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Disposition of antineoplastic agents in the very young child

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Summary Maturation of physiologic processes which govern the disposition of pharmacologic agents can yield significant changes in absorption, distribution, metabolism, and elimination of drugs in neonates, infants and children. However, there are very little data concerning the disposition of anticancer drugs in young children.

Pharmacokinetic data for six anticancer agents were compared in infants less than 1 year of age and children greater than 1 year of age treated at St Jude Children's Research Hospital. No pharmacokinetic data were available for infants <2 months of age. Median methotrexate clearance tended to be lower in four infants (0.26–0.99 years) *vs* 108 children (1–19 years): 80 *vs* 103 ml min^{-1} m^{-2}, respectively ($P = 0.01$). There was no difference in the median 42 h methotrexate concentration. Teniposide systemic clearance and terminal half-life and cytarabine systemic clearance were not different between the two groups. There was no significant difference in etoposide systemic clearance when normalised to body surface area (ml min^{-1} m^{-2}), however a significantly lower systemic clearance relative to body weight (ml min^{-1} kg^{-1}) was observed in two infants, 0.5 to 1 year of age, *vs* 23 children, 3–18 years of age. Doxorubicin systemic clearance was not significantly different between the two groups when systemic clearance was expressed in ml min^{-1} kg^{-1}. However, there was a trend toward a lower rate of systemic clearance in ml min^{-1} m^{-2} in infants. Erythrocyte concentrations of the active 6-mercaptopurine metabolites, 6-thioguanine nucleotides, measured 5 weeks after the start of daily oral 6-mercaptopurine 75 mg m^{-2}, were not significantly different in these two age groups.

These data indicate that for teniposide, etoposide, and cytarabine uniform dosing based on body surface area will yield more similar systemic exposure for both age groups, although substantial interpatient variability exist in all age groups. Methotrexate clearance tends to be lower in infants, although there was no need to decrease dosage in this age group. Moreover, dosing of these drugs based on body weight will generally yield lower systemic exposure in infants than would dosing based on body surface area, since uniform mg kg^{-1} dosing yields a lower mg m^{-2} dosage in infants. Conversely, for doxorubicin a uniform mg kg^{-1} dosage would be more likely to yield similar systemic exposure in both age groups studied. It is clear from these data that a uniform rule for dosage adjustments will not hold for all anticancer drugs in young children. Further evaluation of pharmacokinetic and pharmacodynamic characteristics are required, particularly in neonates and infants, to permit more precise dosage recommendations for antineoplastic agents in the very young child.

The treatment of cancer in the very young child is an important and difficult component of paediatric haematology and oncology. Factors such as rapidly changing maturation of physiologic processes and the lack of published pharmacokinetic and pharmacodynamic data with antineoplastic agents in this population, make the use of chemotherapy in these patients problematic. While recent reviews of the pharmacokinetics of antineoplastic agents in children have been published (Evans, 1989), there is essentially no published data characterising their disposition in the very young child. Herein, we review the developmental changes which may influence the disposition of antineoplastic agents in this population, review pertinent published data, and present pharmacokinetic data from children less than 1 year of age treated for malignancies at St Jude Children's Research Hospital.

Developmental physiology

The effects of maturation on physiologic processes which govern the disposition of pharmacologic agents in the neonate (birth to 1 month) (Besunder, 1988) and infants (1 month–1 year) and children (1 year to 12 years) (Kearns & Reed, 1989; Stewart & Hampton, 1987) have recently been reviewed. While little is known regarding specific alterations in the pharmacokinetics of antineoplastic agents in the very young child (i.e. <1 year of age), there is knowledge of general changes in absorption, distribution, metabolism, and elimination of drugs which can be applied to this population.

Gastrointestinal absorption depends on gastric pH, gastric emptying time, intestinal transit time, and gastrointestinal enzymatic activity, in addition to the chemical characteristics of the drug. Gastric pH at birth approaches neutrality, but within hours falls to between 1.5 and 3 (Morselli, 1980). Gastric acid secretion appears to display a biphasic pattern, with the lowest pH occurring within the first 10 days and increasing between 10 and 30 days of age (Kearns & Reed, 1989). Both basal and stimulated gastric acid secretions are dependent on age, and achieve adult values by 1–2 years of life (Stewart & Hampton, 1987). Gastric emptying time is delayed in the immediate newborn period for both fullterm and preterm neonates and appears to approach adult values within the first 6–8 months of life (Heimann, 1980). Similarly, intestinal motility in the perinatal period is variable and influenced by the presence or absence of food. While fasting or interdigestive motor activity appears to be less in children than in adults (Kearns & Reed, 1989), there are little data quantitating intestinal transit time relative to age. Infants up to 4 months of age have low activity of amylase and other pancreatic enzymes (Lebenthal, 1983). Thus, drugs which require pancreatic enzyme secretions for hydrolysis may demonstrate unreliable absorption. While there are little data characterising changes in drug absorption with age, physiologic information would suggest that it is a complex and variable process.

A number of age-dependent factors can influence distribution of drugs within the body, most notably body composition and plasma protein characteristics. The maturational

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changes in the compartmentalisation and amount of body water and fat have been well characterised (Figure 1). As a percentage of total body weight, the approximate total body water falls from 87% and 75% in the premature and full-term neonate, respectively, to 60% at 1 year, and 55% by adulthood (Friis-Hansen, 1971). Extracellular water falls from 45% of total body water in the full-term neonate to 20% in the adult. The clinical implications of these shifts in body composition have not been fully defined. Another factor which influences drug distribution in the young child is protein binding. There are several physiologic variables which can produce both quantitative as well as qualitative differences in plasma protein binding of drugs (Table I). Albumin, the major drug binding protein in plasma, binds primarily acidic drugs and may also bind to other molecules such as fatty acids and bilirubin. In addition to albumin, drugs bind to globulins, alpha-1 acid glycoprotein, lipoproteins and other proteins. Basic drugs bind more avidly to alpha-1 acid glycoprotein and lipoprotein than to albumin. While affinity of a protein for a drug is difficult to quantitate, many drugs have been found to be less bound to serum proteins in the neonate than in adults (Stewart & Hampton, 1987). Alterations in protein binding of drugs may lead to an increase in the unbound fraction (presumably the pharmacologically active constituent), and thus an increased pharmacologic or toxic response. A highly protein bound drug can displace bilirubin from albumin, with the resulting increase in free bilirubin. Plasma proteins generally approach adult values at 1 year of age. The clinical importance of protein binding changes for antineoplastic agents has not been investigated, although differences in serum albumin concentrations have been found to alter the plasma protein binding of both etoposide (Stewart, 1989) and teniposide (Petros & Evans, unpublished data) in adults.

