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Changes in doxorubicin distribution and toxicity in mice pretreated with the cyclosporin analogue SDZ PSC 833

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Abstract SDZ PSC 833 (PSC 833) is a cyclosporin A analogue that is under clinical investigation in combination with doxorubicin (Dx) or other anticancer agents as a type-1 multidrug resistance (MDR-1)-reversing agent. The present study was focused on the effects of PSC 833 on the distribution and toxicity of Dx in non-tumor-bearing CDF1 male mice. Mice were given PSC 833 i.p. at 30 min before i.v. Dx treatment. Dx levels were determined by a high-performance liquid chromatography (HPLC) assay at different times during a 72-h period following Dx treatment in the serum, heart, intestine, liver, kidney, and adrenals of mice. In all tissues, Dx area under the concentration-time curve (AUC) values were much greater in mice receiving 10 mg/kg Dx in combination with 12.5 or 25 mg/kg PSC 833 than in mice receiving Dx alone. The highest increase in Dx concentrations was found in the intestine, liver, kidney, and adrenals. Lower, albeit significant, differences were found in the heart. PSC 833 did not appear to influence either urinary or fecal Dx elimination or Dx metabolism to a great extent. Doses of PSC 833 devoid of any toxicity potentiated the acute and delayed toxicity of Dx dramatically. The mechanism responsible for this enhanced toxicity has not yet been elucidated but is likely to be related to an increased tissue retention of Dx due to inhibition of the P-glycoprotein (Pgp) pump by PSC 833, as has recently been proposed for cyclosporin A.

Key words MDR · Pgp · SDZ PSC 833

Abbreviations *MDR* Multidrug resistance · *mdr-1 gene* multidrug resistance-1 gene · *Pgp* P-glycoprotein · *PSC 833* SDZ PSC 833 · *Dx* doxorubicin · *HPLC* high-performance liquid chromatography · *AUC* area under the concentration-time curve

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Introduction

The best-characterized mechanism of resistance to anticancer agents is related to expression of the *mdr-1* gene encoding P-glycoprotein (Pgp). Pgp is a membrane-bound transport protein that acts as an energy pump to increase the efflux and reduce the intracellular retention of several structurally unrelated drugs such as anthracyclines, vinca alkaloids, podophyllotoxins, actinomycin D, taxol, and trimetrexate [11, 17, 18, 23, 31]. Several compounds have been reported to be capable of inhibiting Pgp, thus reversing the resistance mechanism. One of the most interesting multidrug resistance (MDR)-reversing agents is cyclosporin A. It can reverse resistance to doxorubicin (Dx) and other drugs transported by Pgp at concentrations that can be achieved in vivo at nontoxic doses [14, 26, 29]. Pgp has also been found to be expressed in normal tissues [13, 28], suggesting that cyclosporin A, as well as other reversal agents, increase the sensitivity of nonmalignant tissues to antineoplastic drugs, thereby increasing the toxicity of the drugs and diminishing their therapeutic index. In mice and rats, cyclosporin A causes a significant increase both in the levels of Dx measured in several types of normal tissue [8] and in Dx toxicity.

Recently, a cyclosporin A analogue, SDZ PSC 833 (PSC 833), which is a potent MDR-reversing agent without the immunosuppressive activity of cyclosporin A, was identified [15, 16, 20, 30]. PSC 833 is under early clinical investigation in combination with Dx or etoposide [6, 12, 22, 25]. In the present study we evaluated whether PSC 833 could change the distribution, metabolism, elimination, and toxicity of Dx in normal mice.

Materials and methods

Animals and drugs

Male CDF1 mice (body weight, 20 ± 2 g) obtained from Charles River Italia (Calco, Italy) were used for these experiments. Procedures involving animals and their care were conducted in conformity with institutional guidelines in compliance with national (D.L. n. 116, G.U., suppl. 40, 18 February 1992) and international laws and policies (EEC Council Directive 86/609, OJ L 358,1, December 12, 1987; NIH Guide for the Care and Use of Laboratory Animals, NIH publication 85–23, 1985).

