Disposition of antipyrine in African patients with Hodgkin's lymphoma

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The pharmacokinetics of antipyrine were studied in 12 healthy volunteers and 10 patients of Kenya African origin with Hodgkin's lymphoma. The half-life of antipyrine was 12.2 ± 1.3 h (mean $\pm$ s.d.), while the apparent volume of distribution (V) was 0.67 ± 0.1 l kg⁻¹ (mean $\pm$ s.d.) and the total body clearance was 40.7 ± 3.2 ml kg⁻¹ h⁻¹ (mean $\pm$ s.d.) in the healthy volunteers. The antipyrine half-life in the patients with advanced Hodgkin's lymphoma was 17.1 ± 2.7 h (mean $\pm$ s.d.). The apparent volume of distribution was 0.72 ± 0.14 l kg⁻¹ (mean $\pm$ s.d.) which was larger than in healthy volunteers ($P < 0.05$). The total body clearance was 30.3 ± 9.4 ml kg⁻¹ h⁻¹ (mean $\pm$ s.d.) and this was reduced compared with that in healthy volunteers ($P < 0.02$). After cytotoxic therapy the half-life in the patients with advanced Hodgkin's lymphoma was significantly decreased to 8.3 ± 1.3 h (mean $\pm$ s.d.) ($P < 0.07$), and the apparent volume of distribution was reduced to 0.65 ± 0.07 l kg⁻¹ (mean $\pm$ s.d.) ($P < 0.05$) while the total body clearance increased to 52.8 ± 5.5 ml kg⁻¹ h⁻¹ (mean $\pm$ s.d.) ($P < 0.01$).

Keywords antipyrine Hodgkin's lymphoma cytotoxic drugs

Introduction

The pharmacokinetics of antipyrine have been investigated in patients with Hodgkin's lymphoma before and after cytotoxic drugs and the data were compared with that derived from a healthy control group.

Methods

Twelve healthy volunteers (5 females, 7 males) and ten patients with Hodgkin's lymphoma (6 females, 4 males) agreed to participate in the study. The healthy volunteers were aged 37 ± 10 years (mean $\pm$ s.d.) and weighed 70 ± 10 kg (mean $\pm$ s.d.) while the patients were aged 39 ± 14 years (mean $\pm$ s.d.) and weighed 68 ± 12 kg (mean $\pm$ s.d.).

The volunteers were drawn from a blood donor group and were in a satisfactory state of health. The diagnosis of Hodgkin's lymphoma was con-

firmed by tissue biopsy and the patients were undergoing treatment for the first time. They were at stage IV of the Ann Arbor classification. All of the volunteers had normal liver and renal functions and had values within the normal ranges for standard haematological tests. The patients maintained a normal haematological status as well as liver and renal function after the study.

The patients received antipyrine twice, once before the beginning of therapy and a second time during the third course of cyclophosphamide, vincristine (Oncovin), prednisone and procarbazine (COPP) therapy. The two groups were fasted overnight. On the following day each received 600 mg of antipyrine in gelatine capsules. Blood samples were collected through a butterfly needle (Abbott) at 0.5, 1, 2, 3, 4, 6, 8 and 24 h. The samples were centrifuged and the plasma was stored at -20° C until analysed by the method of Prescott *et al.* (1973).

Table 1 Antipyrine pharmacokinetic data derived from healthy volunteers and from patients with Hodgkin's lymphoma before and after treatment with cytotoxic therapy

Subject	$t_{1/2}$ (h)	V (l kg ⁻¹)	CL (ml h ⁻¹ kg ⁻¹)
Healthy volunteers	12.2 ± 1.3	0.67 ± 0.10	40.7 ± 3.2
Patients before cytotoxics	17.1 ± 2.7	0.72 ± 0.14	30.3 ± 9.4
Patients after cytotoxic therapy	8.3 ± 1.0	0.65 ± 0.07	52.8 ± 5.5

Data analysis

The data were fitted to a single compartment model with first order absorption using non-linear regression (Nelder & Mead, 1965). Clearance, volume of distribution and elimination half-life were estimated from standard equations (Gibaldi & Perrier, 1975).

