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Mini-Review

Doxorubicin pharmacokinetics in children with cancer

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ABSTRACT

Anthracyclines are highly active against different tumors in both children and adults. Doxorubicin is often adopted, alone or in combination with other anticancer drugs, for the treatment of childhood cancers. Despite their frequent use, the pharmacokinetics of anthracyclines have not been studied systematically in children. The mechanism of action, the toxicity, and the pharmacokinetic profile of doxorubicin will be described. Many data proposed for the use of anthracyclines in childhood cancers are derived from adult studies. Many concerns are raised about their potential toxicity especially in the treatment of young children with doxorubicin. Dosing is empiric and a rational basis for dose modifications in children of different ages is lacking. There are no definitive results on age-dependent changes in doxorubicin clearance. There are only very few pharmacokinetic investigations of doxorubicin in children. It is fundamental for the clinicians to be aware of the toxicity and pharmacologic profile of these anticancer drugs for their safe and optimal clinical use.

KEYWORDS: doxorubicin, children, toxicity, anthracyclines, pharmacokinetics.

Introduction

Anthracyclines are highly active against different solid and hematologic tumors in both children and adults. Anthracyclines along with alkylating agents are among the most used drugs and almost 60% of children diagnosed with cancer receive anthracyclines as part of their treatment [1-3]. The most used anthracyclines are doxorubicin, daunorubicin, idarubicin, and epirubicin. At present, doxorubicin is used predominately for the treatment of solid tumors while daunorubicin is preferred over doxorubicin for the treatment of acute leukemias. Idarubicin is active in acute leukemias and is thus an alternative to daunorubicin in that setting. Epirubicin is like doxorubicin but its antineoplastic activity is less potent. Despite their frequent use, however, the pharmacokinetics of anthracyclines have not been studied systematically in children. Dosing is empiric and a rational basis for dose modifications in children of different ages is lacking [4, 5]. This represents a significant gap in our knowledge of the safe and appropriate use of these important agents.

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Anthracycline mechanisms of action

Despite their extensive clinical utilization, there remains considerable controversy over the mechanisms of action of anthracyclines in cancer cells and their toxic effects on various organs. The following mechanisms have been proposed [6].

The drug, after its penetration inside the cell, concentrates mainly in the nucleus where it can intercalate into the DNA double helix. This leads to inhibition of nucleotide replication and inhibition of DNA and RNA polymerases, including topoisomerase II, an enzyme that promotes the DNA strand breakage and resealing. Intercalation

stabilizes the normally reversible topoisomerase II-DNA complex, resulting in the production of double-strand DNA breaks. Furthermore, the interaction with the DNA-topoisomerase II complex is supposed to be a primary triggering event of a signaling pathway leading to apoptosis. It has been presumed that, through intercalation, the anthracyclines induce an alteration in DNA three-dimensional conformation that arrests the cycle of topoisomerase-II action at the point of DNA cleavage.

Another mechanism of action is the generation of free radicals. The quinone structure of the anthracyclines permit them to act as electron acceptors in reactions mediated by oxoreductive enzymes including cytochrome P450 reductase, NADH dehydrogenase and xanthine oxidase. The addition of free electrons converts the quinone to semiquinone free radicals, which then can readily donate an electron to oxygen, generating superoxide anions. The superoxide anions can cause subcellular damage either directly or can be further converted to hydrogen peroxide and the highly reactive hydroxyl radical. These agents react with lipids, proteins and nucleic acids, resulting in lipid peroxidation, depletion of sulfhydryl-containing peptides, and damage to DNA. Furthermore, doxorubicin can induce alterations of the cell membrane by binding directly to membrane lipids or proteins or induce changes in membrane fluidity by partitioning into the membrane.

Doxorubicin pharmacokinetics

Doxorubicin is mostly administered in the form of hydrochloride salt intravenously since its low bioavailability of only 5% prohibits oral administration [7]. The pharmacokinetics of doxorubicin are linear, and the plasma concentration-time curve is described by a triphasic curve with a distribution half-life of 12 ± 8 minutes, an initial elimination half-life of 3.3 ± 2.2 hours and a terminal phase elimination half-life of 30 ± 14 hours [8, 9].

