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Clinical report

A comparative pharmacokinetic study of doxorubicin and 4′-epi-doxorubicin in children with acute lymphocytic leukemia using a limited sampling procedure

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Antraquinone glycosides are an important class of antineoplastic drugs, frequently used for treatment of a variety of malignancies in children. Doxorubicin (Dox) is the most frequently used drug within this class of antineoplastics. 4′-epi-doxorubicin (Epi), a Dox isomer, was developed with the aim of reducing risks for fatal heart toxicity observed with Dox. The aim of the present study was to investigate the pharmacokinetics of Dox and Epi in children with acute lymphocytic leukemia. In total 31 patients (13 females and 18 males; median age 5.4 years; range 0.73–15.3 years) were studied using a simplified sampling procedure. The pharmacokinetic differences of the two drugs were established by their simultaneous administration. The plasma pharmacokinetics of neither Dox nor Epi correlated with the age of the patients. There were no gender differences in dose-normalized maximum concentrations of neither Dox nor of Epi. The inter-patient variation of the dose-normalized maximum concentrations of Dox and Epi is larger among females than among males. The C_{max} ratio Dox/Epi was 1.39 ± 0.19 (mean ± SD). The pharmacokinetic differences of Dox and Epi in children, although less pronounced than in adults, are still of a magnitude that might be of clinical importance. [© 2000 Lippincott Williams & Wilkins.]

Key words: Anthracyclines, children, dosing, doxorubicin, 4′-epi-doxorubicin, leukemia, pharmacokinetics.

Introduction

Anthraquinone glycosides are frequently used for treatment of a variety of malignancies, including leukemia, in children. Doxorubicin (Dox) is the most frequently used drug within this class of antineoplastics. Unfortunately, fatal heart toxicity due to treatment with Dox has been documented in a large numbers of reports.[1–3] Attempts to reduce risks for heart toxicity include dose fractionation, prolonged infusions, the use of cardio-protectant agents and new drug analogs. Currently, 4′-epi-doxorubicin (Epi) is the most promising new anthraquinone glycoside in clinical use. Studies in adults have shown that patients treated with a cumulative dose of 550 mg/m^2 of Dox and 950 mg/m^2 of Epi have a 5% probability of developing congestive heart failure.[4]

Anthracycline therapy for acute lymphocytic leukemia (ALL) in childhood is associated with even a higher risk for myocardial damage than in adults. Lipshultz *et al.*[3] identified abnormalities of cardiac function in 17% of childhood patients who had received a single dose of only 45 mg/m^2 of Dox. The cumulative dose, age at treatment and gender are important risk factors for children treated with anthraquinone glycosides.[5,6]

The aim of the present study was to investigate factors influencing the pharmacokinetics of Dox and Epi administered as a 24 h constant rate infusion to children with ALL, and also to compare the pharmacokinetics of the two drugs. The pharmacokinetics of Dox and Epi were evaluated by our previously published simplified sampling procedure.[7] The influence of intra-patient variation on Dox and Epi pharmacokinetics was eliminated by treating the patient with a mixture of equal amounts of Dox and Epi during the study period. The drugs were analyzed by reversed-phase liquid chromatography with fluorometric detection.

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Patients and methods

Study approval

The study was approved by the Local Ethics Committee (Karolinska Hospital, no. 94-224). Oral informed consent was obtained from all parents and, when appropriate, also from the children prior to inclusion into the study.

Patients

In total, 31 patients (13 females and 18 males) with ALL were included in the present study. Their median age was 5.4 years (range 0.73–15.3 years). During the study period all patients were in complete remission.

Treatment schedule

Twenty-four of the patients were treated according to the Nordic Society for Pediatric Hematology and Oncology (NOPHO) 92 SR/IR protocol. The remaining seven patients were treated according to the NOPHO 92 HR protocol. However, for the purpose of the present study, the last scheduled course of Dox (i.e. course 3 for the SR/IR group and course 4 for the HR group) was substituted by equal amounts of Dox and Epi, the total dose being equal to the ordinary scheduled dose of Dox.

The administered dose of each anthracycline drug was 19.4 mg/m^2 (median value; range 12.9–21.0 mg/m^2) corresponding to 0.76 mg/kg (median value; range 0.55–1.0 mg/kg).