PSC 833, kindly provided by Sandoz Ltd. (Basel, Switzerland), was freshly dissolved in ethanol and olive oil (0.05:10, v/v). Dx, kindly provided by Pharmacia-Farmitalia-Carlo Erba (Milan, Italy), was freshly dissolved in distilled water.

Pharmacokinetics studies

PSC 833 was injected i.p. into mice at two different doses: 12.5 and 25 mg/kg. Dx was injected i.v. at a dose of 10 mg/kg (corresponding to approximately 30 mg/m^2) at 30 min after PSC 833 administration. At 5, 15, 30, 60, and 90 min and 2, 4, 6, 12, 24, 48, and 72 h after Dx injection, six animals per time point were killed by exsanguination using light ether anesthesia, and serum and tissues (heart, liver, small intestine, kidneys, and adrenals) were removed and frozen at − 20°C until use.

Three groups of ten mice each were housed in metabolic cages until 72 h after Dx and PSC 833 treatment. Urine and feces were collected at different intervals (0–12, 12–24, 24–48, and 48–72 h) and stored immediately at − 20°C until analysis. Six groups of ten mice each were used to assess treatment toxicity and survival.

Analytical assay

Dx and its metabolites were quantified by high-performance liquid chromatography (HPLC) with fluorimetric detection according to a previously described technique [7], with minor modifications. Serum samples to which daunorubicin had been added as an internal standard were extracted with 8 ml of chloroform: isopropanol (1:1, v/v) and centrifuged at 3000 rpm; the organic phase was evaporated to dryness under vacuum. After homogenization in water, tissue samples to which daunorubicin had been added as an internal standard were deproteinized with $AgNO_3$ (33%), extracted with 8 ml of isoproparol, and then processed as described for serum samples. Extracts were injected into the HPLC system, with fluorescence detection being set at an excitation wavelength of 475 nm and an emission wavelength of 580 nm. Separation was achieved with an isocratic solvent system of water:acetonitrile:0.1 *M* phosphoric acid using a 30-cm μBondapak C18 (10-μm) column. Recovery of Dx and its metabolites was 85%–90% for serum and tissue, and the sensitivity was 5 ng/ml for serum and 20 ng/g for tissue.

Pharmacokinetic and statistical analysis

The area under the curve of drug concentration as a function of time [AUC, expressed in micrograms per milliliter times hours (serum) or in micrograms per gram (of tissue) times hours] was calculated by the trapezoidal method over a period of up to 72 h. Statistical significance was assessed by Duncan's test.

Results

Figure 1 shows the serum and tissue levels of Dx determined in mice receiving i.v. injections of 10 mg/kg Dx given either alone or at 30 min after PSC 833 injection at doses of 12.5 and 25 mg/kg. Following drug injection, Dx serum levels decreased very rapidly during the 1st h, corresponding to the distribution phase, then declined very slowly. No marked difference was observed between serum levels found in mice receiving Dx alone versus Dx in combination with PSC 833. In contrast, Dx levels measured in the tissues that were analyzed proved to be higher in mice treated with PSC 833 and Dx than in mice treated with Dx alone. The differences were evident as early as at 4–6 h after treatment and were maintained over subsequent intervals. The quantitative differences observed in Dx levels at 72 h and in AUC values in the three experimental groups are illustrated in Table 1. The most striking differences ($P < 0.01$) were found in the intestine, liver, adrenals, and kidney. In the heart the difference was statistically significant but of lesser magnitude.

In the intestine and adrenals, Dx AUC values were found to be statistically significantly different in the two groups of mice receiving 12.5 or 25 mg/kg PSC 833, whereas no difference was observed in the other tissues. Among the tissues analyzed, Dx metabolites were present in the largest concentration in the kidney and liver.

