the effect on toxicity and efficacy cannot fully be deducted from the scheme as depicted in Table 1.

Many drugs are substrates for phase I (oxidative) and/or phase II (conjugative) metabolizing enzymes. Variant alleles cause in