The body surface area (BSA) of the patients was calculated from the Du Bois formula.[8] The body mass index (BMI) was calculated as weight/(height)^2 and the lean body mass (LBM) as given by James.[9]

Drug solutions were prepared by dilution of commercial available stock solutions of Dox (Adriamycin®) and Epi (Farmorubicin®) (2 mg/ml; Pharmacia & Upjohn, Stockholm, Sweden) with 5% glucose containing 40 mM/l of sodium and 20 mM/l of potassium. The final volume of the prepared infusion solution was 1000 ml. For medical reasons the infusion volume was, however, reduced to 500 ml in three of the patients and to 250 ml in another two patients.

The concentrations of Dox and Epi in all drug solutions were quantified by reversed-phase liquid chromatography (see below). The concentration ratio Dox/Epi was 1.01 (median value; 95% CI 0.98–1.05).

The drug solutions were administered by an IVAC Model 561 infusion pump (Medical Instrument Systems Scandinavia, Täby, Sweden). The infusion rate was constant during the administration of the drug mixture.

Plasma samples

Capillary blood samples were drawn into micro hematocrit capillary tubes (i.d. 1.2 mm; length 75 mm) treated with ammonium heparin (Kebo Lab, Stockholm, Sweden). The plasma fractions were separated by centrifugation for 5 min in an Adams Autocrit Centrifuge (Clay Adams, Parsippany, NJ). The plasma fractions were collected in capped glass vials and stored at -70°C until time of analysis.

Analytical procedure

Dox and Epi were assayed by an analytical procedure based on reversed-phase liquid chromatography with fluorometric detection.[10]

Briefly, 100 μl of plasma sample was mixed with the internal standard (daunorubicin) dissolved in 0.1 M phosphoric acid and transferred into a SepPak C18 extraction column (Waters, Milford, MA). After rinsing with 5 ml of phosphate buffer (pH 7.0) the antraquinone glycosides were eluted with 4 ml of methanol. The elute was evaporated, redissolved in 0.1 M phosphoric acid and injected into a Nova-Pak Phenyl Radial-Pak cartridge (Waters). Acetonitrile, typically 40%, in 0.01 M phosphoric acid was used as the mobile phase. Minor adjustments of the acetonitrile concentration in the mobile phase were sometimes necessary to maintain optimal chromatographic resolution of the anthraquinone glycosides. The fluorometric detector (Model RF-551 spectrofluorometric detector; Shimadzu, Kyoto, Japan) was operated at 501/600 nm.

All plasma concentrations reported are mean values of duplicate analysis.

Pharmacokinetics

A limited sampling model for plasma level monitoring of Dox and Epi was used.[7] Plasma concentrations of Dox and Epi were measured 23 h after the start of the 24 h infusions.

Statistics

The Mann–Whitney *U*-test was used for the comparison of values from two independent populations. Correlations were established by the Spearman rank correlation test. Dispersion of data from two populations was compared by the Bartlett's test for equal variances. $p < 0.05$ was considered as statistically significant.

Results

C_{max} values of neither Dox nor Epi correlated with the age of the patients, after dose normalization based on BSA (mg/m^2), body weight (BW; mg/kg) or (LBM), (Figures 1 and 2). C_{max} values of Dox, after dose normalization based on BSA, were higher in younger children (median age 3.4 years; range 0.73–4.85 years; n=15) than in older children (median age 8.8 years; range 5.42–15.26 years; n=16), p=0.03. The difference of dose-normalized C_{max} values of Epi did not differ between younger and older children.

There were no gender differences in BSA dose-normalized maximum concentrations of Dox or Epi. The inter-patient variations of the dose-normalized maximum concentrations of both drugs were larger among females than among males, p=0.03 and p=0.007 for Dox and Epi, respectively.