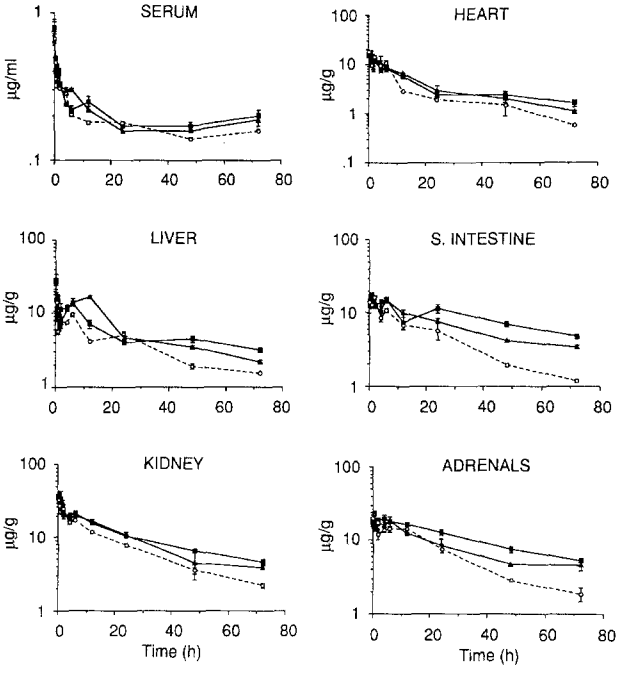

Fig. 1 Disappearance curves generated for Dx in serum and tissues of mice treated with Dx alone (10 mg/kg i.v., ○- - - -○) or with PSC 833 at the i.p. doses of 12.5 (▲——▲) and 25 (■——■) mg/kg. Bars represent SE which are not visible when smaller than the symbols. For further details, see Table 1

Table 1 Dx levels measured at 72 h and AUC values for up to 72 h as determined in male CDF1 mice given Dx alone or in combination with PSC-833[a]

Tissue	Dx		PSC 12.5 + Dx		PSC 25 + Dx	
	Level 72 h[b]	AUC[c]	Level 72 h[b]	AUC[c]	Level 72 h[b]	AUC[c]
Serum	0.16 ± 0.03	13 ± 0.3	0.19 ± 0.02	14 ± 0.60*[1]	0.20 ± 0.02	14 ± 0.90*[1]
Heart	0.57 ± 0.01	198 ± 30	1.07 ± 0.09*[2]	257 ± 23*[1]	1.60 ± 0.23*[2]	260 ± 27*[1]
Intestine	1.19 ± 0.02	328 ± 69	3.41 ± 0.16*[2]	491 ± 15*[1]	4.72 ± 0.29*[4]	625 ± 62*[3]
Liver	1.54 ± 0.01	270 ± 36	2.20 ± 0.10*[2]	405 ± 5*[2]	3.16 ± 0.20*[2]	398 ± 23*[2]
Kidney	2.23 ± 0.14	534 ± 3	3.93 ± 0.25*[2]	696 ± 63*[2]	4.68 ± 0.42*[4]	748 ± 15*[2]
Adrenals	1.90 ± 0.41	486 ± 18	4.63 ± 0.74*[2]	595 ± 65*[1]	5.42 ± 0.42*[2]	791 ± 74*[4]

*[1] $P < 0.05$ vs controls (Duncan's test); *[2] $P < 0.01$ vs controls (Duncan's test); *[3] $P < 0.05$: PSC 25 + Dx vs PSC 12.5 + Dx (Duncan's test); *[4] $P < 0.01$: PSC 25 + Dx vs PSC 12.5 + Dx (Duncan's test)
[a] Six animals per group were used for these studies
[b] Expressed in μg/ml or μg/g tissue
[c] Expressed in μg ml^{-1} h or μg g $tissue^{-1}$ h

Table 2 Dx peak levels and AUC values determined for doxorubicinol and Dx aglycone in the kidney and liver of CDf1 mice receiving Dx alone or in combination with PSC-833

