Drug metabolism and androgen control therapy in prostatic cancer

The drug metabolizing capacity during androgen control therapy was determined in 12 patients with prostatic cancer, using plasma antipyrine half-life as an index. In general, drug metabolizing capacity seemed impaired; the disappearance rate of the test drug decreased in 8 of the patients. In 1 the half-life was unchanged, and in 3 there was shortening. The results suggest that many factors simultaneously affect the drug metabolizing enzymes, and the total effect may be stimulated in the face of therapy known to inhibit these enzymes.

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The most common treatment for metastasizing prostatic cancer during the past 30 years has been orchiectomy combined with estrogen therapy, both of which have an arresting effect on this tumor.[10-12] During the last years metabolic interactions during this therapy have been noticed to occur. Increased thromboembolic complications,[25] disturbances in liver function and jaundice,[7, 14, 17] changes in serum lipid fractions[16] and variability in results of oral glucose tests,[15] and a variety of side effects[4] have been reported.

Decreased activity of hepatic drug metabolizing enzymes after castration have been reported in laboratory animals.[26] It is known that estrogens cause a similar decrease in drug metabolism in test animals[9] and in human females using estrogen[8] and oral contraceptives.[6, 18] Recently low fasting blood glucose levels have been reported in prostatic cancer patients receiving androgen control therapy as well as oral antidiabetic drugs.[15] These may be caused in part by decreased metabolism of antidiabetic drugs as the result of drug interaction.

The prostatic cancer patients are elderly men who often need drugs for other diseases, so that it is important to know whether there are any changes in drug metabolism in these patients. This problem was examined using plasma antipyrine half-life as index of drug metabolizing capacity before androgen therapy and while on it.

Material and methods

The subjects were 12 patients with histologically verified prostatic cancer admitted consecutively during a 5 month

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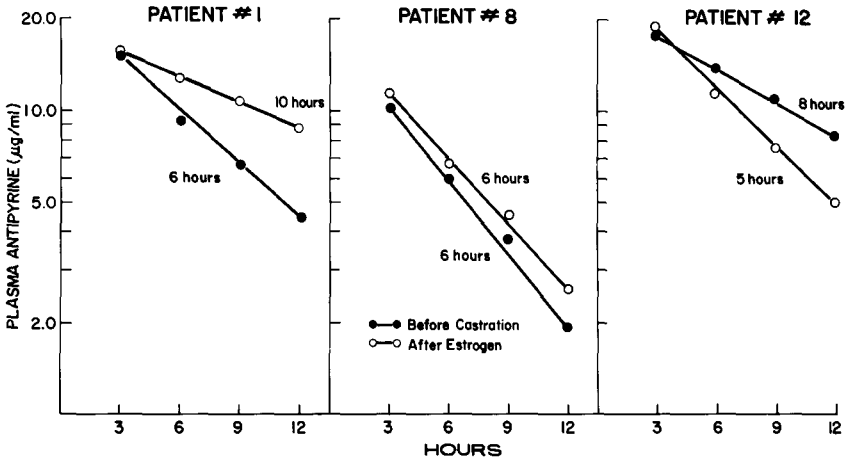

Fig. 1. Changes in plasma antipyrine half-life.

period. In each patient the drug history, as well as sensitivity to drugs and chemicals, was recorded (M. J. K.). All patients were castrated under general anesthesia with induction by thiopental and maintenance with oxygen and nitrous oxide. Alloferin (N-allyl-nortoxiferin) (not on U. S. market) was used as a muscle relaxant, and meperidine was used for pain relief. Estrogen therapy was started the day after castration, giving 500 mg diethylstilbestrol diphosphate intravenously daily for 10 days. Other drug regimen were kept unchanged during 11 days, except for occasional administration of meperidine as an analgesic.

Plasma antipyrine half-life was estimated in each patient before castration and on the tenth day after starting estrogen therapy. The patients were given antipyrine (10 mg per kilogram) in water in the morning after an overnight fast. A blood sample for blank readings was obtained prior to the administration of the drug and was followed by samples drawn at 3, 6, 9, and 12 hours, with precise sampling time being noted. The separated plasma was stored at -20° C. until analyzed in duplicates by the method of Brodie and associates.[1] All samples from the same patients were carried out simultaneously.

Blood samples for the liver function tests were drawn from the patients before castration and on the eleventh day after starting estrogen therapy. The concentrations of serum sodium, potassium, chloride, and creatinine were checked before castration and also several times during therapy. Statistical significance was determined by paired sample t test.

