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Absorption of Adriamycin® Into the Systemic Circulation After Intravesical Instillation with or Without Tween 80 in the Rat

S. Hellsten[1], S. Eksborg[2] and B. Axelsson[3]

1 Department of Urology and Experimental Research, General Hospital, Malmö, Sweden,
2 Karolinska Pharmacy, Stockholm, Sweden, and
3 Wallenberg Laboratory, University of Lund, Lund, Sweden

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Summary. The absorption of Adriamycin® (ADM) into the systemic circulation after intravesical administration, using an experimental model in the rat, was closely related to the volume of the instilled solution and the concentration of the drug. The post instillation plasma concentration of ADM was increased after addition of Tween 80 to the instilled solution but the magnitude of the absorption was still discreet and, from a clinical point of view, negligible.

Key words: Intravesical chemotherapy, Systemic absorption, Adriamycin®, Tween 80.

Introduction

Many drugs have been used for intravesical chemotherapy in patients with bladder carcinoma [14]. Among the antitumour agents most used are Thiotepa [17], Epodyl® [2, 15], Mitomycin C [16] and Adriamycin® (ADM) [3, 4]. A wide variety of new drugs has also been tested in order to improve treatment results. Unfortunately the therapeutic results of clinical studies are difficult to compare since the principles of the administration schedules used are mainly empirical. It is, however, possible to adapt the concentration of the instilled drug and the volume of the instilled solution in relation to the individual bladder capacity to obtain a standardization of the amount of the drug available for absorption through the bladder mucosa [6]. Optimising the pH of the instillate is obtained by the use of a buffer solution as drug solvent. Attempts have also been made to increase the efficacy of the intravesical treatment by promoting penetration of cytostatic agents into urothelial cells by addition of a surface active detergent, Tween 80, [7] or a fibrinolytic enzyme, urokinase [13].

The aim of the present study was to determine the degree of systemic absorption of ADM as a function of the concentration of ADM in the instillate and the volume of the instilled solution. The influence of Tween 80, added to the instillate, on the systemic absorption of ADM was also investigated.

Materials and Methods

Female rats (mean b.w. 207 g, range 170–257 g) were subjected to intravesical instillation of ADM under general anesthesia with intraperitoneal chloral hydrate (360 mg/kg b.w.). A volume of 0.2 and 0.4 ml was instilled using a catheter with an O.D. of 0.75 mm. 80 rats were given ADM dissolved in sterile water and 75 rats were given ADM dissolved in sterile water containing 10% Tween 80. The ADM concentrations used were 1 mg/ml, 2 mg/ml, 3 mg/ml and 4 mg/ml, respectively. At the end of the instillation period (1 h) blood samples were obtained by direct heart puncture. The urinary bladder was exposed by a midline incision of the abdomen followed by removal of the bladder to permit collection of the instilled solution. The concentration of ADM was measured in blood plasma and urine by liquid chromatography [11].

Results

The plasma concentration of ADM was increased when the volume of the instillate was increased from 0.2 to 0.4 ml ($p < 0.01$) (Table 1). The leakage of ADM to the systemic circulation was, however, limited (median values below 100 ng/ml) when pure sterile water was used as drug solvent, even at the highest concentration of ADM in the instilled liquid (4 mg/ml). The plasma ADM concentration was significantly increased when instillation of ADM dissolved in 10% Tween 80 (Table 2) was compared with ADM dissolved in pure sterile water ($p < 0.001$) (Fig. 1).

Discussion

Long-term results of clinical studies concerning the benefit of intravesical chemotherapy in patients with bladder carcinoma are far from consistent. Some recent, controlled

Table 1. Plasma concentration of Adriamycin® after intravesical instillation in the rat

Instillate		Postinstillation ADM plasma concentration (ng/ml)		No. of rats
Concentration of ADM (mg/ml)	Volume (ml)	Mean value	Median value	
1	0.2	5.6	5.0	10
2	0.2	6.9	0	10
3	0.2	24	13	10
4	0.2	25	19	10
1	0.4	44	29	10
2	0.4	34	23	10
3	0.4	67	79	10
4	0.4	76	75	10

Table 2. Plasma concentration of Adriamycin® after intravesical instillation of a mixture of ADM and Tween 80 in the rat

Instillate		Postinstillation ADM plasma concentration (ng/ml)		No. of rats
Concentration of ADM (mg/ml)	Volume (ml)	Mean value	Median value	
1	0.2	17	21	10
2	0.2	21	16	9
3	0.2	79	47	10
4	0.2	118	98	9
1	0.4	58	45	10
2	0.4	171	139	9
3	0.4	202	171	9
4	0.4	339	341	9