The influence of the different dose-normalization principles on the inter-patient variation of the

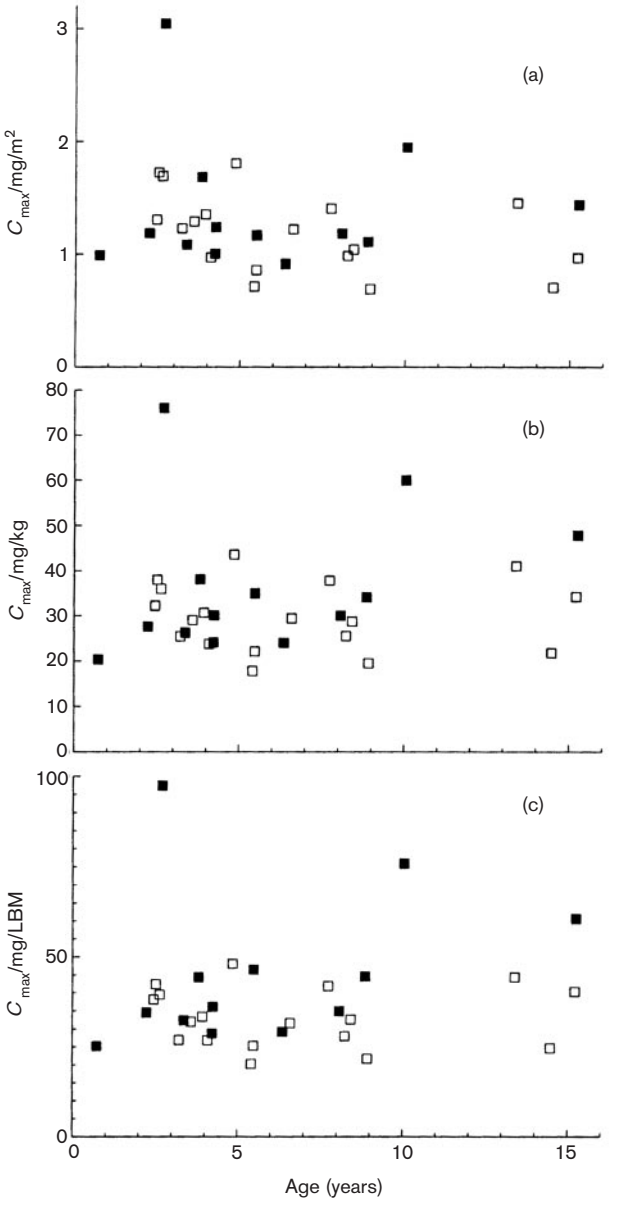

Figure 1. Dose-normalized maximum plasma concentration of Dox in relation to age. Dose normalization based on (a) BSA, (b) BW and (c) LBM. Closed symbols: females. Open symbols: males.

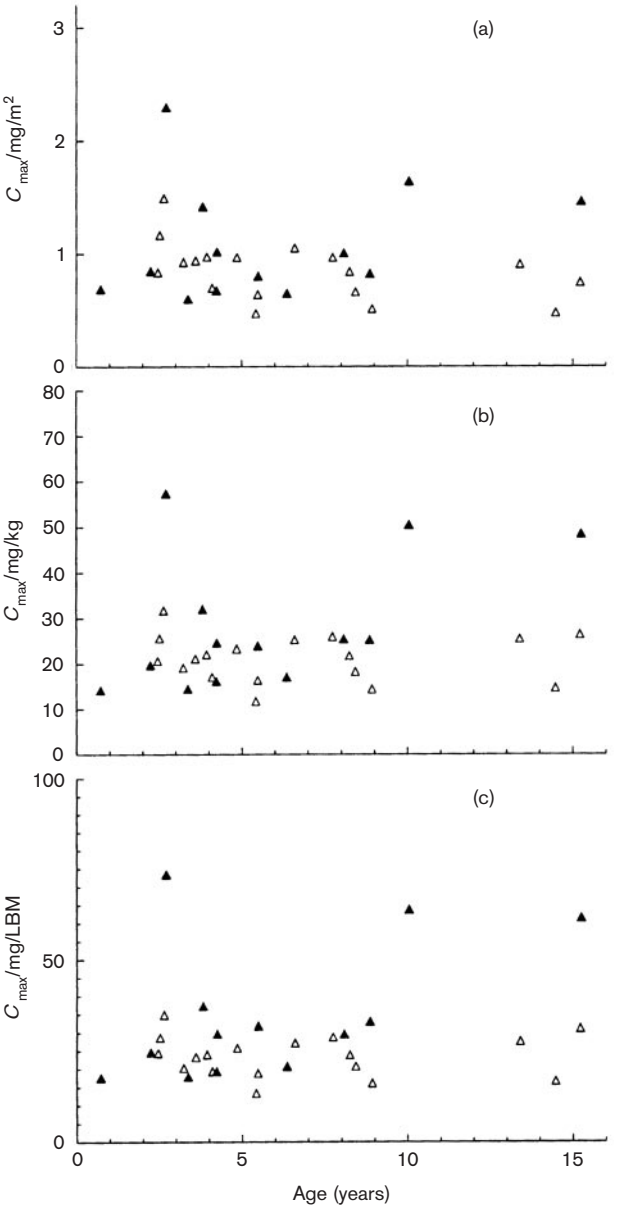

Figure 2. Dose-normalized maximum plasma concentration of Epi in relation to age. Dose normalization based on (a) BSA, (b) BW and (c) LBM. Closed symbols: females. Open symbols: males.