	Dx		PSC 12.5 + Dx		PSC 25 + Dx	
	Peak level[a]	AUC[b]	Peak level[a]	AUC[b]	Peak level[a]	AUC[b]
Kidney						
Doxorubicinol	1.64 ± 0.45	58.60 ± 5.3	1.43 ± 0.03	68.9 ± 7.3	1.34 ± 0.22	66.4 ± 2.9
Dx aglycone	48.10 ± 2.63	440.46 ± 98.8	41.9 ± 0.80	522.96 ± 68.2	43.0 ± 5.84	544.85 ± 95.2
Liver						
Doxorubicinol	1.96 ± 0.20	31.42 ± 3.2	2.25 ± 0.10	22.92 ± 0.5	1.93 ± 0.32	19.77 ± 2.3
Dx aglycone	115.56 ± 7.00	868.77 ± 65.7	116.8 ± 3.70	919.2 ± 60.6	129.6 ± 10.80	694.4 ± 70.3

[a] Expressed in nmol/g tissue
[b] Expressed in nmol g $tissue^{-1}$ h

Table 2 shows the AUC and peak values obtained for the Dx metabolites doxorubicinol and Dx aglycone in these two organs. In the kidney, levels of the metabolites appeared higher in mice receiving Dx in combination with PSC 833 than in those receiving Dx alone, but the differences were not statistically significant. In the liver, levels of the metabolites appeared similar or even slightly lower in mice receiving the combination than in mice receiving Dx alone. Due to the experimental variability, these differences are not statistically significant and should thus be interpreted with caution. The major metabolite present was Dx aglycone.

The renal and fecal elimination of Dx, doxorubicinol, and Dx aglycone is illustrated in Fig. 2. The cumulative urinary elimination of Dx and doxorubicinol corresponded to less than 15% and 2% of the Dx dose, respectively, whether determined in the group of mice receiving Dx alone or in the two other groups of mice receiving PSC 833 pretreatment. During the 24 to 72-h interval the urinary elimination of doxorubicinol was significantly higher in mice receiving Dx in combination with PSC 833. However, the total excretion of this metabolite was negligible in relation to the Dx dose, being in all groups less than 2%. The cumulative fecal elimination of Dx, doxorubicinol, and Dx aglycone corresponded to approximately 2%, 1%, and 2% of the Dx dose, respectively, and did not appear to be influenced by PSC 833 pretreatment.

Figure 3 shows the weight change (Fig. 3A) and survival (Fig. 3B) of mice treated with Dx or PSC 833 alone or with a combination of the two. The Dx-PSC 833 combination induced significant weight loss and a high rate of toxic death, whereas both PSC 833 alone and Dx alone were well tolerated. The weight loss observed in mice receiving the combination followed a biphasic pattern involving an initial decrease during the first few days after treatment, with a nadir occurring on the 4th day, followed by recovery on day 20 and a delayed weight loss preceding animals' death. At 90 days after treatment with the combination of 10 mg/kg Dx and 12.5 or 25 mg/kg PSC 833, the percentage of surviving mice was 20% or 30%, respectively, whereas no death was observed in the group of mice receiving PSC 833 or Dx alone.

Discussion

The present study shows that PSC 833 modifies the tissue distribution of Dx in mice and increases its toxicity. PSC 833 pretreatment caused a significant increase in Dx concentration in the liver, intestine, kidney,

