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Urinary excretion of prostacyclin and thromboxane degradation products in patients with ovarian malignancy: effect of cytostatic treatment

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Summary We studied the effect of ovarian cancer and its chemotherapy on the urinary excretion of prostacyclin (PGI_2) and thromboxane A_2 (TxA_2) hydration and metabolic products. In six patients we measured 6-keto-$PGF_{1\alpha}$ and 2,3-dinor-6-keto-$PGF_{1\alpha}$ (PGI_2 products) and thromboxane B_2 (TxB_2) and 2,3-dinor-TxB_2 (TxA_2 products) by HPLC followed by radioimmunoassay before, during and after the combined infusion of cisplatin, 4'epi-adriamycin and cyclophosphamide. Before the first cytostatic infusion, the urinary excretion of prostanoids was on average 4.4–5.8 times higher than in patients with ovarian endometriosis ($n=19$). The infusion of cytostatics led to a 50–120% rise in the excretion of prostanoids during the first post-infusion 9 hours, but in the subsequent 10 hours their ouput was 25–45% below the initial value and remained low for at least 2 weeks. Following repetitive courses of cytostatics (2–4 per patient), prostanoid excretion tended to normalise. These data suggest that ovarian cancer is associated with increased production of PGI_2 and TxA_2, and that cytostatics suppress this production. This may be of biological significance in tumour behaviour and in the effect of cytostatics.

Arachidonic acid metabolites can modulate cancer promotion, growth, and spread (Karmali, 1983, 1987; Bennett, 1984; Deliconstantinos, 1987). Vasodilator, anti-aggregatory prostacyclin (PGI_2) and vasoconstrictor, pro-aggregatory thromboxane A_2 (TxA_2) are especially important in this regard, since their balance may determine, at least partly, the potential of some cancers to grow and spread. This theory has been supported by some studies (Honn & Meyer, 1981 Honn *et al.*, 1983*a*), but also disputed by other data (Stamford *et al.*, 1986). That prostaglandins and prostanoids may be of significance for tumour behaviour gains support from the data that prostaglandin synthesis inhibitors increase the survival time of mice transplanted with mammary carcinoma (Bennett *et al.*, 1982). Ovarian cancer grows aggressively, sends out metastases early and is often accompanied by deep vein thrombosis (Fox, 1985); the latter phenomenon may well be a sign of disturbed PGI_2/TxA_2 balance. We showed recently that this cancer, as compared with healthy ovarian tissue, produces *in vitro* an 11-fold excess of 6-keto-prostagladin $F_{1\alpha}$ (6-keto-$PGF_{1\alpha}$, the hydration product of PGI_2) and a 30-fold excess of thromboxane B_2 (TxB_2, the hydration product of TxA_2) (Aitokallio-Tallberg *et al.*, 1988), and that patients with ovarian cancer excrete increased amounts of 6-keto-$PGF_{1\alpha}$ in their urine (Aitokallio-Tallberg *et al.*, 1987).

A combination of cisplatin, 4'epi-adriamycin and cyclophosphamide is most often used for treating advanced ovarian malignancy (Hainsworth *et al.*,1988). These agents inhibit the division of cancer cells by disturbing DNA double-helix formation (Chabner, 1982). Prostanoids can influence cell growth and division, perhaps through cyclic AMP (Gorman *et al.*, 1977; Thaler-Dao *et al.*, 1984).

It is well established that cytostatics can release various classic prostaglandins *in vitro* (Berstock *et al.*, 1979; Bennett *et al.*, 1982), but there are only a few data on the effect of cytostatics on PGI_2 and TxA_2 production. High circulating levels of 6-keto-$PGF_{1\alpha}$ and TxB_2 in patients with gynaecological malignancies (Ylikorkala *et al.*, 1981; Alam *et al.*, 1982; Sundström *et al.*, 1986) decreased following administration of cytostatics by 30–40% (Ylikorkala *et al.*, 1981) or by 52% (Alam *et al.*, 1982).