Results

Age, clinical findings of the patients on admission, bromsulphalein (BSP) retention, and the half-life of antipyrine are listed in Table I. The mean value (± S.D.) for antipyrine in all patients was 7.7 ± 1.8 hours before castration and 9.7 hours on the tenth day on estrogen. The difference is statistically significant ($p < 0.05$). In 8 patients the half-life was significantly increased ($p < 0.01$) from the average of 7.5 hours to the average of 11.1 hours. In 3 patients the half-life was decreased from the average of 9.0 hours to the average of 7.0 hours (decrease not significant; $p > 0.05$). In 1 patient the antipyrine half-life was unchanged.

The BSP retention tests were elevated in 11 of the patients. The average retention was 3.7% (45 minutes test) before castration, and on the eleventh day it was 5.3 ($p < 0.05$). In only 5 cases was the retention above the normal range (6.0%). The mean values for serum glutamic pyruvic transaminase, serum alkaline phosphatase, and serum bilirubin were, before castration, 16.6 Wroblewsky units, 3.99 Bessey-Lowrey

Table I. *Antipyrine half-life and BSP retention during androgen therapy*

Patient No.	Age (yr.)	Condition	Metastases	BSP-retention (%)		Antipyrine half-life (hr.)		
				Before	After	Before	After	Change (%)
1	68	Poor	+	3.5	7.2	6.0	10.0	+66
2	70	Good	–	12.0	12.7	11.0	9.0	–18
3	65	Poor	+	5.4	7.2	7.0	9.0	+28
4	79	Good	–	4.9	5.8	8.0	11.0	+37
5	67	Poor	+	1.5	2.6	5.0	12.0	+140
6	78	Good	–	1.8	2.2	7.0	12.0	+78
7	74	Good	–	1.6	2.2	7.0	10.0	+28
8	62	Poor	–	1.6	3.6	6.0	6.0	±0
9	81	Poor	–	2.2	5.0	8.0	7.0	–12
10	78	Good	–	5.5	6.2	9.0	11.0	+22
11	67	Poor	–	3.7	2.7	11.0	14.0	+27
12	70	Poor	–	0.3	7.1	8.0	5.0	–37
Mean	71.7			3.6	5.4	7.7	9.7	+11
S.D.	6.5			3.1	3.1	1.8	2.6	
p*				0.05		0.05		

*p values calculated by paired sample t test.

units, and 0.7 mg%; and after the estrogen treatment, 20.4 Wrbl units, 4.97 B-L units, and 0.8 mg%. These changes were not statistically significant.

When the patients were grouped on the basis of their general condition into those with good and those with poor general condition, we found that the antipyrine half-life in the former group was 8.4 hours and in the latter group 7.2 hours before castration. The respective values after estrogen therapy were 10.4 hours and 8.7 hours. The differences between the corresponding mean values in these two groups were not significant. No statistically significant correlation was found between a change in antipyrine half-life and that in any liver function test.

Nine of the patients received other drugs for concurrent disease: 8 for urinary tract infections, 3 for coronary artery diseases, 2 for congestive heart diseases, 3 for pain relief, and 1 for diabetes mellitus. The drugs were found not to interfere with the determination of antipyrine.

None of the patients had any side effects from the antipyrine.

Discussion

Antipyrine is almost completely metabolized in the liver by hydroxylating enzymes.[2] In man, the metabolism of antipyrine is under genetic control,[23] but the activity of antipyrine hydroxylating enzymes can be enhanced or decreased by medicaments or environmental chemicals.[13, 23] The change in the half-life of plasma antipyrine therefore reflects hepatic antipyrine hydroxylating activity.[23, 25] According to our results, drug metabolism in patients with prostatic cancer is decreased during androgen therapy; there was a prolongation in the half time of the test drug. Compatible reports have been published in castrated animals,[9, 26] in estrogen-pretreated animals, and in human females.[6, 8, 18]

Although little is known about the factors affecting drug metabolism,[20] it may be assumed that drug-metabolizing enzymes are induced, by drugs as well as by other factors, in patients who have concurrent disease and are in poor condition. This assumption is supported by the observation that the change in antipyrine half-life was less marked in patients in poor general condition. The effect of diseases on drug metabolism has not yet been fully investigated, but marked improvement in the liver function in patients has been reported after heart failure has been successfully treated.[21]

In the liver function tests, significant

changes were noted only in BSP retention. While no interrelationships were noted between the changes of the half-life of antipyrine and that of BSP retention, we demonstrated that the activity of antipyrine hydroxylating enzymes need not correlate with slight changes in the liver function tests.

Therapy with estrogen may cause retention of sodium and water,[19] and surgery may have a similar effect.[27] A slight increase in the total body water was observed while concentrations of serum electrolytes varied within a normal range.* While the antipyrine half-lifes were individually calculated from the postabsorption phase of the curve, it is probable that small changes in absorption and distribution of antipyrine had no significant effect on its metabolism.[3, 15]

Elderly people often have diseases that require many drugs.[5, 22, 28] Our results emphasize the importance of individualized drug therapy for patients with prostatic cancer.

*Unpublished observation.

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