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Antipyrine metabolism in patients with disseminated testicular cancer and the influence of cytostatic treatment

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Summary. *Antipyrine plasma clearance and rates of metabolite formation were measured on four occasions in eight patients with disseminated nonseminomatous testicular cancer. Antipyrine tests were performed before, during (2×), and after treatment with a combination of cisplatin (P), vinblastin (V), and bleomycin (B). Pretreatment values were compared with a male control group (n = 14) matched for age and body weight. Antipyrine plasma clearance was 20% higher in patients with testicular cancer (first experiment) than in the control group. This difference was mainly due to a 35% higher clearance for production of 3-hydroxymethylantipyrine (HMA), while clearance for production of norantipyrine (NORA) and 4-hydroxyantipyrine (OHA) was not significantly different from the control group. A reduction in CL_{HMA} was observed after complete remission (fourth experiment), indicating that the presence of the tumor may be related to a selective increase of HMA formation. Treatment with the PVB combination resulted in a 30% increase in antipyrine plasma clearance (second and third experiments), whereas the rates of formation of the main metabolites of antipyrine were all increased to the same extent. These accelerating effects of PVB treatment persisted for at least 6 weeks after the start of the last treatment cycle.*

The data presented in this paper demonstrate that the presence of a testicular tumor and the use of cytostatics can have an accelerating and partially selective effect on oxidative drug-metabolizing enzyme activity in man.

Introduction

Large interindividual differences are observed in the disposition of drugs that are predominantly metabolized by enzymes in the liver [2]. These differences are caused by differences in drug-metabolizing enzyme activity [5]. In patients with malignancies, the presence of a tumor and the administration of anticancer drugs may contribute to these differences, since certain diseases and drug treatments have been shown to influence hepatic enzyme activities [37]. A decrease in such activity was generally observed in tumor-bearing animals [18]. In patients with lung cancer a small increase in antipyrine clearance became apparent [3], though this increase could also have been caused by smoking [19, 34]. The presence of prostatic cancer shortened antipyrine half-life [26], while gastric cancer [14] and leukemia [15] seemed to have no effect. In patients with hepatoma, normal antipyrine half-lives were observed [27], but in metastatic liver cancer antipyrine elimination was seriously impaired irrespective of the primary tumor [15, 27].

Little is known about the effects of cytostatic agents on drug-metabolizing enzyme activity in man. Higuchi et al. [15] found a 40% reduction of antipyrine clearance in patients with leukemia after treatment with a combination of daunorubicin, cytosine arabinoside, 6-mercaptopurine, and prednisolone, but the influence of a possible transfusion-related hepatitis could not be excluded. Animal and in vitro studies also showed inhibition of hepatic enzyme activity by carmustine [41], cyclophosphamide, 5-fluorouracil, methotrexate [7, 17], vincristine, actinomycin D [7], bleomycin [23], and doxorubicin [35]. Although testicular neoplasms are rare, amounting to only 1% of all malignant tumors in man, they are the main cause of cancer death in men aged 25–34 years [22]. Recently a combination of *cis*-diamminedichloroplatinum (cisplatin), vinblastin, and bleomycin (PVB) was proved to be highly effective in the treatment of disseminated testicular nonseminoma [13, 28].

In our study we tried to establish the influence of testicular cancer on hepatic drug-metabolizing enzyme activity by measuring antipyrine plasma clearances and rates of formation of antipyrine metabolites. Antipyrine is widely used as a model compound to assess oxidative hepatic drug-metabolizing enzyme activity, since it is metabolized extensively in the liver and its elimination is independent of protein binding and liver blood flow [38]. The usefulness of the antipyrine test has recently been extended by including the analysis of the main metabolites of antipyrine: 4-hydroxyantipyrine (OHA), norantipyrine (NORA), and 3-hydroxymethylantipyrine (HMA) [9]. The formation of these metabolites is catalyzed by different isoenzymes of the cytochrome P-450 system. The rates of formation or clearances for production of the metabolites can be assessed by measuring total antipyrine clearance and cumulative renal metabolite excretion [6, 8, 10, 29].