Currently, PGI_2 and TxA_2 production *in vivo* is best assessed by measuring their urinary degradation products (FitzGerald *et al.*, 1983; Fischer *et al.*, 1986; Ylikorkala *et al.*, 1986). The present study was designed to study the effect of cisplatin, 4'epi-adriamycin and cyclophosphamide in combination on the urinary output of PGI_2 and TxA_2 degradation products in patients with ovarian cancer.

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Patients and methods

Five patients with ovarian serous adenocarcinoma and one with ovarian endometrioid adenocarcinoma were studied. They were between 15 and 73 years of age (mean 51); three were premenopausal and three post-menopausal. In two women cancer was limited to the ovaries, but it had spread to stage III–IV in four patients. Five patients had an elevated (>65 IU ml^{-1}) cancer antigen 125 (CA-125) concentration, measured immunoradiometrically (Centocor Inc., Malvern, PA, USA). The endometrioid cancer patient with normal CA-125 had an increased ($>3\mu g\,l^{-1}$) serum carcinoembryonic antigen concentration (CEA), measured immunoradiometrically (Abbott Laboratories, North Chicago, IL, USA). As the control group we studied 19 women with laparoscopically confirmed endometriosis affecting the ovaries. They were between 22 and 43 years of age (mean 33), and otherwise were healthy. The severity of endometriosis was scored in the range from 5 to 80 points (mean 28.9, American Fertility Society classification).

All cancer patients underwent laparotomy. Surgery was radical (total hysterectomy with bilateral oophorectomy, omental resection) only in the patient with endometrioid cancer. In three patients most of the cancer tissue was removed, but no resection was possible in the other two cases.

All cancer patients received the same treatment, beginning two weeks after surgery, with intravenous injection of cyclophosphamide ($500\,mg\,m^{-2}$) and 4'epi-adriamycin ($40\,mg\,m^{-2}$). Physiological saline (1000 ml) was infused concomitantly to guarantee adequate diuresis. Two or three hours later cisplatin ($50\,mg\,m^{-2}$) was started as an intravenous infusion over 5–7 hours; mannitol (15%, 500 ml i.v.) and furosemide (20 mg i.m.) were also given. This regimen was repeated on two to four occasions at 4-week intervals, and altogether 19 courses were studied.

Urines were collected for: (1) 4–6 hours before the start of cytostatics; (2) 5 hours from the start of the treatment; (3) 4 hours after the second sample; (4) 10 hours after the third sample; (5) 4–6 hours 2 weeks later. In addition we collected samples from four patients 4 weeks after the last cytostatic treatment.

The non-malignant control group collected their 24-hour urines the day before laparoscopy. During the study no subject took any drug (except for cytostatics) known to affect prostanoid synthesis.

A 100 ml sample of each urine was frozen and stored at −25°C for 2–5 months until assayed for products of PGI_2 (6-keto-$PGF_{1\alpha}$ and 2,3-dinor-6-keto-$PGF_{1\alpha}$) and TxA_2 (TxB_2 and 2,3-dinor-TxB_2). This storage does not affect the prostanoids (Aitokallio-Tallberg *et al.*, 1988). In brief, 10 ml of acidified urine (pH 3.0, 1M HCl) were passed through Sep Pak C18 cartridges (Waters Association, Milford, USA). Retained prostanoids were eluted with ethyl acetate, evaporated to dryness, and put through HPLC (water/acetonitrile/acetic acid, 69.95:30.0:0.05, 2 ml min^{-1}). After 2 min the first fraction (I) was collected over 1.5 min; this contained 6-keto-$PGF_{1\alpha}$ and dinor-TXB_2. The second fraction (II), collected for 3.5 min starting 0.25 min after the first one, contained dinor-6-keto-$PGF_{1\alpha}$ and TxB_2. Fraction I was assayed for 6-keto-$PGF_{1\alpha}$, using ^{3}H-6-keto-$PGF_{1\alpha}$ as the tracer, 6-keto-$PGF_{1\alpha}$ as the standard, and an antibody raised against 6-keto-$PGF_{1\alpha}$ in rabbits (Ylikorkala & Viinikka, 1981). For dinor-TxB_2, ^{3}H-TxB_2 was used as the tracer, dinor-TxB_2 as the standard and rabbit TxB_2 as the antibody (Viinikka & Ylikorkala, 1980) because this antibody has approximately 40% cross-reactivity with 2,3-dinor-TxB_2. Fraction II was assayed for TxB_2 using ^{3}H-TxB_2 as the tracer, TxB_2 as the standard and TxA_2 antibody (Viinikka & Ylikorkala, 1980). For dinor-6-keto-$PGF_{1\alpha}$ we used ^{3}H-6-keto-$PGF_{1\alpha}$ as the tracer, dinor-6-keto-$PGF_{1\alpha}$ as the standard and the 6-keto-$PGF_{1\alpha}$ antibody (Ylikorkala & Viinikka, 1981) because this antibody has approximately 20% cross-reactivity with 2,3-dinor-6-keto-$PGF_{1\alpha}$. The details of the methods are give elsewhere (Ylikorkala *et al.*, 1987). Prostanoid excretion is expressed as pg min^{-1}.