Results

Table 1 summarises the pharmacokinetic data. In the healthy volunteers the half-life of antipyrine was 12.2 ± 1.3 h (mean ± s.d.), while the apparent volume of distribution (V) was 0.67 ± 0.1 l kg⁻¹ (mean ± s.d.) and the total body clearance was 40.7 ± 3.2 ml kg⁻¹ h⁻¹ (mean ± s.d.). The (mean ± s.d.) half-life of antipyrine in patients with Hodgkin's disease was 17.1 ± 2.7 h before treatment with cytotoxic drugs. This was longer than in healthy volunteers. The apparent volume of distribution was 0.72 ± 0.14 l kg⁻¹ (mean ± s.d.) which was larger than in healthy volunteers ($P < 0.05$). The total body clearance was 30.3 ± 9.4 ml kg⁻¹ h⁻¹ (mean ± s.d.) and this was significantly reduced compared with that in normal volunteers ($P < 0.02$).

After three courses of COPP, the half-life of antipyrine was 8.3 ± 1.3 h (mean ± s.d.). This was shorter than the half-life of antipyrine before treatment and in normal patients ($P < 0.01$).

The apparent volume of distribution was 0.65 ± 0.07 l kg⁻¹ (mean ± s.d.) which was reduced compared with that before treatment ($P < 0.05$),

but did not differ significantly from the apparent volume of distribution in normal volunteers. Total body clearance was 52.8 ± 5.5 ml⁻¹ kg⁻¹ h⁻¹ (mean ± s.d.) ($P < 0.01$).

Discussion

In the normal volunteers the pharmacokinetic parameters were similar to those that have been reported in Caucasians, Mongoloids and Africans, suggesting that the pharmacokinetics of antipyrine is not altered appreciably by racial factors (Brodie & Axelrod, 1950; Yoshimura *et al.*, 1971; Fraser *et al.*, 1976). Although antipyrine studies have been carried out in cancer patients, this appears to be the first in lymphoma patients. In these patients, the half-life of antipyrine was prolonged while the total body clearance of antipyrine was decreased.

This study has shown that after cytotoxic therapy with cyclophosphamide, vincristine, prednisone and procarbazine the half-life and apparent volume of distribution of antipyrine were significantly reduced, while the total body clearance was increased. The latter finding suggests enzyme induction by cyclophosphamide and prednisone (Faber *et al.*, 1974; D'Incalci *et al.*, 1979).

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References

- Brodie, B. B. & Axelrod, J. (1950). Fate of antipyrine in man. *J. Pharmac. exp. Ther.*, **98**, 97–104.
- Boobis, A. R., Brodie, M. J., Kahn, G. C., Toverud, E. L., Blair, I. A., Murray, S. & Davies, D. S. (1981). Comparison of the three main oxidative metabolites of antipyrine in man. *Br. J. clin. Pharmac.*, **12**, 771–777.
- Danhof, M., Verbeeck, R. M. A., Van Bostel, E. J., Boeijsinga, J. K. & Breimer, D. D. (1982). Differential effects of enzyme induction on antipyrine formation. *Br. J. clin. Pharmac.*, **13**, 379–382.
- D'Incalci, M., Bolis, G., Facinetti, T., Mangioni, C., Morasca, L., Morazzoni, P. & Salmona, M. (1979). Decreased half-life of cyclophosphamide in patients under continual treatment. *Eur. J. Cancer*, **19**, 7–10.
- Faber, O. K. & Mouridusen, H. T. (1974). The biotransformation of cyclophosphamide in man. Influence of prednisone. *Acta Pharmac. Tox.*, **35**, 195–200.

- Fraser, H. S., Bulpitt, C. J., Kahn, C., Mould, G., Mucklow, J. C. & Dollery, C. T. (1976). Factors affecting antipyrine metabolism in West African villagers. *Clin. Pharmac. Ther.*, **20**, 369–376.
- Gibaldi, M. & Perrier, D. (1975). *Pharmacokinetics. Drugs and the Pharmaceutical sciences*, Vol. I, ed. Swarbrick, J. New York: Marcel Dekker.
- Nelder, J. A. & Mead, R. (1965). A Simplex method for function minimisation. *Computers*, **7**, 308–313.
- Prescott, L. F., Adjepon-Yamoah, K. K. & Roberts, E. (1973). Rapid gas-liquid chromatographic estimation of antipyrine in plasma. *J. Pharm. Pharmac.*, **25**, 205–207.
- Yoshimura, Shimeno, H. & Tsukambo, H. (1971). Metabolism of drugs LXX. Further study of antipyrine metabolism. *Chem. Pharm. Bull. Tokyo*, **19**, 41–45.

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