Short half-life can be due to rapid distribution in tissues. The large tissue distribution is also apparent by the large volume of distribution, which ranges from 809 to 1214 L/m^2. Distribution into tissues occurs by a rapid diffusion process as well as by carrier-facilitated uptake into cells. One drug transporter facilitating uptake of doxorubicin is the solute carrier SLC22A16, an organic ion transporter. Export is mediated by the multidrug efflux pump, P-glycoprotein. Cummings & McArdle measured doxorubicin concentrations in various healthy tissues such as liver, spleen, lymph nodes, muscle, kidney, lung and haematopoietic cells as well as in tumour cells and found that the concentration within those cells exceeded plasma concentrations by 10 to 500-fold [10]. Elimination from tissues occurs only slowly with a terminal phase elimination half-life of 30 hours and longer. It was shown that even weeks after administration doxorubicin remains in various cells [9].

Doxorubicin is rapidly metabolised into the 13-hydroxyl metabolite doxorubicinol by cytoplasmic NADPH-dependent aldoketoreductases. Aldoketoreductases are present in a variety of cells, but particularly in red cells, liver and kidney cells. Like doxorubicin, doxorubicinol is cytotoxic, but the cytotoxic potential is only one-tenth of that of doxorubicin. Therefore, the clinical significance of it is thought to be minimal [9]. On the other hand, some data suggest that anthracycline cardiotoxicity is mediated especially by doxorubicinol [11].

The terminal half-life of doxorubicinol is similar to that of doxorubicin and the relative exposure, i.e. the ratio between the area under the curve (AUC) of doxorubicinol compared to doxorubicin ranges between 0.4 to 0.9 [9]. Other metabolites of doxorubicin are the poorly water-soluble aglycones, doxorubicinone and 7-deoxydoxorubicinone. They are formed by an NADPH-dependent, cytochrome reductase-mediated cleavage of the amino sugar. In contrast to doxorubicin and doxorubicinol they are non-cytotoxic, but their formation is accompanied by free radical formation, which may contribute to the cardiotoxic activity of doxorubicin [9]. 50 to 85% of plasma doxorubicin is bound to proteins [7]. Plasma clearance is in the range 324 to 809 mL/min/m^2 and is predominantly by metabolism and biliary excretion. Approximately 40% of the dose appears in the bile in 5 days, while only 5-12% of the drug and its metabolites appear in the urine during the same time period.

Doxorubicin pharmacokinetics are highly variable, with an almost 10-fold inter-patient variation of the area under the plasma concentration–time curve, but so far, no firm relation to clinical outcome has been observed.

Due to its extensive metabolism in the liver, changes in hepatic function induced by concomitant therapies may affect doxorubicin metabolism, pharmacokinetics, therapeutic efficacy and/or toxicity. After repeated injections, no accumulation in plasma occurs [12].

Data in children

There are only very few pharmacokinetic investigations of doxorubicin in children in the literature. Apart from the study by Thompson *et al*., all previous studies used a limited sampling schedule in which only one sample shortly before the end of infusion was collected. These sampling strategies are based on the results by Eksborg *et al*. who showed, in a study with adult patients, that the AUC of doxorubicin is linearly correlated with the maximum plasma concentration of the drug at the end of a constant 2 or 4-h infusion [13].

All paediatric studies detected high inter-patient variations as described before for adults. Frost *et al*. analysed the pharmacokinetics of doxorubicin in 112 children with acute lymphoblastic leukemia and found a more than 10-fold difference in dose normalized plasma concentrations between patients [14]. Hempel *et al*. in the only study to determine intra-individual variation, reported high deviations ranging from 3 to 198% with a median of 26% [15].

Adult data suggest gender-related differences in clearance. A significantly higher median doxorubicin clearance in men compared to women (1088 mL/min/m^2 versus 433 mL/min/m^2) was observed [9]. This gender difference was also observed by Palle *et al*. in 37 children with acute myeloid leukemia [16]. Neither Hempel *et al*. nor Eksborg *et al*. detected this gender difference for children [13, 15].

Trial results concerning age-dependent variations in clearance of doxorubicin are contradictory. In a study with 13 children, McLeod showed a statistically significant age dependency normalized to body surface area (BSA) when the systemic clearance in infants <2 years of age was compared with that of children >2 years of age, but he did not find this dependency when clearance was normalized to body weight [16].