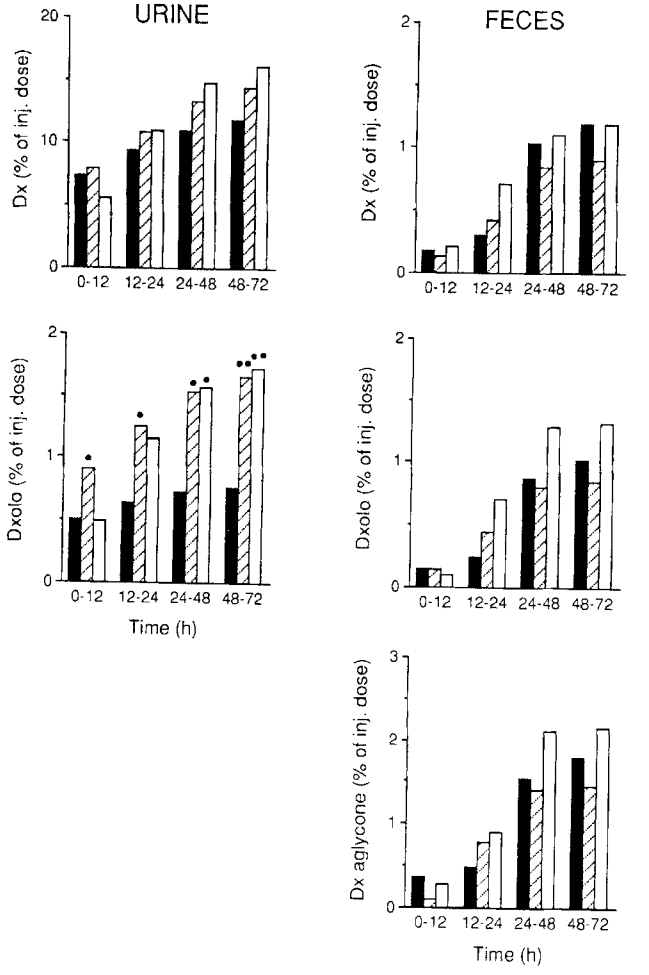

Fig. 2 Urinary and fecal elimination of Dx and its metabolites as determined in mice receiving Dx alone (10 mg/kg, ■) or with PSC 833 at the i.p. doses of 12.5 (▨) and 25 (□) mg/kg. $^{\bullet}P < 0.05$; $^{\bullet\bullet}P < 0.01$ (Duncan's test)

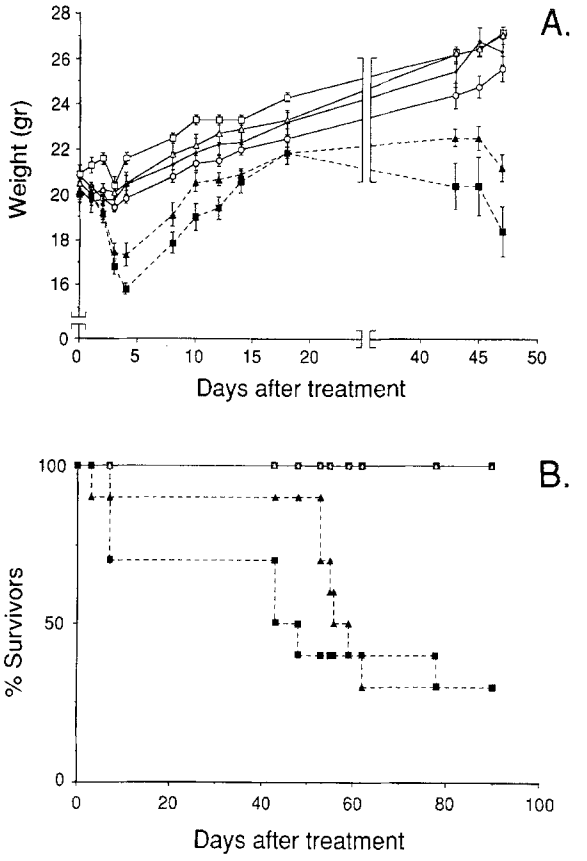

Fig. 3 **A** Body-weight changes and **B** duration of survival as determined in untreated mice (——) and in mice treated with Dx alone (10 mg/kg, ○——○), with PSC 833 alone (12.5 mg/kg, Δ——Δ; or 25 mg/kg, □——□), or with the combination of PSC 833 (12.5 mg/kg, ▲– – –▲; or 25 mg/kg, ■– – –■) and Dx

adrenals, and heart. The increase in Dx tissue levels did not appear to be the result of a change in Dx metabolism or elimination. In fact, the differences observed in the levels of Dx metabolites and in the urinary and fecal elimination of Dx and its metabolites doxorubicinol and Dx aglicone were of small extent in mice pretreated with PSC 833 as compared with mice receiving Dx alone. It seems more likely that PSC 833 inhibits the efflux of Dx from tissues by inhibiting Pgp [3–5, 16, 30], which is known to be expressed not only in MDR tumors but also in normal tissues.