Many organs and tissues in the body, including blood, liver, lungs, kidney, and gastrointestinal tract, are capable of metabolising drugs. Metabolism can be separated into two major types. Phase I reactions are those which involve chemical biotransformation of a molecule, usually to more water soluble and often inactive metabolites. The second type of metabolism, phase II reactions, involve conjugation of a drug or phase I metabolite with endogenous molecules (e.g. glucuronic acid, sulfate), rendering them more water soluble.

Table I Physiological variables potentially altering plasma protein binding of drugs[a]

Parameter	*Neonate*	*Infant*	*Child*
Total protein	↓	↓	~
Plasma albumin	↓	~	~
Foetal albumin	+	–	–
Plasma globulin	↓	↓	~
Unconjugated bilirubin	↑	~	~
Free fatty acids	↑	~	~
Blood pH	↓	~	~
Alpha-1 acid glycoprotein	↑	NA	~

[a]Relative to adult values. Adapted with permission from Radde, I.C., 1985. Key: ↓, Decreased relative to adult values, ↑, Elevated relative to adult values. ~, Same as adult values, +, Present, –, Absent, NA not available.

Phase I reactions are often catalysed by the mixed-function oxidase system and typically involve substrate oxidation. Concentrations of the various forms of cytochrome P-450 and cytochrome P-450 reductase are important determinants of the rate of metabolism. Most hepatic P-450 enzymes are functional in human foetal and neonatal liver. However, the activity of some P-450 enzymes is absent at birth (e.g. mephenytoin hydroxylase), while the quantity and activity of other enzymes approximates 20–70% of adult values (Pelkonen, 1973). There appears to be a positive relationship of increasing enzyme activity with age, from birth to 5 weeks (Aranda, 1974). Clinically this has been exemplified by increasing metabolic clearance with age, seen with drugs such as phenobarbital (Neims, 1976), caffeine (Aldridge, 1979), and theophylline (Tserng, 1983), over 1 week to 30 months of age (Figure 2). Since a number of antineoplastic agents require bioactivation for cytotoxic effects (e.g. cylophosphamide, ifosfamide) or metabolism for their inactivation (e.g. daunorubicin, vincristine, fluorouracil), decreased metabolic activity could result in either inability to form the active moiety or prolongation of cytotoxic activity, depending on the drug.

An example of a phase II reaction is the conjugation of glucuronic acid with a drug molecule. Other examples include glutathione conjugation, sulfation, and acetylation. UDPG-glucuronyltransferase activities toward bilirubin, morphine,

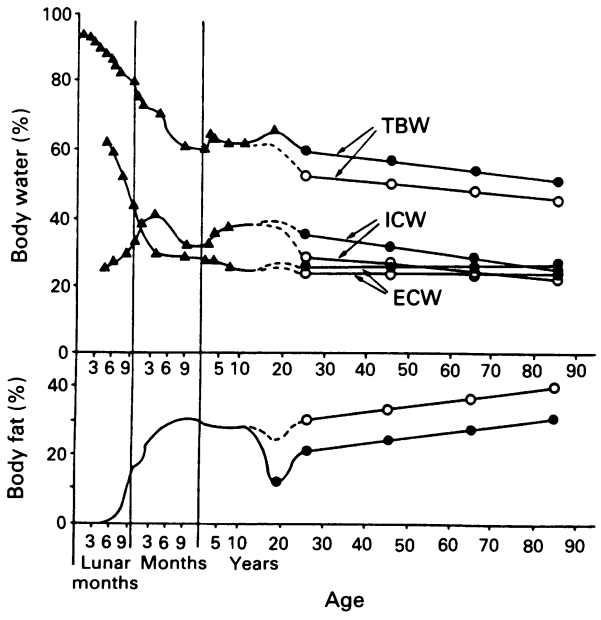

Figure 1 Developmental changes in total body water (TBW), intercellular water (ICW), extracellular water (ECW), and body fat content relative to age and sex. Key: ▲ = both sexes, ● = males, ○ = females. Adapted with permission from Friis-Hansen, 1971.

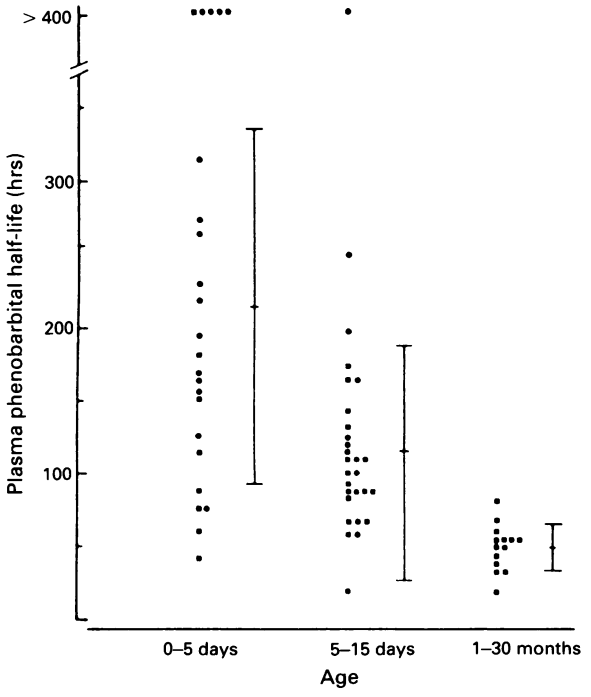

Figure 2 Developmental changes in phenobarbital plasma half-life with age. Reproduced, with permission, from the Annual Review of Pharmacology and Toxicology, Vol. 16, 1976 by Annual Reviews Inc.

and chloramphenicol are depressed at birth and reach adult levels in children by 3 years of age (Leakey, 1987; Milsap & Szefler, 1986). However, glucuronidation of 5-hydroxytryptamine appears to be as high in neonatal livers as in adults (Leakey, 1987). This suggests that not all glucuronidases appear to be under the same developmental regulation. Levy (1975) has shown that a shift from sulfation to glucuronidation of acetaminophen occurs over the pedatric age range.