Materials, patients and methods

Drugs. Antipyrine (A) was obtained from a commercial source (Brocacef, Maarssen, The Netherlands). 3-Hydroxymethylantipyrine (HMA), norantipyrine (NORA), and 4-hydroxyantipyrine (OHA) were synthesized according to previously described methods [11, 20, 21]. *cis*-Diamminedichloroplatinum (Platinol) was obtained from Bristol-Myers; vinblastin (Velbe) from Lilly, and bleomycin (Bleomycin) from Lundbeck, through the Pharmacy of the University Hospital at Groningen, The Netherlands.

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Human experiments. Eight patients with disseminated non-seminomatous testicular tumors (Table 1) were treated with a combination of *cis*-diamminedichloroplatinum (P), vinblastin (V), and bleomycin (B). A group of 14 healthy male adults of comparable age and weight (Table 2) was used as control group. P was given daily on days 1–5, 20 mg/m^2 in 300 ml mannitol with 20 mg chlorpromazine as a 2-h IV infusion in saline, by means of an arteriovenous shunt. An IV bolus of V 1.2 mg/kg was given on days 1 and 2. B (30 mg) was infused with about 15 min on days 2, 9, and 16. Four treatment cycles were given, each new cycle starting on day 22 from the 1st day of the cycle before (Fig. 1). No other drugs were given before or during the experiments, except acetylsalicylic acid (Ascal, 500 mg twice daily PO) to prevent obliteration of the AV shunt.

Antipyrine (A) was injected as a 500-mg IV bolus 2 days before the start of cytostatic treatment (day −2, expt. I), 1 week after the start of treatment (day 8, expt II), just before the second treatment cycle (day 18, expt III), and 6 weeks after the start of the last treatment cycle (day 106, expt IV; Fig. 1). Heparinized blood samples were taken at 0, 3, 6, 9, 12, 24, 28, and 32 h after antipyrine administration for determination of antipyrine plasma half-life ($t^1/_2$), apparent volume of distribution (V_d), and clearance *(CL)*. Urine was collected at intervals during a period of 48 h to determine the amounts of antipyrine excreted and its main metabolites. Plasma and urine samples were stored at −20° C until analyzed by methods previously described [9, 30].

Table 1. Patient characteristics

Patient	Symbol	Age (years)	Body weight (kg)			
			I	II	III	IV
1	○	41	72	69	68	71
2	△	18	70	65	67	69
3	□	38	81	79	78	75
4	✶	23	61	64	62	–[a]
5	●	30	57	52	51	–[a]
6	▲	24	84	78	77	–[a]
7	■	29	67	64	63	–[a]
8	+	24	60	59	59	62
Patient mean ± SD ($n = 8$)		28 ± 8	69 ± 10	66 ± 9	66 ± 9	69 ± 5
Control mean ± SD ($n = 14$)		26 ± 4	73 ± 9			

[a] Not determined, because these patients did not participate in expt. IV

Calculations. Antipyrine half-life ($t_{1/2}$) was calculated by least-squares regression analysis of the log plasma concentration versus time curves. The apparent volume of distribution (V_d) was calculated by dividing the given dose by the extrapolated value of antipyrine concentration at time zero. The clearance *(CL)* of antipyrine from plasma and the clearances for production of the metabolites *(CL_m)* of antipyrine were calculated according to the following equations:

$$CL = D/AUC \tag{1}$$

$$CL_m = f_m \times CL \tag{2}$$

in which D is the given dose, AUC is the area under the plasma concentration time curve and f_m is the fraction of the dose excreted as metabolite m in urine, upon extrapolation of the 48-h value to infinity, using antipyrine half-life [8].