At the end of each urine collection, serum and urine creatinine were measured and the creatinine clearance determined.

The prostanoid excretion data are given as means ± s.e. The significances of the difference were analysed by Student's *t* test for paired and unpaired data as appropriate. To illustrate better the effect of cytostatics, the values during their administration are given as percentages of the pretreatment levels.

Results

Before cytostatics were given, the prostanoid excretion in cancer patients was clearly higher than in the patients with endometriosis (Table I). The increases were: 6-keto-$PGF_{1\alpha}$ 4.9-fold ($P<0.0025$), dinor-6-keto-$PGF_{1\alpha}$ 4.4-fold ($P<0.002$), TxB_2 5.8-fold ($P<0.0125$) and dinor-TxB_2 4.5-fold ($P<0.0005$).

The cytostatic infusions were accompanied by a 50–120% rise in the 5-h excretion of PGI_2 and TxA_2 products (Figure 1). This stimulation was strongest for 6-keto-$PGF_{1\alpha}$ and TxB_2 excretion. Between 9 and 19 h after the start of infusion the excretion for all prostanoids was 35–45% below the pretreatment levels. This reduction persisted for at least 2 weeks (Figure 1). The pattern of urinary prostanoid excretion during infusion of cytostatics was constant from one course to another.

Overall the amounts of PGI_2 products fell after repetitive courses with chemotherapy (Table I). This was not the case in the output of TxA_2 products which on average did not change when the data following all cytostastic courses were considered as a whole (Table I). However, when only the last cytostastic course was considered, the excretion of TxA_2 products decreased in four patients who responded favourably to cytostatics, but remained high in two patients who showed no response to treatment. There was also a good correlation between decreases in serum CA-125 or CEA levels and in urinary excretion of TxA_2 products (Table II).

The mean creatinine clearance was approximately 20 ± 5% lower 9 and 19 h after giving the cytostatics ($P = 0.06$, Figure 1). No significant relationship was seen between individual prostanoid excretion and creatinine clearance, occurrence of side-effects, or counts of leucocytes and platelets.