The kidney represents a primary route of elimination for many medications. Renal elimination of drugs is dependent on glomerular filtration, tubular secretion processes, and renal blood flow. There is evidence of morphologic and functional tubular immaturity at birth. While there appear to be slight differences in the development of organic acid and organic base transport, tubular function appears to be fully developed by 7 months of age (Siegel & Moran, 1981). Renal blood flow increase with age as a result of an increase in cardiac output and a decrease in peripheral vascular resistance (Besunder, 1988). The kidneys of the neonate receive only 5% of total cardiac output compared to up to 25% for adults. Renal blood flow also appears to increase in proportion to the development of the renal tubules, demonstrating adult rates by 5 months of age. At birth, glomerular filtration rate (GFR) is approximately 40 ml min^{-1} 1.73 m^{-2} for the term infant, although intersubject variability is great in these estimates (Milsap & Szefler, 1986). Adult values for GFR are reached by 2.5–5 months of age. The clinical implications for maturation of GFR become apparent when considering drugs that are primarily eliminated by glomerular filtration (e.g. methotrexate, carboplatin). A direct correlation between gestational age and digoxin clearance has been established (Collins-Nakai, 1982), increasing from 1.35 l h^{-1} 1.73 m^{-2} at 26–29 weeks gestation, to 1.77 l h^{-1} 1.73 m^{-2} at 30–32 weeks, to 3.54 l h^{-1} 1.73 m^{-2} at 33–40 weeks. The half-life and clearance of aminoglycoside antibiotics are prolonged in preterm and term neonates, and approach adult values with improvement in GFR (Szefler, 1980). These data indicate that cancer chemotherapeutic agents that depend upon renal function for elimination will be cleared more slowly in the neonate and consequently will have lower plasma clearance, with an increased risk of exaggerated pharmacologic effects (e.g. toxicity).

Anticancer drugs in young children

There have been few published observations regarding the disposition of antineoplastic agents in the very young child. Most reports have been anecdotal in nature and essentially no large pharmacokinetic studies have been reported.

In studies of intrathecal therapy in children, Bleyer (1977) demonstrated the potential importance of age-related anatomical differences. The volume of the central nervous system is relatively larger in younger children and does not correlate well with body surface area in the pediatric age range (Figure 3), since CNS volume reaches 80–90% of adult values by age 4–6 years, yet BSA does not reach adult values until about age 16–18 years. This suggests that mg m^{-2} dosing of intrathecal therapy would yield relatively lower cerebrospinal fluid concentrations in younger children, *vs* adolescents and adults. Among 47 patients (aged 3–39 years) treated with six preventative intrathecal injections of methotrexate at a dose of 12 mg m^{-2}, neurotoxicity was significantly more common in adults, while the risk of the occurrence of meningeal leukaemia was higher in younger children than in older individuals (Bleyer, 1977). Cerebrospinal fluid (CSF) concentrations following the intrathecal methotrexate were found to vary 100-fold, with lower concentrations observed in younger children. A group of patients treated with a constant dose (12 mg) had much less variation in CSF methotrexate levels than patients receiving mg m^{-2} dosing. These results have led to the use of dosage regimens for intrathecal methotrexate which are selected on the basis of age, rather then BSA.

The National Wilms' Tumor Study reported 17 toxic deaths among 803 children treated with the second National Wilms' Tumor Study protocol (Jones, 1984). Of particular concern were four infants under 1 year of age with group 1 or 2 disease, who had toxic deaths. Subsequent patients less than 1 year of age received a 50% reduction in doses of vincristine, dactinomycin, and/or doxorubicin. There was no statistically significant difference in therapeutic effect seen in infants treated with either full-dose or half-dose chemotherapy. The National Wilms' Tumor Study also reported severe hepatotoxicity in five non-irradiated patients treated with a single dose of dactinomycin and vincristine (Green, 1988). While the patients all were exposed to additional potentially hepatotoxic agents (vincristine, anaesthesia), the authors felt that the contribution of dactinomycin warranted a reduction in dosage from 60 μg kg^{-1} to 45 μg kg^{-1} for those patients less than 30 kg. Follow-up studies of the hepatotoxicity of this reduced regimen have shown a reduction (3.7% *vs* 14.3%) in the frequency of severe hepatic toxicity encountered in the early weeks of therapy (Green, 1990).

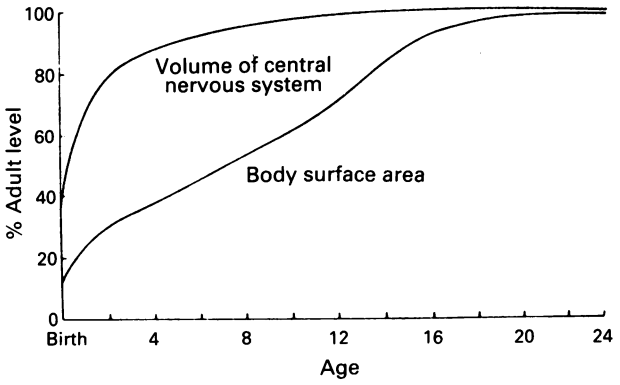

Figure 3 Maturation changes in CNS volume relative to body surface area. Bleyer, 1977 with permission.