Statistical analysis for the comparison of controls and patients before treatment was performed with Student's t-test. Intertest and interpatient variations were evaluated by two-way analysis of variance followed by Student modification of the Newman-Keuls test.

Results

Table 1 shows the characteristics of the individual patients, mean values of the control group, and the symbols used for each patient in Figs. 2 and 3. Ages and body weights were much the same for both groups, and moderate alcohol drinkers and smokers were equally represented. In Table 2 the mean of the data obtained are given, while individual results are shown in Figs. 2 and 3. Total antipyrine plasma clearance was higher in untreated cancer patients (expt I: 3.8 l/h) than in the control group (3.1 l/h), while no difference in V_d was observed. The patients had considerably shorter elimination half-lives than the control group (7.8 versus 11.1 h). CL_{HMA} was higher than in controls (11.3 versus 8.4 ml/min), while CL_{OHA} and CL_{NORA} were not significantly different.

Treatment with the combination of cytostatics (PVB) resulted in an increase of antipyrine clearance from 3.8 to 4.6 l/h and a shortening of $t_{1/2}$ from 7.8 to 6.6 h (expt I versus expt II; Fig. 2 and Table 2). The small changes in body weight (Table 1) And in V_d (Table 2) of the patients were not statistically significant.

Clearance for production of the metabolites had also increased after treatment. This was significant for CL_{NORA}: from 14.2 to 18.3 ml/min (I versus II) and CL_{HMA}: from 11.3 to

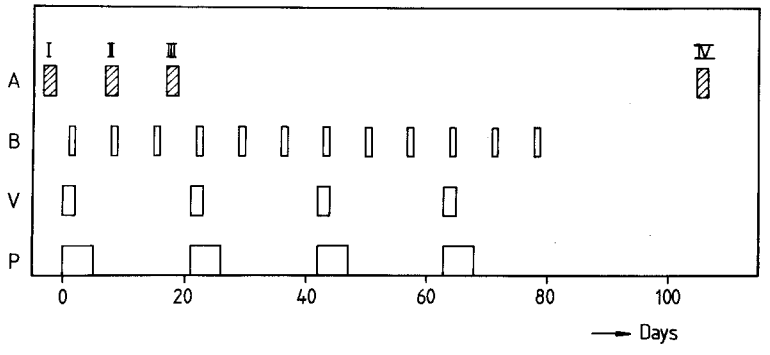

Fig. 1. Design of cytostatic treatment with cisplatin *P)*, vinblastin *(V)*, and bleomycin *(B)*, and the performance of antipyrine tests *(A)*

Table 2. Pharmacokinetic data for antipyrine and its main metabolites in 14 controls (C) and in patients with disseminated nonseminomatous testicular cancer before (I), during (II and III), and after (IV) treatment with a cisplatin, vinblastin, and bleomycin combination chemotherapy

	C ($n = 14$)	I ($n = 8$)	II ($n = 8$)	III ($n = 8$)	IV ($n = 4$)
$t_{1/2}$ (h)	11.1 ± 1.8	7.8 ± 1.0[a]	6.6 ± 1.1[b]	6.2 ± 1.2[b]	6.8 ± 1.3
V_d (l)	48.2 ± 7.4	41.8 ± 4.4	42.6 ± 4.6	42.6 ± 5.2	44.4 ± 5.3
CL (l/h)	3.1 ± 0.6	3.8 ± 0.6[a]	4.6 ± 0.9[b]	4.8 ± 1.1[b]	4.7 ± 1.2[b]
CL_{OHA} (ml/min)	15.6 ± 4.0	17.8 ± 5.4	21.1 ± 7.2	22.1 ± 8.1	20.3 ± 9.5
CL_{NORA} (ml/min)	14.0 ± 6.1	14.2 ± 2.5	18.3 ± 2.8[b]	16.4 ± 5.0	17.3 ± 3.5
CL_{HMA} (ml/min)	8.4 ± 2.7	11.3 ± 3.6[a]	13.6 ± 3.6	14.2 ± 3.3[b]	12.2 ± 3.6[c]

