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The effect of age on the pharmacokinetics of ifosfamide

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The effect of age on the pharmacokinetics of ifosfamide was studied in 20 patients with advanced non small cell lung cancer. A positive correlation was found between the elimination half-life of ifosfamide and age ($r = 0.48$, $0.05 < P < 0.01$). This was due to an increase in volume of distribution with age ($r = 0.66$, $0.001 < P < 0.01$). Total plasma clearance, renal clearance and non renal clearance did not change with age. Age did not affect the autoinduction of ifosfamide metabolism. Further studies are needed to demonstrate any adverse effects of ifosfamide in the elderly.

Keywords ifosfamide pharmacokinetics age

Introduction

The pharmacokinetics of many drugs are known to alter with age (Crooks *et al.*, 1976). With the increasing effectiveness of chemotherapy in the management of some malignant diseases there is an increasing probability of anti-cancer agents being prescribed for more elderly patients. It is, therefore, important to document any alterations in the pharmacokinetics of these agents with age in order to alert the clinician to the possible need to alter prescribing habits.

Ifosfamide(I) {3-(2 chlorethyl) -2 -(2 chlorethylamino) tetrahydro -2H -1, 2, 3 oxazaphosphorine oxide} (Mitoxana) is a structural isomer of the oxazaphosphorine cyclophosphamide, a widely used alkylating agent. It is a 'prodrug' that requires biotransformation in order to become cytotoxic. This occurs mainly in the liver (Brock & Hohorst, 1963) by the action of a mixed function oxidase, producing the active metabolites 4-hydroxyifosfamide (Connors *et al.*, 1974) and isophosphoramide mustard (Brock, 1983). Ifosfamide is less myelosuppressive than cyclophosphamide (Brade *et al.*, 1986) but is more urotoxic (Teufel & Pfleiderer, 1986). However, with the introduction of the uroprotector Mesna (uromitexan) in 1982 (Bryant *et al.*, 1980) urotoxicity is now largely avoidable. It has been shown that ifosfamide is one of the most active drugs in the treatment of bronchogenic carcinoma (Hoeffer *et al.*, 1974). Since patients with this form of cancer will include a substantial proportion of elderly patients we have studied the effect of age on ifosfamide kinetics.

Methods

Patients

Twenty patients with advanced non small cell lung cancer (one patient had metastatic carcinoma of the oesophagus) were treated with intravenous ifosfamide according to two regimens:

(i) Ifosfamide 1.5 g m^{-2} i.v. daily for 5 days (17 patients).

(ii) Ifosfamide 1.5 g m^{-2} i.v. daily for 3 days (3 patients).

In all patients ifosfamide was administered as a 30 min infusion in 250 ml of normal saline. All patients were given equidose Mesna as a 12 h i.v. infusion in 1 l of normal saline directly after each infusion of ifosfamide.

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Sample collection and storage

Serial blood samples were collected at 0, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 6, 9 and 24 h after drug infusion on each day of ifosfamide administration in addition to 24 h urine samples. The blood samples were centrifuged immediately; the serum was separated and stored at −20° C. Urine samples were also stored at −20° C.

Analytical methods

Serum and urinary ifosfamide concentrations were measured by h.p.l.c. (Margison *et al.*, 1986).

Total alkylating activity in the serum was measured using a modification of the method of Friedman & Boger (1961) in which the colour developed by reaction with nitro-benzyl-pyridine is extracted into ether containing 5% w/v triethylamine. Bischloroethylamine was used as a standard and values extrapolated from the standard curve were converted to $\mu g\ ml^{-1}$ equivalents of nor nitrogen mustard. As ifosfamide reacts weakly with nitro-benzyl-pyridine a second standard curve was constructed from serum containing ifosfamide at therapeutic concentrations. The contribution of ifosfamide to the total alkylating activity of the sample could therefore be determined and a value for the alkylating activity of ifosfamide metabolites could be assessed.

Kinetic analysis

Serum ifosfamide concentration-time profiles were fitted by a bi-exponential function using the iterative non linear computer programme MODFIT as described by McIntosh & McIntosh (1980). Coefficients and exponents were used to calculate half-lives ($t_{½}$), area under the curve (AUC) and the volume of distribution. Total clearance (CL) was calculated from Dose/AUC and renal clearance from (CL_R) from the amount recovered in the 24 h urine divide by AUC.

Values of the non renal clearance (CL_{NR}) were determined from ($CL-CL_R$).

Estimation of total body water

This was calculated from tables (Edelman & Liebman, 1959).

Statistical methods

To determine any correlation between pharmacokinetic parameters and age a series of univariate analyses were performed. The pharmacokinetic parameters used were those measured on day 1 because of the known effect of fractionating ifosfamide dosage over several days on its pharmacokinetics (Lind *et al.*, 1989). In addition an attempt was made to correlate age with any change in pharmacokinetic parameters over the 3 or 5 days of ifosfamide administration. The percentage change in a prameter (% ∂P) was estimated from $[(Pf-P1)/P1]\times100$ where Pf = the pharmacokinetic parameter on the final day of ifosfamide administration and P1 = the pharmacokinetic parameter on the first day of ifosfamide administration. The rates of change of pharmacokinetic parameters (R) were calculated from % $\partial P/T$ where T = the total duration of treatment in days.