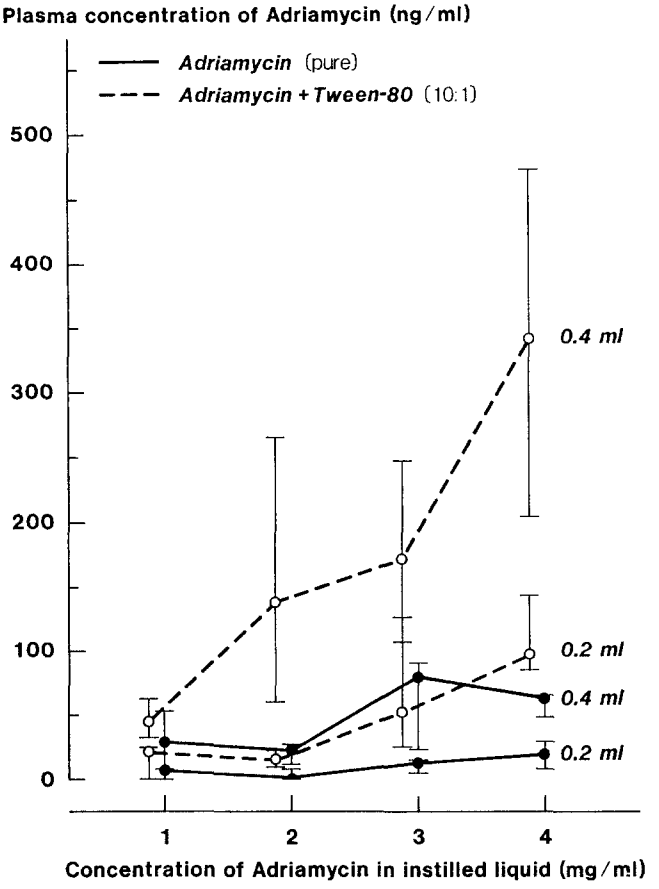

Fig. 1. Plasma concentration of Adriamycin® after 1 h of intravesical instillation in the rat (median values with 25% and 75% percentiles)

clinical studies, however, suggest a lower frequency of local tumour progess after prophylactic intravesical chemotherapy in patients with superficial bladder carcinoma [9, 10]. A standardization of the amount of the drug available for cellular uptake by the bladder carcinoma cells can be the base for a therapeutic schedule as has been discussed by Eksborg and co-workers [6]. Using the proposed schedule a mean concentration of ADM within the urinary bladder of about 300 μg/ml can be obtained which is well above the level required to kill urothelial malignant cells in tissue cultures [18]. The results of the present study underline the influence of the volume of the instillate and the concentration of the drug in the instilled liquid on the magnitude of the leakage of the drug into the systemic circulation. The postinstillation plasma level of ADM was significantly increased after doubling the instillation volume and by a fourfold increase of the drug concentration. Our results are in accordance with those by Engelmann et al. [8] although these authors studied the influence of the volume only without varying the drug concentration. However, the absolute plasma concentration of ADM after intravesical instillation in both studies was negligible from a clinical point of view as compared to an intravenous bolus injection. This observation corresponds well with clinical studies.

Patients subjected to intravesical instillation immediately after transurethral resection of bladder tumours [12] do not suffer from systemic side effects. An increasing systemic absorption of ADM per se indicates an improved penetration of the wall of the urinary bladder. It might also imply an increased uptake of the cytostatic drug into the bladder mucosa irrespective of the presence of tumour. A degree of leakage of the drug into the systemic circulation should be acceptable providing that an increased uptake of the drug into the urinary bladder wall is obtained. This principle is presently under further investigation using isotope labelled ADM.

Previous clinical studies [11] using ^{3}H-Doxorubicin have revealed that the drug penetrated almost as well into the normal urothelium as in papillary tumour lesions whereas the uptake into the tumour base was only about 15–20% of that amount. We showed that the postinstillation ADM

plasma level increased significantly after addition of Tween 80 to the instilled ADM solution contrary to Engelmann et al. [8] who found that after one hour of instillation there was a reduced systemic absorption of ADM in the presence of Tween 80 as a solvent. The intracellular uptake of ADM was not measured in their study and they also failed to confirm the results by Bridges et al. [1] who found an increased staining of the luminal edge of the bladder epithelium in the presence of Tween 80 indicating either adsorption of Tween 80 onto the epithelial surface or stimulation of the production of mucopolysaccarides of the epithelium by Tween 80. The question whether an improved permeability of ADM through the bladder wall, obtained by addition of Tween 80 to the instillate is combined with an increased tissue concentration of ADM hence remains open for further investigation of the normal and tumour harboring rat bladder. As already reported by Eksborg and co-workers [7] Tween 80 has successfully been used as a drug solvent in patients with bladder carcinoma resistant to previous intravesical therapy with pure ADM although the exact mechanism for the enhancement still remains unexplained.

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Dr. S. Hellsten
Department of Urology
and Experimental Research
General Hospital
S-21401 Malmö
Sweden