Mean values ± SD, are given
[a] Significant difference when I compared with C ($P < 0.05$)
[b] Significant difference when II, III, and IV compared with I ($P < 0.05$)
[c] Significant difference when IV compared with III ($P < 0.05$)

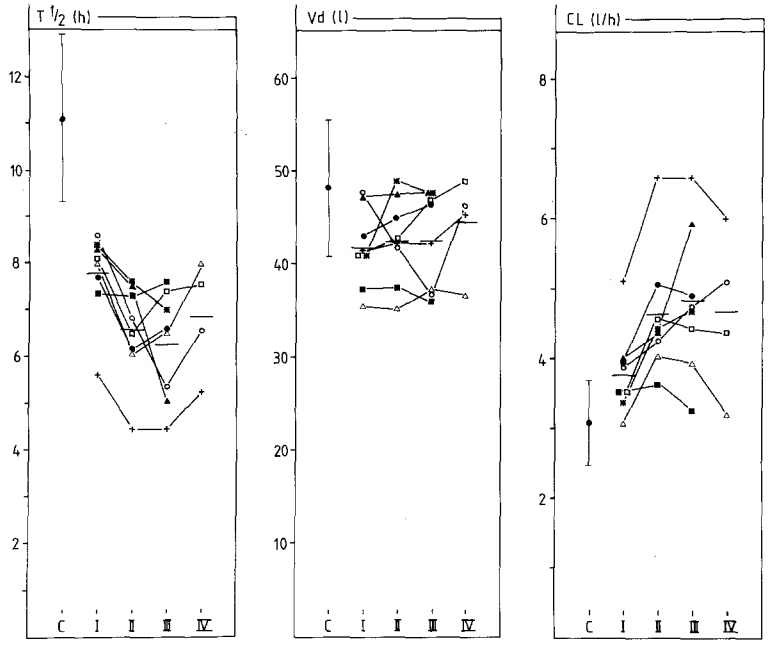

Fig. 2. Individual values of elimination half-life ($t_{1/2}$), apparent volume of distribution (V_d), and plasma clearance *(CL)* of antipyrine in eight patients with disseminated nonseminomatous testicular cancer before *(I)*, during *(II, III)*, and after *IV)* treatment with a cisplatin, vinblastin, and bleomycin combination chemotherapy. The *horizontal lines* indicate mean values. Of 14 controls *(C)*, mean values ± SD are given