There have been several reports describing vincristine neurotoxicity in young children. An early report observed several infants with leukaemia who suffered severe reactions to vincristine (Allen, 1978). The infants became hypotonic and developed an inaudible cry and weak suck after receiving several doses of vincristine. The authors also observed that children with poor nutritional status, those who were bedridden, and patients with altered liver function may have an elevated risk for the development of vincristine neurotoxicity. Neurologic and hepatic toxicities following vincristine, prednisone, and L-asparaginase or doxorubicin therapy for acute lymphoblastic leukaemia, were retrospectively evaluated in 44 patients (Woods, 1981). Seven of nine patients with BSA less than 0.5 m^2 had evidence of vincristine-related neurologic toxicity, including four patients in which it was severe. This incidence of neurotoxicity was statistically greater than that seen in the larger children (Table II). All seven infants with neurotoxicity had elevated hepatocellular and/or hepatocanalicular enzymes. One possible explanation offered for this increased incidence of toxicity was that infants may have a decreased ability to metabolise vincristine, whether developmentally related or iatrogenic secondary to L-asparaginase or methotrexate (Woods, 1981). This decrease in metabolic

Table II Incidence of neurotoxicity and hepatotoxicity in children receiving treatment for ALL

	Group 1 $<0.5\ m^2$ *n = 9*	*Group 2* $0.5–0.7\ m^2$ *n = 20*	*Group 3* $0.7–1\ m^2$ *n = 6*	*Group 4* $>1\ m^2$ *n = 9*
Mean BSA	0.36	0.62	0.82	1.4
Mean weight (kg)	7.2	14.4	21	47
Mean age (months)	7	33	71	156
Neurologic dysfunction[a]	7/9	6/20	0/6	1/9
Hepatic dysfunction[a]	7/9	1/20	0/6	1/9

[a] $P < 0.05$ for group 1 *vs* groups 2–4. Adapted with permission from Woods *et al.*, 1981.

clearance would result in a higher systemic exposure to vincristine and therefore a greater probability of toxicity. Evaluation of vincristine pharmacokinetics in 39 patients with either haematologic malignancies or solid tumours revealed an increase in systemic exposure in patients with elevated serum alkaline phosphatase, when compared to those with normal values (Van den Berg, 1982). A disproportionate rise in vincristine plasma concentration at doses exceeding 1 mg m^{-2} was also observed. These findings provide indirect evidence to support the relationship between abnormal liver function tests and vincristine neurotoxicity. An alternative explanation would be that the infant's neurologic system may be in a more primitive state of development, and thereby more sensitive to vincristine's effect. Because an infant's BSA is relatively great in proportion to body weight, Woods *et al.* proposed a dosage scheme which converted the vincristine dosage to a mg kg^{-1} basis, thereby allowing for a lower mg m^{-2} total dose to be administered. This mg kg^{-1} regimen was suggested for use in all patients with BSA less than 1 m^2. It is on the basis of this report, as well as the above mentioned developmental findings, that many centres prefer to empirically use dosage normalised to body weight as opposed to BSA when determining doses for infants less than 1 year of age or less than 6 kg of body weight. Use of a lower dose per BSA in infants would in effect have the same result: a lower total dose in infants compared to children.

Thus far, no further studies have been published evaluating the effect of these changes on either toxicity or oncolytic response, or whether the empirical use of body weight *vs* BSA has a sound pharmacological and physiological basis. It is well recognised that the ratio of body weight to BSA (kg m^{-2}) changes from a value of 18 at 1 month of age, to 25 at age 5 years, 30 at 10 years, and 40 at >20 years of age (Figure 4, panel a). As depicted in Figure 4 (panel b), the changing ratio of body weight/BSA in infants and children yields a higher mg kg^{-1} dose in younger children when a uniform mg m^{-2} dosage is used for all age children. An unanswered question is whether infants should receive a lower mg kg^{-1} dosage of a given drug, which would be appropriate if their rate of drug clearance is lower when normalised to body weight (ml min^{-1} kg^{-1}). Although there could be a sound pharmacokinetic basis for the empiric dosing of vincristine and other drugs on a mg kg^{-1} basis, specific pediatric pharmacokinetic studies of each anticancer drug are needed to clarify this issue.

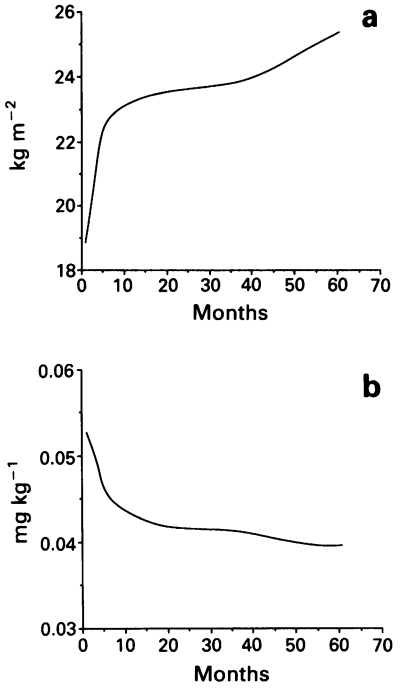

Figure 4 **a**, Changes in the body weight (kg)/body surface area (m^2) ratio with age; **b**, mg kg^{-1} corresponding to a uniform mg m^{-2} dose.

Table III Overview of methotrexate therapy in protocols X, XI, XII

Protocol	*Dose*	*Hydration*
Total X	1 gm m^{-2} over 24 h	100 ml m^{-2} h^{-1} × 42–48 h
Total XI	2 gm m^{-2} over 2 h	200 ml m^{-2} h^{-1} × 8 h
Total XII	0.9–3.7 gm m^{-2} over 24 h	100 ml m^{-2} h^{-1} × 48 h

Disposition of antineoplastic agents in infants and children at St Jude Children's Research Hospital

To provide additional insights into pharmacokinetic differences in young children, we have reviewed our pharmacokinetic data for a number of anticancer drugs, and compared results obtained in infants less than 1 year of age to data from children greater than 1 year of age. All of these studies were performed as part of clinical treatment protocols, after informed parental consent. None of these patients were selected for pharmacokinetic studies on the basis of any clinical features; essentially all studies were routinely performed as part of a front-line treatment protocol, in patients with normal renal and liver function. It should be emphasised that the youngest child in whom we have pharmacokinetic data is 2 months of age; extrapolation of our results to children <2 months may not be warranted. In addition, the paucity of infants with malignancies limit the number of patients studied.