Table 1. Dosing of Dox and Epi to children with ALL

	Dox			Epi		
	C_{max}/mg/m^2	C_{max}/mg/kg	C_{max}/mg/LBM	C_{max}/mg/m^2	C_{max}/mg/kg	C_{max}/mg/LBM
Mean	1.28	32.5	38.3	0.94	24.0	28.3
Min	0.69	17.8	20.3	0.47	11.6	13.2
Max	3.04	76.0	97.4	2.29	57.2	73.3
SD	0.46	12.1	15.9	0.39	10.6	13.9
VC%	35.9	37.2	41.5	41.0	44.2	49.2

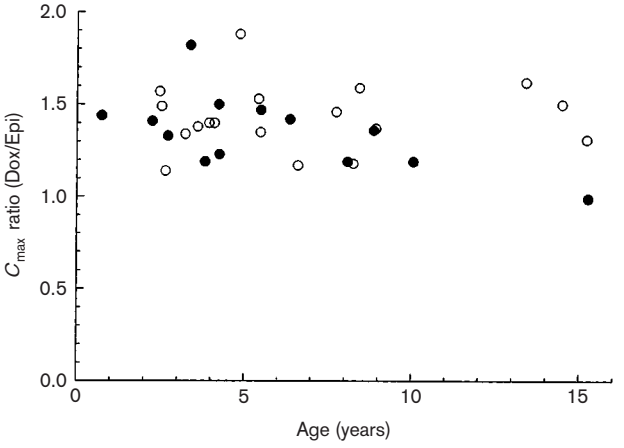

Figure 3. Relative maximum plasma concentration of Dox and Epi and age. Closed symbols: females. Open symbols: males.

maximum plasma concentration is summarized in Table 1, indicating that dose normalization based on BSA might give a lower inter-patient variation of a pre-determined target plasma concentration than dosing base on BW or LBM.

BSA-normalized C_{max} values did not correlate with BMI for Dox or Epi (data not shown). Dose-normalized C_{max} values of Dox and Epi tended to be higher in patients with low BMI [C_{max}/mg/m^2: 1.33 (Dox) and 0.98 (Epi); mean values; BMI: 12.2–16.3 kg/m^2, n=15] than in patients with high BMI [C_{max}/mg/m^2: 1.21 (Dox) and 0.89 (Epi); mean values; BMI: 16.7–21.5 kg/m^2, n=16] (p= 0.06 and p=0.02 for Dox and Epi, respectively).

The C_{max} ratio Dox/Epi was 1.39 ± 0.19 (mean value $\pm$ SD) and was not affected by the age of the patients (Figure 3).

Discussion

Cancer chemotherapeutic agents have a lower therapeutic index than most other groups of drugs. The difference between an underdose and an overdose is small, and the consequences of either are life-threatening. Variation between individuals in response to chemotherapy is a great clinical problem and variation in drug exposure, measured by the area under the plasma (blood) concentration time curve (AUC), might be a major contribute to it.[11] Therefore, cancer chemotherapy needs precise and reliable prescription methods. Generally, dosing of antineoplastic drugs is based on BW or BSA. Recently, LBM was suggested to be further evaluated and tested in dose-optimizing studies of Epi.[12]

The pharmacokinetic goal of dosing is to obtain a pre-determined AUC value even though the targets of anticancer drugs are localized in the tumor cells, since pharmacokinetic studies in plasma obviously are more realistic than in tumor tissue. The relationship between drug concentrations in plasma and tumors has not been extensively studied; however, a good correlation between Dox concentration in plasma and tumors has been established.[13–15] Relationships between plasma concentration, host toxicity and tumor response have been reported for a number of antineoplastic drugs, including Dox,[16,17] suggesting that the dose to be administered could be adjusted to result in pre-determined plasma concentrations, in order to achieve a predictable outcome, i.e. to produce a more consistent therapeutic effect while at the same time minimizing toxicity.