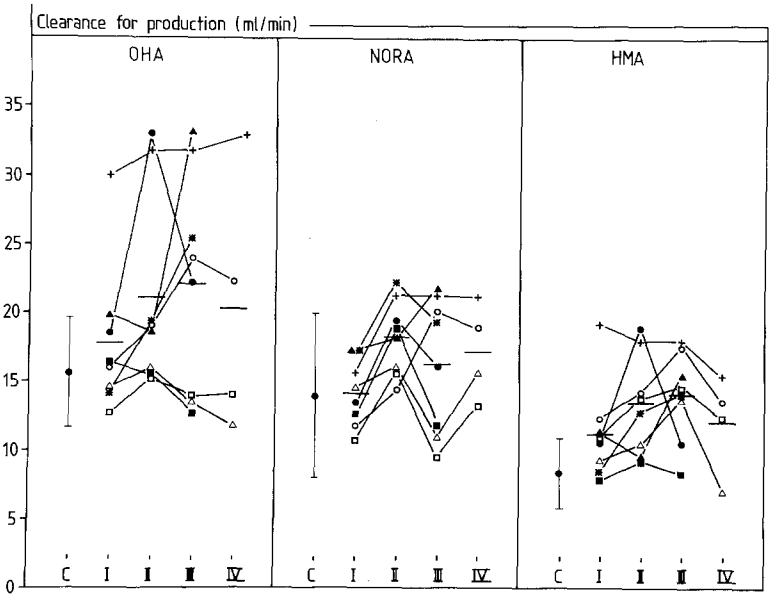

Fig. 3. Individual values of the clearance for production of 4-hydroxyantipyrine *(OHA)*, norantipyrine *(NORA)*, and 3-hydroxymethylantipyrine *(HMA)* in eight patients with disseminated nonseminomatous testicular cancer before *(I)*, during *(II, III)*, and after *(IV)* treatment with a cisplatin, vinblastin, and bleomycin combination chemotherapy. The *horizontal lines* indicate mean values. Of 14 controls *(C)*, mean values ± SD are given

14.2 ml/min (I versus III), but not for CL_{OHA}. The results of experiment III did not differ from those of experiment II (Table 2 and Fig. 3). Six weeks after the start of the last treatment cycle (expt IV) antipyrine clearance was still about the same as in experiment III. Of the metabolites, CL_{HMA} had decreased significantly from 14.2 to 12.2 ml/min.

Discussion

The aim of the present study was to assess the influence of the presence of disseminated nonseminomatous testicular tumors and the influence of PVB treatment on hepatic function. In such patients, however, conventional (qualitative) liver function tests such as gamma-glutamyltranspeptidase (GGT), alkaline phosphatase (AP), serum glutamyl oxalate transaminase (sGOT), and serum glutamyl pyruvate transaiminase (sGPT) cannot be used, since these enzymes are formed in the tumor and are released during PVB treatment due to tumor cells lysis [36]. Protein synthesis is also a parameter that cannot be used in this situation, and therefore antipyrine was chosen as a test drug for oxidative hepatic function, since its elimination kinetics have been widely used in assessing the activity of hepatic microsomal drug-metabolizing enzymes in man [2, 5, 6, 16, 37, 38]. Previously published studies with antipyrine indicated that lung cancer [3] and prostatic cancer [26] exerted a slight inducing effect, while gastric cancer [14], leukemia [15], or hepatoma [27] seemed to have no effect. Antipyrine metabolism was only impaired when metastases were located in the liver [15, 27].

Our results in patients with disseminated testicular cancer (all without liver metastases) are basically in agreement with these previous results, since antipyrine plasma clearance was about 20% higher in patients before treatment as compared to an age- and weight-matched control group (Table 1 and Fig. 2). In the previous studies with antipyrine, however, only antipyrine elimination half-lives or total plasma clearance were measured. The approach of measuring clearances for production of the three major metabolites enabled us to investigate the possible selective effects of the presence of tumor tissue and the administration of the anticancer drugs on the oxidative drug-metabolizing enzyme activity of different isoenzymes of cytochrome P-450 [6]. Comparison of the results obtained before PVB treatment (expt I) with those obtained in the control group indicated that the higher total clearance in the patients was mainly due to a 35% higher clearance for production of HMA. This result is interesting considering that in studies with such well-known inducers of drug metabolism as antipyrine [12], pentobarbital [12], and rifampicin [31, 33], HMA formation was found to be least susceptible to induction. Moreover, formation of HMA was affected less than formation of NORA and OHA in alcoholic liver cirrhosis [32].

The effect of PVB treatment was investigated in a longitudinal study in the same panel of patients (Fig. 1). In contrast to the inhibiting effect of PVB treatment on enzymes involved in thyroid hormone metabolism [40], in our study PVB treatment resulted in an increase of antipyrine clearance (expt II versus expt I; Table 2 and Fig. 2) by about 25%. During treatment, similar increases were observed for all three main metabolites of antipyrine (expts II and III), indicating nonselective induction. The increase in CL_{OHA} was less pronounced than the increase in CL_{NORA} (expt II) and CL_{HMA} (expt III).