High-dose methotrexate

Methotrexate disposition was evaluated in patients with acute lymphocytic leukaemia (ALL) treated with TOTAL Therapy protocols X, XI, XII at St Jude Children's Research Hospital (Evans, 1986; Christenson, 1988; Evans, 1990) (Table III). Systemic methotrexate systemic clearance and plasma methotrexate concentration at 42 h in infants <1 year of age were compared with children >1 year of age treated according to the same protocols. Plasma samples were obtained at the end of the methotrexate infusion and 42 h from the start of the infusion. Systemic clearance was determined by either the ratio of intravenous infusion rate to concentration at steady state (Toxal X) or by fitting a two compartment model to the concentration-time data using a Bayesian algorithm (Total XII).

Plasma samples were anlaysed by enzyme immunoassay (Total X) (EMIT, Syva, Palo Alto, CA) or by fluorescence polarisation (Total XI, XII) (TDx, Abbott, Dallas, Texas). Statistical differences in methotrexate systemic clearance and 42 h concentration median values were assessed by Wilcoxon rank sum method. Median methotrexate systemic clearance was compared for five infants (0.26–0.99 yrs) and 257 children (1–19 yrs) treated on protocols X (methotrexate 1 gm m^{-2}) and XII (methotrexate 1.5 gm m^{-2}). Methotrexate systemic clearance was not measured in protocol XI. When data from the two protocols were combined, there was no statistically significant difference between the median systemic clearance in infants *vs* children (86 *vs* 89 ml min^{-1} m^{-2}; $P = 0.75$). When analysed separately, infants ($n = 4$) treated with protocol XII, had a significantly lower systemic clearance than children ($n = 108$), 80 *vs* 103 ml min^{-1} m^{-2}; $P = 0.01$ (Figure 5). Regression analysis did not show a significant relationship between increasing age and methotrexate systemic clearance within the infant group. There was no statistically significant difference in methotrexate concentrations (0.18 μM *vs* 0.21 μM; $P > 0.05$) when the median 42 h methotrexate concentration in 11 infants (0.26–0.9 yrs) was compared to 312 children (1–19 yrs) treated with 2 gm m^{-2} over 2 h on protocol XI.

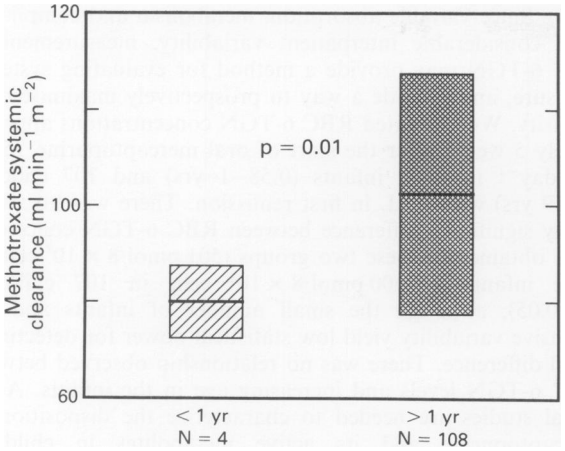

Figure 5 Median methotrexate systemic clearance in four infants *vs* 108 children treated on St. Jude protocol XII.

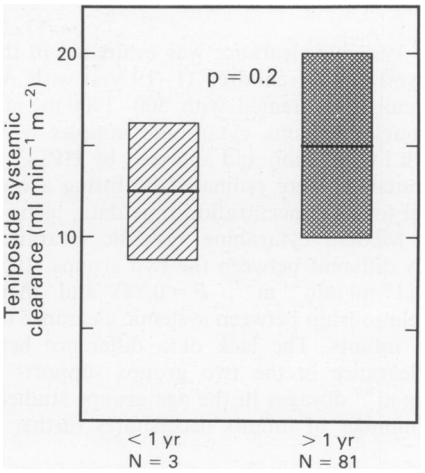

Figure 6 Teniposide systemic clearance in three infants *vs* 81 children.

There was not an apparent difference between toxicity or leucovorin requirements for the infants on the three protocols. Two of six courses in the one infant on protocol X resulted in mild mucositis and diarrhoea, which did not require hospitalisation or additional leucovorin. This infant received 60–84 mg m^{-2} of leucovorin, consistent with the dose specified in protocol X (69 mg m^{-2}). Eleven infants received 22 courses of methotrexate on protocol XI. Four of 22 courses resulting in vomiting, diarrhoea, or oral thrush, while two of 22 courses lead to mucositis. The infants received 45–135 mg m^{-2} of leucovorin (protocol dosage regimen: 99 mg m^{-2}). Four of 11 infants (36%) had grade 1–2 gastrointestinal toxicity, compared with 30/71 older children (42%) with grade 1–4 gastrointestinal toxicity (Christensen, 1988). The infants did tend to receive more i.v. hydration than the older children, median 200 ml m^{-2} h^{-1} × 10 h *vs* 200 ml m^{-2} h^{-1} × 8 h. One of ten courses in the four infants on protocol XII resulted in oral ulcers. The infants received 90–160 mg m^{-2} of leucovorin (protocol dosage regimen: 90 mg m^{-2}).

Thus, it appears that methotrexate was equally or better tolerated by the 16 infants; despite an apparently lower systemic clearance in infants, at least on protocol XII. Therefore, it appears safe to use methotrexate dosage regimens which are standardised on the basis of BSA, at least in infants > 3 months of age. The consistent 42 h plasma concentration among infants and children also indicates similar methotrexate disposition in the two age groups.

Teniposide and etoposide

Teniposide (VM-26) systemic clearance and terminal half-life were evaluated in three infants (0.64–0.87 yrs) and 81 children (1–19 yrs) with ALL in first complete remission, treated with 320–500 mg m^{-2} course^{-1} for 1–5 courses (Evans, 1990). Plasma teniposide samples were obtained during and after a 4 h i.v. infusion and analysed by HPLC (Sinkule & Evans, 1984). Pharmacokinetic parameters were estimated by fitting a two compartment model to the concentration-time data, using a Bayesian algorithm. Median teniposide systemic clearance and terminal half-life were not significantly different between infants and children (Figure 6). No relationship between increasing age and either pharmacokinetic parameter was observed in three infants 6 to 11 months of age. The lack of a difference between total systemic clearance in the two groups supports the use of uniform mg m^{-2} dosages in the age groups studied, although plasma protein binding and unbound drug systemic clearance must be compared before this can be established with certainty.