The pharmacokinetics of Dox and Epi have been extensively studied in adults.[14,18,19] The pharmacokinetics of the anthraquinone glycosides are highly variable with an almost 10-fold inter-patient variation of AUC despite standardization of the dose based on BSA.[20] The need for individualization of doses based on measured plasma concentrations of the anthraquinone glycosides has been pointed out as a result of the many reports of their large inter-patient variation.[21,22] However, only scant data concerning the pharmacokinetics of Dox in children have so far been published,[23–27] while pharmacokinetic data of Epi in children have been lacking until now.

In the present study we used the maximum plasma concentrations of Dox and Epi as a substitute for

measuring the total AUC.[7] This simplified technique for pharmacokinetic monitoring has previously been applied in a study of the pharmacokinetics of Epi in patients with breast cancer.[28] Calculations showed that plasma concentrations of Dox and Epi 23 h after the start of a 24 h infusion are less than 0.5% lower than C_{max}, reached at the end of the infusion. Capillary blood sampling was used in the present study for ethical and practical reasons.[29]

Comparative studies of Dox and Epi in adults have shown that the pharmacokinetics of the two drugs are very similar.[30–34] In the present study, the influence of intra-patient variation in Dox and Epi pharmacokinetics was eliminated by treating the patients with a mixture of equal amounts of Dox and Epi at one study occasion only. This technique has previously been used for comparative pharmacokinetic studies of the two drugs after i.v. and intrahepatic administration to adult patients, and enables evaluation of even minor differences in their pharmacokinetics.[31,32]

Previous studies of dose normalization and age dependency of Dox clearance in children are conflicting. McLeod *et al.*[27] observed a lower clearance, normalized for BSA, in children younger than 2 years as compared to children aged 2–20 years, while weight-normalized clearance did not differ in the two age groups.[27] In contrast, Crom *et al.*[26] found that plasma clearance of Dox, normalized to BSA, was not related to age, but clearance normalized to weight was lower in patients above the median age of 10.5 years.

The results in the present study did not show a correlation between age and plasma pharmacokinetics of Dox and Epi after dose normalization based on BSA (mg/m^2), BW (mg/kg) or LBM (Figures 1 and 2). Influence of age on the pharmacokinetics of Dox cannot, however, be excluded, since C_{max}/mg/m^2 was higher in the younger than in the older groups of children, which is in accordance with the results presented by McLeod *et al.*[27] Our data do not support an assumption of an age-dependent pharmacokinetics of Epi.

The results in Table 1 indicate that dose normalization based on BSA might give a lower, although not significant, inter-patient variation of a pre-determined target plasma concentration than dosing based on BW or LBM. It must be emphasized that even a dose normalization based on BSA still results in an 4- to 5-fold inter-patient variation of the maximum plasma concentration. The results in Table 1 also indicate that the inter-patient variation of dose-normalized C_{max} might be lower for Dox than for Epi, but this difference is not statistically significant.

A comparison of C_{max} values in the present study and in our previous study of adult breast cancer patients[28] shows that dosing based on BSA results in similar plasma concentrations of Epi in children and adults, under the assumption that identical infusion rates are used. In contrast, dosing based on BW results in lower plasma concentrations of Epi in children than in adults. The inter-patient variation of the dose-normalized C_{max} values of Epi were higher in children with ALL than in breast cancer patients (p=0.002), underlining the difficulties of a proper dosing of anthraquinone glycosides to children.

The body composition is considered as an important variable in the pharmacokinetics of antineoplastic drugs,[35] even though relative little attention has been paid to this fact when optimizing drug treatment. However, in a study of the fat body mass and the pharmacokinetics of oral 6-mercaptopurine in children with ALL, it was found that the AUC values increased with decreasing weight/height percentile, an index of the fat body mass.[36]

The BMI values of the patients in the present study were within the range 12.2–21.5 kg/m^2, corresponding to 73–149% of BMI values observed in healthy, aged-matched children. A correlation between the values of C_{max} for Dox and Epi, normalized for the dose in mg/m^2, and BMI could not be established. However, dose-normalized C_{max} values of Dox and Epi tended to be higher in patients with low BMI than in patients with high BMI. This is in accordance with the observations that clearance of xenobiotics in malnourished children in general is lower than in well-nourished children.[37]