For the patient group as a whole, the results of experiment III were not significantly different from those of experiment II, indicating persistence of increased enzyme activity (Table 2). Individual results, however (Figs. 2 and 3), showed marked interindividual differences. In some patients a decrease in enzyme activity became apparent, while in others a further increase was observed. In most cases the changes in metabolite clearances paralleled the changes in total plasma clearance.

No data are available on the effects of P, V, and B separately on hepatic drug-metabolizing enzyme activity in man. It can only be speculated that the increase in drug-metabolizing enzyme activity observed in this study is primarily associated with cisplatin, since platinum was shown to accumulate in the liver, resulting in detectable levels up to 4 weeks after cisplatin administration [4]. Moreover, for platinum a mean γ-phase elimination half-life of 174 h as been reported [25]. The elimination half-life of B is about 4 h [1] and that of V about 24 h [24], so that they are not likely to give rise to a high degree of accumulation. Furthermore, B and vincristine, a compound related to V, have been reported to inhibit hepatic mixed-function oxidases in rats [7, 23]. However, there may be large interspecies differences between isoenzymes of cytochrome P-450 in man and rat, and therefore no definite answer can be given to the question as to which anticancer drug has which effect on drug-metabolizing enzyme activity. There is probably no influence of the concomitantly administered chlorpromazine, since identical changes in antipyrine metabolism to those given in Table 2 were observed in two patients after PVB treatment without chlorpromazine. Other factors known to influence hepatic drug metabolism [39] were well controlled. The composition of the diet, for instance, was kept quite constant, and only minimal changes in body weight occurred (Table 1).

Six weeks after the start of the last treatment cycle a fourth antipyrine test was performed. Antipyrine plasma clearance was still elevated and not significantly different from that in experiments II and III. This persistent effect may be related to the long elimination half-life of P [25] and its accumulation in the liver and other body tissues [4]. The inductive effect, however, did not persist evenly in the formation of all three metabolites of antipyrine. CL_{HMA} was significantly reduced in comparison with experiment III, whereas CL_{NORA} and CL_{OHA} remained unchanged. In view of the initially elevated values of CL_{HMA} in untreated patients compared with the control group, and the nonselective effects of PVB treatment, the preferential reduction in CL_{HMA} may be associated with the disappearance of all tumor tissue. After termination of treatment, complete remission was confirmed in all patients by surgical and histological examination.

Data presented in this paper demonstrate that both the presence of a malignant fast-growing tumor and treatment with a PVB combination may have an accelerating effect on oxidative drug-metabolizing enzyme activity in man in vivo, though they were shown to have slightly differential effects on the different forms of cytochrome P-450. Assuming that antipyrine clearance provides a satisfactory reflection of liver function [6, 16, 32, 38], it can be concluded that the presence of testicular tumors and PVB treatment have no profound effect on it.