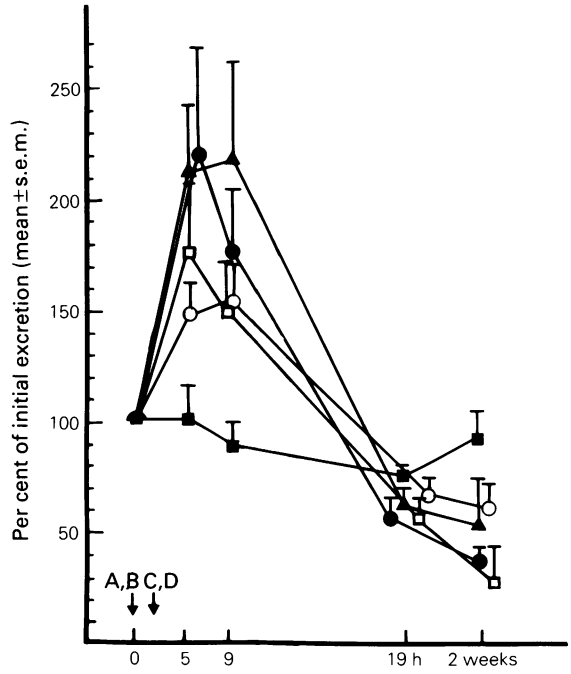

Figure 1 Changes in urinary excretion of 6-keto-$PGF1_{1\alpha}$ (●), dinor-6-keto-$PGF_{1\alpha}$ (○), TxB_2 (▲), dinor-TxB_2 (□) and creatinine clearance (■) during the cytostatic treatment and two weeks later. Values are percentages of initial levels (mean±s.e.). **A**, i.v. injection of cyclophophamide and 4'epi-adriamycin; **B**, infusion with physiological saline; **C**, i.m. injection of furosemide and i.v. infusion of mannitol; **D**, i.v. cisplatin infusion.

Table I Urinary excretion of prostacyclin (PGI_2) and thromboxane (TxA_2) hydration and metabolic products (pg min^{-1}, mean±s.e.) in patients with ovarian cancer and endometriosis.

Subjects	*No. of samples*	*6-keto-$PGF_{1\alpha}$*	*Dinor-6-keto-$PGF_{1\alpha}$*	*TxB_2*	*Dinor-TxB_2*
Patients with ovarian cancer ($n = 6$)					
before 1st cytostatic course	6	157.3±73.3[a,b]	185.7±81.5[c,d]	80.2±54.0[e]	263.0±102.0[f]
before 2nd–5th cytostatic courses	17	42.9± 8.9[b]	58.2± 7.9[d]	81.2±60.0	259.0± 99.0
Patients with endometriosis ($n = 19$)	19	32.4± 4.5[a]	42.4± 3.1[c]	13.8± 3.5[e]	57.9± 8.6[f]

Cancer patients excreted more urinary PGI_2 and TxA_2 products than did patients with endometriosis. Overall the amount of PGI_2 products fell after repetitive courses with chemotherapy (all data following cytostatic courses are lumped together), but the mean excretion of TxA_2 products did not change (see individual pre-treatment and post-treatment values in Table II). [a]$P<0.0025$, [b]$P<0.009$, [c]$P<0.002$, [d]$P<0.008$, [e]$P<0.0125$, [f]$P<0.0005$.

Table II Individual urinary prostanoid excretion (pg min^{-1}) and serum Ca-125 (IU ml^{-1}) or CEA ($\mu g\ l^{-1}$) levels before the first and after the last cytostatic course, and the clinical response to treatment.

	6-keto-$PGF_{1\alpha}$		*Dinor-6-keto-$PGF_{1\alpha}$*		*TxB_2*		*Dinor-TxB_2*		*Ca-125/CEA*		
Patient	*Before the 1st cytostatic course*	*After the last cytostatic course*	*Before the 1st cytostatic course*	*After the last cytostatic course*	*Before the 1st cytostatic course*	*After the last cytostatic course*	*Before the 1st cytostatic course*	*After the last cytostatic course*	*Before the 1st cytostatic course*	*After the last cytostatic course*	*Clinical response*
1	63	27	94	82	31	21	160	169	279	30	80% reduction in tumour size
2	135	45	150	68	19	24	196	330	3150	2500	no response
3	88	5	112	6	35	4	325	8	5440	100	tumour disappeared
4	86	66	79	67	25	35	62	300	2604	3023	no response
5	519	18	590	10	350	8	740	52	250	29	tumour disappeared
6	53	40	89	43	21	8	96	30	33	CEA 12	80% reduction in tumour size

The excretion of prostacyclin products decreased in all patients, but the excretion of thromboxane products decreased only in patients who responded favourably to treatment (patients 1, 3, 5 and 6).