Etoposide systemic clearance was evaluated in two infants (0.5–1 yrs) and 23 children (3–18 yrs) with acute myelogenous leukaemia, treated with 2–3 gm m^{-2} administed as a 96 h continuous i.v. infusion for 1–3 courses, as part of remission induction therapy. Plasma etoposide samples were obtained during and after the infusion, and analysed by HPLC (Sinkule & Evans, 1984). Pharmacokinetic parameters were estimated by fitting a two compartment model to the concentration-time data, using a Bayesian algorithm. Median etoposide systemic clearance was compared when normalised to both body weight (kg) and body surface area (m^2). There was no statistically significant difference in systemic clearance between the two groups when systemic clearance was normalised to BSA (ml min^{-1} m^{-2}), however a significantly lower systemic clearance relative to body weight (ml min^{-1} kg^{-1}) was observed (Figure 7). A linear relationship between increasing systemic clearance with increasing age was evident for the infants (0.5–1 yrs), regardless of whether normalised to body weight or BSA. This trend was not present when all age paediatric patients were considered. These findings, in a small number of infants, are consistent with maturation of enzyme activity responsible for etoposide metabolism, during the first year of life. Moreover, the pooled systemic clearance data for infants and children suggest that uniform etoposide dosage regimens based on BSA (i.e. mg m^{-2}) are more appropriate for infants and children, as dosage calculations based on body weight (mg kg^{-1}) would have resulted in a larger variation in both steady state concentrations and drug exposure (area under the concentration-time curve; AUC) for the infants studied. However, the apparent maturational changes in etoposide systemic clearance, small study group, lack of plasma protein binding data, and the absence of etoposide data in infants less than 6 months of age do not permit precise dosage recommendations for patients less than 1 year of age.

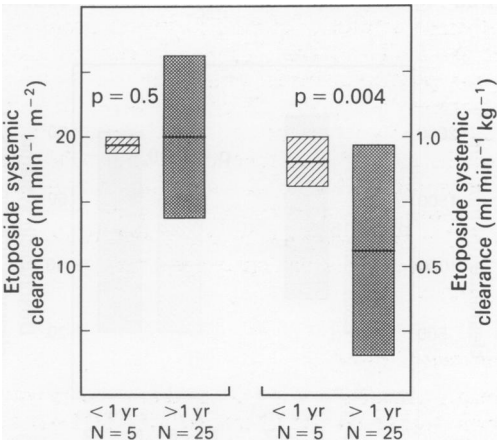

Figure 7 Etoposide systemic clearance in infants *vs* children. *n* = number of courses in two infants and 23 children.

Cytarabine

Cytarabine systemic clearance was evaluated in three infants (0.64–0.9 yrs) and 64 children (1–19 yrs) with ALL in first complete remission, treated with 500–1700 mg m^{-2} $course^{-1}$ for 1–5 courses. Plasma cytarabine samples were obtained during a 4 h i.v. infusion and analysed by HPLC. Pharmacokinetic parameters were estimated by fitting a one compartment model to the concentration-time data, using a Bayesian algorithm. Median cytarabine systemic clearance was not significantly different between the two groups (1053 ml min^{-1} m^{-2} *vs* 1117 ml min^{-1} m^{-2}; $P = 0.84$) and there was no observed relationship between systemic clearance and increasing age in infants. The lack of a difference between total systemic clearance in the two groups supports the use of uniform mg m^{-2} dosages in the age groups studied, although the small number of infants necessitates further evaluation.

Doxorubicin

Disposition of the anthracycline antibiotic, doxorubicin, was evaluated in four infants (0.17–0.83 yrs) and 56 children (1.3–20 yrs) receiving treatment with 35–90 mg m^{-2} for a variety of solid tumours. Plasma samples were anlaysed by HPLC and systemic clearance was determined by the ratio of dose/AUC. Systemic clearance was compared when normalised to both body weight (kg) and body surface area (m^{-2}). There was no statistically significant difference seen between the two groups when systemic clearance was expressed in ml min^{-1} kg^{-1} (42 ml min^{-1} kg^{-1} *vs* 51 ml min^{-1} kg^{-1}; $P = 0.6$), however, there was a trend toward a lower rate of systemic clearance in ml min^{-1} m^{-2} (790 ml min^{-1} m^{-2} *vs* 1500 ml min^{-1} m^{-2}; $P = 0.07$). This difference was statistically significant (813 ml min^{-1} m^{-2} *vs* 1540 ml min^{-1} m^{-2}; $P = 0.015$) when infants <2 years of age were compared with those children >2 years of age (Figure 8). While further evaluation is necessary, these data indicate that there may be a lower ml min^{-1} m^{-2} systemic clearance of doxorubicin in children <2 years of age. While the weight normalised systemic clearance (ml min^{-1} kg^{-1}) tended to be lower, the difference was not statistically significant. These data would support the use of lower mg m^{-2} doses in children under 2 years of age, or the use of body weight to dose doxorubicin in young children. However, only eight infants less than 2 years of age were available for study. It remains to be determined whether these data hold for a larger population of infants or other anthracyclines.

Mercaptopurine

Mercaptopurine has been an important component of ALL therapy for greater than 20 years. Recent reports have demonstrated a relationship between red blood cell (RBC) concentration of the active mercaptopurine metabolites, thioguanine nucleotides (6-TGN), and both antileukaemic response and toxicity (Lennard, 1987; 1989; Schmiegelow, 1990). Since variable absorption, metabolism and compliance yield considerable interpatient variability, measurement of RBC 6-TGN may provide a method for evaluating systemic exposure, and provide a way to prospectively maximise dose intensity. We evaluated RBC 6-TGN concentrations approximately 5 weeks after the start of oral mercaptopurine 75 mg m^{-2} day^{-1} in three infants (0.58–1 yrs) and 107 children (2–19 yrs) with ALL in first remission. There was no statistically significant difference between RBC 6-TGN concentrations obtained in these two groups (501 pmol/8 $\times$ 10^8 cells in three infants *vs* 400 pmol/8 $\times$ 10^8 cells in 107 children; $P > 0.05$), although the small number of infants and the extensive variability yield low statistical power for detecting a small difference. There was no relationship observed between RBC 6-TGN levels and increasing age in the infants. Additional studies are needed to characterize the disposition of mercaptopurine and its active metabolites in children. Obviously, the rare (1/300) child who inherits a deficiency in thiopurine methyltransferase, is at substantial risk of mercaptopurine toxicity, regardless of age (Lennard, 1990).