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References

1. Alberts DS, Chen H-S, Liu R, Himmelstein KJ, Mayersohn M, Perrier D, Gross J, Moon T, Broughton A, Salmon SE (1978) Bleomycin pharmacokinetics in man. I. Intravenous administration. Cancer Chemother Pharmacol 1: 177
2. Alván G (1978) Individual differences in the disposition of drugs metabolized in the body. Clin Pharmacokinet 3: 155
3. Ambre J, Graeff J, Bures F, Haupt D, Deason K (1977) Antipyrine metabolism in bronchogenic carcinoma. J Med 8: 57
4. Balis FM, Holcenberg JS, Bleyer WA (1983) Clinical pharmacokinetics of commonly used anticancer agents. Clin Pharmacokinet 8: 202
5. Breimer DD (1983) Interindividual variations in drug disposition. Clinical implications and methods of investigation. Clin Pharmacokinet 8: 371
6. Breimer DD, Vermeulen NPE, Danhof M, Teunissen MWE, Joeres RP, Van der Graaff M (1984) Assessment and prediction of in vivo oxidative drug metabolizing activity. In: Benet LZ, Levy G (eds) Pharmacokinetics, a modern view. Plenum Press, New York (in press)
7. Capel I, Jenner M, Pinnock MH, Williams DC (1978) The effect of anticancer drugs on the plasma disposition of antipyrine and the biliary excretion o phenolphthalein in the rat. Biochem Pharmacol 27: 1413
8. Danhof M, Breimer DD (1982) Studies on the different metabolic pathways of antipyrine in man; oral versus i.v. administration and the influence of urinary collection time. Eur J Clin Pharmacol 21: 433
9. Danhof M, De Groot-Van der Vis E, Breimer DD (1979a) Assay of antipyrine and it primary metabolites in plasma, saliva and urine by high-performance liquid chromatography and some preliminary results in man. Pharmacology 18: 210
10. Danhof M, Krom DP, Breimer DD (1979b) Studies on the different metabolic pathways of antipyrine in rats. Influence of phenobarbital and 3-methylcholanthrene treatment. Xenobiotica 9: 695
11. Danhof M, Teunissen MWE, Breimer DD (1982a) 3-Hydroxymethylantipyrine excretion in urine after an oral dose of antipyrine: A reconsideration of previously published data and synthesis of a pure reference substance. Pharmacology 24: 184
12. Danhof M, Verbeek RMA, Van Boxtel CJ, Boeijinga JK, Breimer DD (1982b) Differential effects of enzyme induction on antipyrine metabolite formation. Br J Clin Pharmacol 13: 379
13. Einhorn LH, Donohue J (1977) *cis*-Diamminedichloroplatinum, vinblastine and bleomycin combination chemotherapy in disseminated testicular cancer. Ann Intern Med 87: 293
14. Higuchi T, Nakamura T, Uchino H (1978) Microsomal enzymes in patients with gastric carcinoma as determined by plasma half-life of antipyrine. Gann 69: 753
15. Higuchi T, Nakamura T, Uchino H (1980) Microsomal enzymes in patients with acute leukemia as determined by plasma half-life of antipyrine. Cancer Chemother Pharmacol 5: 55
16. Homeida M, Roberts CJC, Halliwell M, Read AE, Branch RA (1979) Antipyrine clearance per unit liver volume; an assessment of hepatic function in chronic liver disease. Gut 20: 596
17. Høyem-Johansen T, Slørdal L, Høylandskjaer A, Aarbakke J (1980) The effect of antineoplastic drugs on the pharmacokinetics of antipyrine in the rat. Acta Pharmacol Toxicol 47: 279
18. Kato R, Takanaka A, Takahashi A (1970) Decrease in the substrate interaction with cytochrome P-450 in drug hydroxylation by liver microsomes from rats bearing Walker 256 carcinosarcomas. Gann 61: 359
19. Kellermann G, Jett JR, Luyten-Kellermann M, Moses HL, Fontana RS (1980) Variation of microsomal mixed function oxidase(s) and human lung cancer. Cancer 45: 1438
20. Knorr L, Pshorr P (1897) Ueber das 1-phenyl-2,3-dimethyl-4oxy-5-pyrazolon (4-oxy-antipyrine). Liebigs Ann Chem 293: 49
21. Koike E, Iida H, Okauna M, Kashioka A (1954) Organic pigments. II. Synthesis of 1-phenyl-3-methyl-5-pyrazolone and its derivatives. J Chem Soc Jpn 57: 56