The importance of body composition on anthracycline pharmacokinetics in adults is conflicting. Hence, an increase of Dox AUC and prolonged elimination rate in obese patients has been reported.[38] Dox clearance decreased and the elimination rate increased with increasing percentage ideal body weight. In contrast, the pharmacokinetics of Epi, administered as a 2 h infusion to breast cancer patients, did not show a correlation between the maximum plasma concentration of Epi and degree of obesity.[28] It should be emphasized that these patients had considerably higher BMI values than the patients in the present study.

An addition to higher risks for abnormalities of cardiac function,[5,6] nausea associated with anthracycline-containing regimes is more severe in girls than in boys.[39] Moreover, superior treatment results in females with high-risk ALL in childhood have also been found using anthracycline-containing regimes.[40] The observed gender differences in side effects and therapeutic efficacy might be explained by a lower clearance of the anthracyclines in females, previously observed for Dox in adults with normal liver biochemistry.[41,42] In the present study it was not

possible to demonstrate statistical differences of the dose-normalized maximum concentrations of Dox or of Epi between males and females. The inter-patient variations of the dose-normalized maximum concentrations of both drugs were, however, larger among females than among males, with the highest dose-normalized C_{max} values observed in three of the girls. Thus, it cannot be ruled out that the observed gender differences in side effects and therapeutic efficacy of the anthracyclines in children might be of a pharmacokinetic origin.

The pharmacokinetic differences of Dox and Epi are significantly less pronounced than in adults (C_{max} ratio Dox/Epi in children versus AUC ratio Dox/Epi in adults, p=0.02.[31,32] Hence, the reduction of systemic side effects obtained by substituting Dox with Epi might be less pronounced in children than in adults, since the reduced toxicity of Epi in comparison with Dox has been suggested to be the consequence of differences in pharmacokinetic behavior characterized by constantly lower plasma concentrations of Epi.[30] However, the pharmacokinetic differences of the two drugs in children are still of such a magnitude that substituting Dox with Epi most likely will be of clinical importance.

The relative efficacy of Dox and Epi has been extensively debated. Dox and Epi are equivalent *in vitro* against many cancer cells lines. Epi is even more effective against gastric cancer cells than Dox.[43] A large number of studies concerning the relative efficacy of Dox and Epi for the treatment of patients with neoplastic diseases have also been presented. In a recent review it was stated that Dox and Epi are equipotent in the treatment of breast cancer when used as single drug as well as in combination with other antineoplastic drugs.[4] Epi has a more favorable therapeutic index than Dox in second-line advanced breast cancer.[44] The use of equimolar doses of Dox and Epi in advanced soft tissue sarcoma produced response rates which did not differ significantly.[45] In the treatment of non-Hodgin's lymphoma Epi was as effective as Dox in terms of patients' response to therapy.[46] Epi has proved to have higher efficacy than Dox given intravesically after complete resection of stage T_a/T_1 bladder carcinoma by prolonging time to first recurrence and decreasing the recurrence rate.[47] The relative efficacy of Dox and Epi in the treatment of leukemia has so far not been evaluated, but the uptake of Epi in leukemic cells is higher than of Dox in patients with acute leukemia, as a result of its higher lipophilic character.[48] However, the clinical implication of this finding is still unclear.

Doses of Epi used clinically are in general 30–50% higher than the doses of Dox, due to the fact that the hematopoietic toxicity of Epi is considerably lower than Dox.[46,49] This might be clinical advantageous since a steep dose–response curve has been observed for Epi, at least for breast cancer patients.[4] The dose-response relationship is less obvious for Dox.[50]

Conclusions

The plasma pharmacokinetics of neither Dox nor Epi correlated with the age of the patients.

Dose normalization based on BSA gives lower, but statistically non-significant, inter-patient variation of a pre-determined target plasma concentration than dosing based on BW or LBM.

There were no gender differences in dose-normalized maximum concentrations neither of Dox nor Epi.

The inter-patient variation of the dose-normalized maximum concentrations of Dox and Epi are larger among females than among males.

The pharmacokinetic differences of Dox and Epi in children are less pronounced than in adults, but are still of a magnitude that might be of clinical importance.

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