In contrast Palle *et al*. found no difference in clearance (normalized to BSA) between those age groups [17]. Frost *et al*. found differences in doxorubicin plasma concentrations normalized for dose [14]. The highest concentrations were found in children aged 4-6 years followed by children aged 2-4 years and then by all other age groups. On the other hand, other research groups found no clear age-dependency in the Cmax of doxorubicin.

No clear correlation of patient characteristics (weight, BMI, aspartate aminotransferase, bilirubin, serum protein, creatinine) with doxorubicin Cmax or clearance have been observed so far in children, but most studies did not involve enough patients in order to produce significant results. Only Thompson *et al*. found an association between pharmacokinetics and body composition, with a lower doxorubicinol clearance in children with body fat above 30% [18].

No correlation between body fat and doxorubicin was detected. Palle *et al*. found a correlation between the effect of doxorubicin and its pharmacokinetics in children with newly diagnosed acute myeloid leukemia. Patients with complete remission had higher plasma concentrations and a lower clearance than patients not reaching complete remission. These results again highlight the need for further investigating doxorubicin pharmacokinetics in children [17, 19-22].

Doxorubicin toxicities

Doxorubicin has a narrow therapeutic index. A serious side effect and the most common acute dose-limiting toxicity of this drug is myelosuppression. Reversible leucopaenia and/or neutropaenia are the predominant manifestations. Thrombocytopaenia and anaemia may also occur. In addition, secondary acute myelogenous leukaemia may occur following treatment. Other acute doxorubicin-induced toxicities include, but are not limited to, mucositis, stomatitis, alopecia, nausea, and vomiting [23-28].

Bone marrow suppression and mucositis are equally present after bolus administration, however

mucositis is more frequent with weekly dosing or continuous infusion. A major problem of doxorubicin, and a factor limiting the cumulative dose of doxorubicin, is cardiotoxicity, both acute and chronic.

The mechanisms behind the cardiotoxic effects of doxorubicin are not fully understood, but lipid peroxidation and the generation of free radicals seem to have major roles. Many normal tissues contain free radical-scavenging enzymes such as catalase and glutathione peroxidase, which detoxify free radicals and prevent or limit tissue damage. Myocardial tissue is relatively deficient in these enzymes and is therefore susceptible to free radical damage [23].

Furthermore, free radicals damage the mitochondrial membranes and thus interfere with energy production. Energy depletion reduces the ability of cardiac myocytes to contract effectively, which in turn can affect heart function. Anthracycline-induced cardiotoxicity may manifest by early/acute changes or by delayed/late-onset cardiotoxicity [29-38].

The most non-invasive method of monitoring myocardial toxicity has been the assessment of left ventricular (LV) systolic function, with either radionucleotide ventriculography or echocardiography. Fractional shortening and LV ejection fraction are the most commonly used measurements [39-45]. At present, there is growing interest in the use of biomarkers for the detection of cardiac injury. BNP, NT-proBNP and cardiac troponins T and I are currently widely used for the detection of cardiac injury [46-59].

Drug interactions

There are very few drug interactions documented for the anthracyclines. Heparin, by binding to the aminosugar of doxorubicin and daunomycin, can create insoluble aggregates. Therefore, the coadministration of heparin and doxorubicin can lead to an increase in the doxorubicin clearance [60, 61]. Anthracyclines can act as radiosensitizers of normal tissue. This can have a significant impact on the sequelae of antineoplastic treatments especially when the heart is involved and receiving both anthracyclines and radiotherapy [62-66]. In rodents, drugs that diminish tissue glutathione pools, such as 1,3-bis (2-chloroethyl)-1-nitrosourea (BCNU) and acetaminophen, can sensitize the liver to injury.

Conclusion

Although anthracyclines can exhibit a range of adverse effects such as myelosuppression, mucositis or cardiotoxicity, they are drugs highly active against different tumors in both children and adults. Therefore, it is fundamental for the clinicians to know the clinical pharmacokinetics of these anticancer drugs for their optimal clinical use.

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CONFLICT OF INTEREST STATEMENT

The authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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