22. Mackay EN, Sellers AH (1966) A statistical review of malignant testicular tumors based on the experience of the Ontario Cancer Foundation Clinics. Can Med Assoc J 94: 889
23. Montgomery MR, Furry J, Fernandez S (1981) Bleomycin inhibits hepatic mixed function oxidation. Res Commun Chem Pathol Pharmacol 34: 278
24. Nelson RL, Dyke RW, Root MA (1980) Comparative pharmacokinetics of vindesine, vincristine and vinblastine in patients with cancer. Cancer Treatment Rev 7S: 17
25. Riley CM, Sterson LA (1984) Recent advances in clinical analysis of cisplatin. Pharm Int 5: 15
26. Sotanieni EA, Kontturi MJ, Larmi TK (1973) Drug metabolism and androgen control therapy in prostatic cancer. Clin Pharmacol Ther 14: 413
27. Sotaniemi EA, Pelkonen RO, Mokka RE, Huttunen R, Viljakainen E (1977) Impairment of drug metabolism in patients with liver cancer. Eur J Clin Invest 7: 269
28. Stoter G, Sleijfer DT, Vendrik CPJ, Schraffordt Koops H, Struyvenberg A, Van Osterom AT, Brouwers TM, Pinedo HM (1979) Combination chemotherapy with *cis*-diammine-dichloro-platinum, vinblastin and bleomycin in advanced testicular non-seminoma. Lancet I: 941
29. Teunissen MWE, Joeres RP, Vermeulen NPE, Breimer DD (1983) Influence of 9-hydroxyellipticine and 3-methylcholanthrene treatment on in vivo antipyrine metabolite formation. Xenobiotica 13: 223
30. Teunissen MWE, Meerburg-Van der Torren JE, Vermeulen NPE, Breimer DD (1983) Automated HPLC determination of antipyrine and its main metabolites in biological fluids, including 4,4′-dihydroxyantipyrine. J Chromatogr 278: 367
31. Teunissen MWE, Bakker W, Meerburg-Van der Torren JE, Breimer DD (1984a) Influence of rifampicin treatment on antipyrine clearance and metabolite formation in patients with tuberculosis. Br J Clin Pharmacol (in press)
32. Teunissen MWE, Spoelstra P, Koch CW, Weeda B, Van Duijn W, Janssens AR, Breimer DD (1984b) Antipyrine clearance and metabolite formation in patients with alcoholic cirrhosis. Br J Clin Pharmacol (in press)
33. Toverud EL, Boobis AR, Brodie MJ, Murray S, Bennett PN, Withmarsh V, Davies DS (1981) Differential induction of antipyrine metabolism by rifampicin. Eur J Clin Pharmacol 21: 155
34. Tschanz C, Hignite CE, Huffman DH, Azarnoff DL (1977) Metabolic disposition of antipyrine in patients with lung cancer. Cancer Res 37: 3881
35. Van Boxtel CJ, Chrastil J, Wilson JT (1979) Inhibition of drug oxidation and stimulation of NADH oxidase in vitro by doxorubicin and triferric doxorubicin. Pharmacology 19: 5
36. Van 't Sant P, Sleijfer DT, Schraffordt Koops H, Suurmeijer AJH, Willemse PHB, De Bruin HWA, Marrink J, Ockhuizen Th (1984) The pattern of gamma-glutamyl transpeptidase, alkaline phosphatase, serum glutamyl oxalate transaminase and serum glutamyl pyruvate transaminase in patients with disseminated nonseminomatous testicular tumors. Eur J Cancer Clin Oncol 20: 209
37. Vesell ES (1977) Genetic and environmental factors affecting drug disposition in man. Clin Pharmacol Ther 22: 659
38. Vesell ES (1979) The antipyrine test in clinical pharmacology: conceptions and misconceptions. Clin Pharmacol Ther 26: 275
39. Vesell ES, Penno MB (1983) Assessment of methods to identify sources of interindividual pharmacokinetic variations. Clin Pharmacokin 8: 378
40. Willemse PHB, Sleijfer DT, Sluiter WJ, Schraffordt Koops H, Doorenbos H (1982) Alterations in thyroid hormone metabolism during chemotherapy in patients with testicular carcinoma. Clin Endocrinol 16: 303
41. Wilson VL, Larson RE, Moldowan MJ (1982) A non-invasive method for the study of hepatic drug metabolism in rodents: antineoplastic drug effects on antipyrine metabolism in mice. Chem Biol Interact 40: 159

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