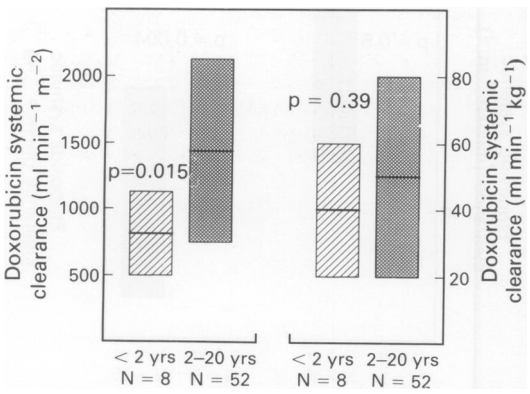

Figure 8 Doxorubicin systemic clearance in eight infants less than 2 years of age *vs* 52 children greater than 2 years of age.

Discussion

While the paucity of antineoplastic agent pharmacokinetics and pharmacodynamic data makes it difficult to precisely determine drug dosages in the very young child, knowledge of maturation effects on drug disposition, coupled with the available literature, allow tentative recommendations to be made. Changes in activity of the cytochrome P-450 system and enzymes responsible for conjugation of drugs (e.g. glucuronyltransferases) may, to some extent, explain age-related differences in toxicity and response. Since a number of antineoplastic agents require bioactivation for cytotoxicity (e.g. cyclophosphamide, ifosfamide) or metabolism for inactivation (e.g. daunorubicin, vincristine, etoposide, tenoposide), decreased metabolic activity could result in either inability to form the active moiety or prolongation of cytotoxic activity. The clinical implications for maturation of renal function become apparent when considering drugs that are primarily eliminated by glomerular filtration (e.g. methotrexate, platinum compounds). Cancer chemotherapeutic agents that depend upon renal function for elimination may be excreted more slowly in the neonate and consequently will have lower plasma clearance, with an increased potential risk of exaggerated pharmacologic effects (e.g. toxicity) if dosage reductions are not made.

The use of body weight for determining drug dosage has been recommended for infants <1 year of age (Woods, 1981). While this drug dosing scheme is largely empirical, data summarised herein indicate that it may have a pharmacokinetic basis for selected drugs (e.g. doxorubicin), which have a lower systemic clearance normalised per BSA (ml min^{-1} m^{-2}) in infants and children <2 years of age. Conversely, doxorubicin systemic clearance normalised to body weight (ml min^{-1} kg^{-1}) was not significantly different in our patients <2 years of age. These data indicate that children <2 years of age may have greater systemic exposure (AUC) to doxorubicin if a uniform mg m^{-2} dosage is given to all patients; while a uniform mg kg^{-1} dosage would be more likely to yield similar systemic exposure in both age groups. However, there is considerable interpatient variability in doxorubicin clearance, and age accounts for only a small portion of this variability. Further evaluation of larger numbers of infants is required to verify these findings. It is not known whether these data with doxorubicin apply to other anticancer drugs metabolised by similar pathways (e.g. other anthracyclines).

It appears that infant 2–12 months of age have a significantly lower systemic clearance of methotrexate (given as a 24 h continuous infusion) than older children. While caution is advised, all of our infants were able to tolerate the protocol doses of methotrexate and leucovorin without experiencing more toxicity or exhibiting delayed methotrexate excretion at 42 h.

For the other extensively metabolised anticancer drugs we have studied in infants (i.e. teniposide, etoposide, cytarabine), we found no differences in drug clearance (normalised to BSA) when infants are compared to older children. This suggest that empirical dosing of these drugs based on body weight (mg kg^{-1}) will generally yield lower systemic exposure in infants, since uniform mg kg^{-1} dosing yields a lower mg m^{-2} dosage for infants. If infants are more susceptible to adverse effects at the same systemic exposure, such dosage reductions may be appropriate. Otherwise, such dosage reductions may inappropriately lower systemic treatment intensity in these younger patients. Further evaluation of pharmacokinetic and pharmacodynamic characteristics are required, particularly in neonates and infants, to permit more precise dosage recommendations for antineoplastic agents in the very young child.

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References

ALDRIDGE, A., ARANDA, J.V. & NEIMS, A.H. (1979). Caffeine metabolism in the newborn. *Clin. Pharmacol. Ther.*, **25,** 447.

ALLEN, J.C. (1978). The effects of cancer therapy on the nervous system. *J. Pediatr.*, **93,** 903.

ARANDA, J.V., MACLEOD, S.M., RENTON, K.E. & EADE, N.R. (1974). Hepatic microsomal drug oxidation and electron transport in newborn infants. *J. Pediatr.*, **85,** 534.

BESUNDER, J.B., REED, M.D. & BLUMER, J.L. (1988). Principles of drug biodisposition in the neonate (part 1). *Clin. Pharmacokinetics*, **14,** 189.

BLEYER, W.A. (1977). Clinical pharmacology of intrathecal methotrexate. II. An improved dosage regimen derived from age-related pharmacokinetics. *Cancer Treat. Rep.*, **61,** 1419.

CHRISTENSON, M.L., RIVERA, G.K., CROM, W.R., HANCOCK, M.L. & EVANS, W.E. (1988). Effect of hydration on methotrexate plasma concentrations in children with acute lymphocytic leukemia. *J. Clin. Oncol.*, **6,** 797.

COLLINS-NAKAI, R.L., NG, P.K., BEAUDRY, M.A., OCEJO-MORENO, R., SCHIFF, D. & VAN PETTEN (1982). Total body digoxin clearance and steady-state concentrations in low birth weight infants. *Dev. Pharmacol. Therap.*, **4,** 61.

EVANS, W.E., CROM, W.R., ABROMOWITCH, M. & 5 others (1986). Clinical pharmacodynamics of high-dose methotrexate in acute lymphocytic leukemia. *N. Engl. J. Med.*, **314,** 471.