Discussion

Through their effects on vascular wall–platelet interaction, PGI_2 and TxA_2 may be important in cancer metastasis and spread. It is generally thought that PGI_2 or its dominance over TxA_2 should prevent metastasis (Honn *et al.*, 1981, 1983*b*), but this theory has also been disputed (Stamford *et al.*, 1986). The picture may be partly unclear due to difficulties in assessing PGI_2 and TxA_2 production *in vivo*. Currently, *in vivo* PGI_2 and TxA_2 synthesis is usually studied by measuring their urinary products (FitzGerald *et al.*, 1983; Fischer *et al.*, 1986; Ylikorkala *et al.*, 1986). Urinary 2,3-dinor-6-keto-$PGF_{1\alpha}$ is considered the best index of systemic PGI_2 production (Rosenkranz *et al.*, 1980; Brash *et al.*, 1983), whereas urinary 6-keto-$PGF_{1\alpha}$ may originate primarily from the kidneys (Patrono *et al.*, 1982). Circulating platelets are the main source of urinary TxB_2 and 2,3-dinor-TxB_2 (Roberts *et al.*, 1981), although renal tissue may also produce them, particularly TxB_2 (Patrono *et al.*, 1983). In the present work we measured all four of these prostanoids.

The main purpose of this study was to evaluate the effects of cytostatics on PGI_2 and TxA_2 production. Because inter-individual variations in prostanoid excretion are large (Fischer *et al.*, 1986), we studied the effect of repetitive courses of cytostatics. Previously we found increased urinary excretion of 6-keto-$PGF_{1\alpha}$ in patients with ovarian malignancy (Aitokallio-Tallberg *et al.*, 1987). We now show that in these patients 2,3-dinor-6-keto-$PGF_{1\alpha}$, TxB_2 and 2,3-dinor-TxB_2 are also excreted excessively into urine. These rises are probably in part related to the cancer, because they are higher than those in the control group of patients with endometriosis who may also have increased PGI_2 and TxA_2 production (Dawood *et al.*, 1984; Ylikorkala *et al.*, 1984). We assume that the excess prostanoids arise either from the cancer cells (Aitokallio-Tallberg *et al.*, 1988), or possibly in part elsewhere in the body as a result of paraneoplastic changes. The question of the role of prostanoid stimulation in the growth and spread of ovarian cancer remains open.

Cytostatic therapy of ovarian cancer, applied in clinical routine (Hainsworth *et al.*, 1988), led similarly to a rise and then a fall in the urinary output of PGI_2 and TxA_2 products. Because the treatment did not alter renal function significantly, the changes in urinary prostanoids presumably reflect altered synthesis and/or release of PGI_2 and TxA_2 during cytostatic infusion. Cytostatics damage and/or kill both cancerous and healthy cells, which may explain the initial rise in prostanoid output in our work. Perhaps cell death was so marked that it was reflected in later suppression of prostanoid output. In the case of TxA_2 suppression, a decrease in platelet count induced by the cytostatics might be a factor, although individual excretion and platelet counts did not correlate. Furthermore, prostanoid excretion started to decrease sooner than did platelet numbers, suggesting that thrombopenia does not explain the suppression of TxA_2 products.

We do not know which of the cytostatics caused prostanoid changes. Although cytostatics, especially cisplatin, affect renal tissue and function (Von Hoff & Rosencweig, 1979), creatinine clearance in out patients showed little or no change. Furosemide could also have been a factor, because it was reported to increase the output of PGI_2 and TxA_2 products (Wilson *et al.*, 1983), but this was not confirmed by others (Mackay *et al.*, 1984; Franchi *et al.*, 1987).

The most important finding of the present work was the decrease in excretion of PGI_2 and TxA_2 products in patients responding well to cytostatics, and the normalisation of excretion in many patients concomitantly with reduction in tumour mass. This supports the role of prostanoids in cancer (Honn & Meyer, 1981; Bennett, 1984). Of the two prostanoids studied, TxA_2 may be more important for the progress of ovarian cancer, since it remained unchanged in patients who did not respond to chemotherapy.

In conclusion, patients with ovarian cancer excreted more urinary PGI_2 and TxA_2 products than did patients with endometriosis. A combination of cisplatin, cyclophosphamide and 4'epi-adriamycin initially stimulated these outputs, but after repetitive courses caused a constant suppression.

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