Even though PSC 833 alone was devoid of detectable toxicity at the doses used, the combination of PSC 833 with tolerable Dx doses resulted in severe delayed toxicity. It seems reasonable to theorize that the increased toxicity might be related to the increase in Dx tissue concentrations, although the precise mechanism of toxicity remains to be elucidated. The delayed toxicity occurring at 40–50 days after the single Dx dose given 30 min after PSC 833 injection may have been the result of cardiotoxicity related to elevated Dx concentrations in the heart. It is unlikely that the high toxicity of the Dx and PSC 833 combination is due to bone marrow toxicity, since death would have occurred much earlier in this case.

The finding that PSC 833 markedly increases the toxicity of Dx in mice is of potential relevance, considering that this combination is presently under early clinical investigation [2, 10, 27]. Indeed, the preclinical data obtained in the present study suggest caution in giving Dx doses in combination with PSC 833 that are as high as those normally used. It should be noted that in mice pretreated with PSC 833, Dx serum levels were only slightly greater than those found after treatment with Dx alone. Although these differences were statistically significant, they were much less marked than those found in tissues. Therefore, it seems important to consider that small differences in Dx serum levels may mislead to an underestimation of the differences existing in tissues, which may be more closely related to clinical toxicity.

The results obtained in the present study are very similar to those recently published by Colombo et al. [8] on the interaction of cyclosporin A with Dx in rats and mice. Cyclosporin A pretreatment caused a significant increase in Dx tissue levels and a dramatic increase in its toxicity. Additionally, in the case of cyclosporin A, clinical reports show that this peptide can induce profound changes in the pharmacokinetics of Dx [1, 24] or other drugs that are substrates for Pgp, such as etoposide [21]. There are also indications that cyclosporin A causes an increase in the acute toxicity of etoposide in cancer patients [32]. No delayed toxicity was reported, which may be related to the unsuitability of patients undergoing phase I clinical trial for long-term evaluation because of their brief life expectancy.

The data presented in this paper suggest that Dx doses should be reduced when the drug is combined with PSC 833. The crucial question is whether the combination of PSC 833 with relatively low doses of Dx will produce effects equivalent to those provided by full doses of Dx alone or whether the reversing agent will cause an increase in the therapeutic index of Dx particularly in the case of tumors expressing high levels of Pgp. An increase in the therapeutic index could occur if the reversing agent induces a greater increase in Dx concentration in the tumor than in normal tissues, which represent a target of Dx toxicity. Another unresolved question is whether the interaction between PSC 833 and Dx is unique only to combinations of these two drugs or whether such an interaction also holds true for any combination of an MDR-reversing agent with an antitumor drug that is a substrate for Pgp [19].

If the PSC 833-induced increase in Dx toxicity is due to its ability to inhibit Pgp, it seems likely that similar effects will occur with other reversing agents, provided that they achieve tissue levels sufficiently high to inhibit the membrane glycoprotein. However, it is possible that increased toxicity will not play the same role for all anticancer agents. For example, because of its cardiotoxicity, Dx may be the drug least suitable for combination with an MDR-reversing agent, but for other noncardiotoxic antitumor agents, exacerbation of toxicity may be less acute. It is also noteworthy that some species-specific differences may exist in the expression of Pgp in normal tissues. For example, it appears that Pgp expression is higher in the murine heart [9] as compared with the human heart [13]. Elucidation of the degree and mechanisms of toxicity of various drug combinations in mice and humans may provide a guide for a more rational reevaluation of the efficacy of MDR-reversing agents.

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