EVANS, W.E., PETROS, W.P., RELLING, M.V., CROM, W.R., MADDEN, T., RODMAN, J.H. & SUNDERLAND, M. (1989). Clinical pharmacology of cancer chemotherapy in children. *Ped. Clin. N. Am.*, **36,** 1199.

EVANS, W.E., RODMAN, J.H., PETROS, W.P. & 6 others (1990). Individualized doses of chemotherapy for children with acute lymphocytic leukemia (ALL). *Proc. Am. Soc. Clin. Oncol.*, **9,** 69.

FRIIS-HANSEN, B. (1971). Body composition during growth: in vivo measurements and biochemical data correlated to differential anatomical growth. *Pediatrics*, **47,** 264.

GREEN, D.M., FINKLESTEIN, J.Z., NORKOOL, P. & D'ANGIO, G.J. (1988). Severe hepatic toxicity after treatment with single-dose dactinomycin and vincristine. *Cancer*, **62,** 270.

GREEN, D.M., NORKOOL, P., BRESLOW, N.E., FINKELSTEIN, J.Z. & D'ANGIO, G.J. (1990). Severe hepatic toxicity after treatment with vincristine and dactinomycin using single-dose or divided-dose schedules: a report from the national Wilms' tumor study. *J. Clin. Oncol.*, **8,** 1525.

HEIMANN, G. (1980). Enteral absorption and bioavailability in children in relation to age. *Eur. J. Clin. Pharmacol.*, **12,** 43.

JONES, B., BRESLOW, N.E. & TAKASHIMA, J. (1984). Toxic deaths in the second national Wilms' tumor study. *J. Clin. Oncol.*, **2,** 1028.

KEARNS, G.L. & REED, M.D. (1989). Clinical pharmacokinetics in infants and children. *Clin. Pharmacokinetics*, **17**(S1), 29.

LEAKEY, J.E.A., HUME, R. & BURCHILL, B. (1987). Development of multiple activities of UDP-glucuronyltransferase in human liver. *Biochem. J.*, **243,** 859.

LEBENTHAL, L., LEE, P.C. & HEITLINGER, L.A. (1983). Impact of development of the gastrointestinal tract on infant feeding. *J. Pediatr.*, **102,** 1.

LENNARD, L. & LILLEYMAN, J.S. (1987). Are children with lymphoblastic leukaemia given enough 6-mercaptopurine? *Lancet*, **2,** 785.

LENNARD, L. & LILLEYMAN, J.S. (1989). Variable mercaptopurine metabolism and treatment outcome of childhood lymphoblatic leukemia. *J. Clin. Oncol.*, **7,** 1816.

LENNARD, L., LILLEYMAN, J.S., VAN LOON, J. & WEINSHILBOUM, R.W. (1990). Genetic variation in response to 6-mercaptopurine for childhood acute lymphoblastic leukaemia. *Lancet*, **336,** 225.

LEVY, G., NARINDER, N.K., SODA, D.M., TSUZUKI, O. & STERN, L. (1975). Pharmacokinetics of acetaminophen in the human neonate; formation of acetaminophen glucuronide and sulfate in relation to plasma bilirubin concentration and D-glucaric acid excretion. *Pediatrics*, **55,** 818.

MILSAP, R.L. & SZEFLER, S.J. (1986). Special pharmacokinetic considerations in children. In *Applied Pharmacokinetics*, Evans, W.E. *et al.* (eds), p. 302. Applied Therapeutic: Spokane.

MORSELLI, P.L., FRANCO-MORSELLI, R. & BOSSI, L. (1980). Clinical pharmacokinetics in newborns and infants: age related differences and therapeutic implications. *Clin. Pharmacokinetics*, **5,** 485.

NEIMS, A.H., WARNER, M., LOUGHMAN, P.M. & ARANDA, J.V. (1976). Developmental aspects of the hepatic cytochrome P450 monoxygenase system. *Ann. Rev. Pharmacol. Toxicol.*, **16,** 427.

PELKONEN, O., KALTIALA, E.H., LARMI, T.K.I. & KARKI, N. (1973). Comparison of activities of drug-metabolizing enzymes in human fetal and adult livers. *Clin. Pharmacol. Ther.*, **14,** 840.

SCHMIEGELOW, K. & BRUUNSHUUS, I. (1990). 6-thioguanine nucleotide accumulation in red blood cells during maintenance chemotherapy for childhood acute lymphoblastic leukemia, and its relation to leukopenia. *Cancer Chemother. Pharmacol.*, **26,** 288.

SIEGEL, S.E. & MORAN, R.G. (1981). Problems in the chemotherapy of cancer in the neonate. *Am. J. Pediatr. Hemat. Oncol.*, **3,** 287.

SINKULE, J.A. & EVANS, W.E. (1984). High-performance liquid chromatographic analysis of the semisynthetic epipodophyllotoxins teniposide and etoposide using electrochemical detection. *J. Pharm. Sci.*, **73,** 164.

STEWART, C.F. & HAMPTON, E.M. (1987). Effect of maturation on drug disposition in pediatric patients. *Clin. Pharm.*, **6,** 548.

STEWART, C.F., PIEPER, J.A., ARBUCK, S.G. & EVANS, W.E. (1989). Altered protein binding of etoposide in patients with cancer. *Clin. Pharmacol. Ther.*, **45,** 49.

SZEFLER, S.J., WYNN, R.J., CLARKE, D.F., BUCKWALD, S., SHEN, D. & SCHENTAG, J.J. (1980). Relationship of gentamicin serum concentrations to gestational age in preterm and term neonates. *J. Pediatr.*, **97,** 312.

TSERNG, K.Y., TAKIEDDINE, F.N. & KING, K.C. (1983). Developmental aspects of theophylline metabolism in premature infants. *Clin. Pharmacol. Ther.*, **33,** 522.

VAN DEN BERG, H.W., DESAI, Z.R., WILSON, R., KENNEDY, G., BRIDGES, J.M. & SHANKS, R.G. (1982). The pharmacokinetics of vincristine in man. *Cancer Chemother. Pharmacol.*, **8,** 215.

WOODS, W.G., O'LEARY, M. & NESBIT, M.E. (1981). Life-threatening neuropathy and hepatotoxicity in infants during induction therapy for acute lymphoblastic leukemia. *J. Pediatr.*, **98,** 642.