Results

The twenty patients receiving intravenous ifosfamide had a median age of 60 years (range 40–71 years). A weak but statistically significant positive correlation between the elimination half-life on the first day of ifosfamide administration and age was observed (Figure 1a) ($r = 0.48$, $0.01 < P < 0.05$). The median half-life of ifosfamide elimination in patients under the age of 60 years was 3.85 h (range 1.82–8.15 h) compared with a median value of 6.03 h (range 3.89–7.45 h) in those over the age of 60 years. No correlation was observed between body clearance, non renal clearance or renal clearance of ifosfamide with age even when these parameters were normalised to body weight or surface area (Figure 1b). The median total clearance (CL) in those patients less than 60 years of age was 74.5 ml min^{-1} (range 53.17–188.83 ml min^{-1}) whilst in those over the age of 60 years the median total clearance (CL) was 80.50 ml min^{-1} (range 63.25–146.26 ml min^{-1}, $P > 0.05$, Mann-Whitney test). Likewise there was no significant difference in the non renal clearance between the two age groups (CL_{NR}) (64.74 ml min^{-1}, range 29.74–138.64 ml min^{-1} *vs* 61.87 ml min^{-1}, range 47.03–90.44 ml min^{-1}, $P > 0.05$, Mann-Whitney test). No significant difference between the renal clearances (CL_R) in each age group was observed (10.08 ml min^{-1}, range 2.54–50.20 ml min^{-1} *vs* 10.89, range 4.22–17.97 ml min^{-1}, $P > 0.05$, Mann-Whitney test).

However, the volume of distribution V correlated positively with age ($r = 0.66$, $0.001 < P < 0.01$). This correlation remained statistically significant after correction for total body weight ($r = 0.58$, $0.01 < P < 0.05$) (Figure 1c) and body surface area ($r = 0.64$, $0.001 < P < 0.01$). No significant correlation was demonstrated

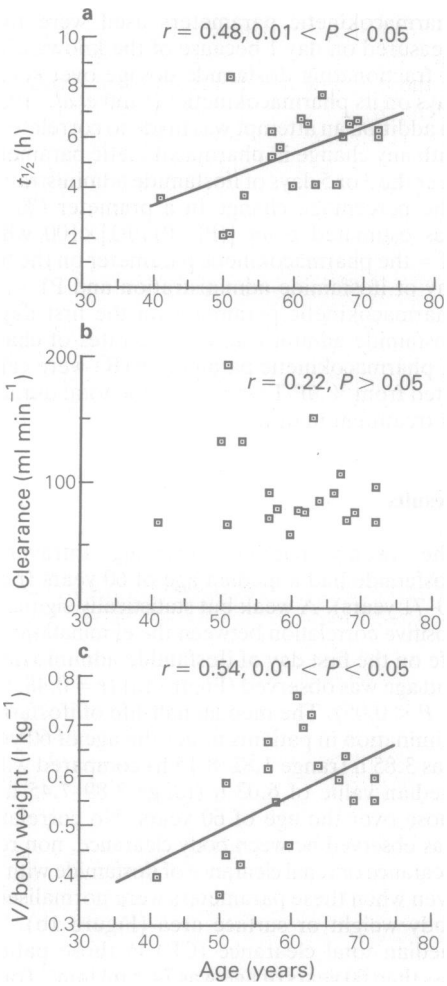

Figure 1 a) Correlation of ifosfamide with age, b) total serum clearance of ifosfamide *vs* age and c) correlation of volume of distribution (V) corrected for total body weight *vs* age.

between V and plasma albumin. The median volume of distribution (V) in those patients over the age of 60 years was 40 l (range 33–52 l), which was significantly more than the estimated total body water for this group of patients (median 38 l, range 15–45 l) ($0.01 < P < 0.05$ Wilcoxon signed rank test).

No significant differences were seen in the area under the metabolite alkylating activity curve between the two age groups (145.00 μg ml^{-1} h equivalents of nor nitrogen mustard, range 34.51–335.40 *vs* 121.05, range 24.22–182.59 μg ml^{-1} h equivalents of nor nitrogen mustard, $P > 0.05$ Mann-Whitney test).

With regard to changes in the pharmacokinetic parameters over the 3 or 5 days of administration there was a fall in the elimination half-life associated with an increase in total and non renal clearance of ifosfamide. There was no change in V or in the renal clearance of ifosfamide. These results are discussed elsewhere (Lind *et al.*, 1989). No correlation was observed between age and percentage change in pharmacokinetic parameters (∂% P) or the rate of change of these parameters (R). No correlation was observed between age and area under the serum metabolite alkylating activity curve or the peak level of serum metabolite alkylating activity.

Discussion

A weak positive correlation was observed between age and the elimination half-life of ifosfamide. This was not due to a decreased total or non renal clearance of ifosfamide, suggesting that there is no decline in the ability of the liver to metabolise the drug with increasing age, but appeared to be due to an increased volume of distribution. No change in serum metabolite alkylating activity supports the view that there is no impairment of ifosfamide biotransformation with increasing age. As there was no correlation between plasma albumin and volume of distribution it seems unlikely that decreased plasma protein binding was the cause of the increased volume of distribution. The volume of distribution in patients over the age of 60 years of age was significantly higher than the estimated total body water. Although the difference was slight this is in contrast to previous data (Allen *et al.*, 1976) and suggests that ifosfamide may distribute into body fat. Therefore, increasing body fat or an increase in the body fat to lean weight ratio in the elderly may be the cause of the observed increase in V with age.

No correlation was observed between any change in the pharmacokinetic parameters over the 3 or 5 days of administration and age. These changes in pharmacokinetic parameters have been attributed to enzyme induction resulting in accelerated ifosfamide metabolism (Lind *et al.*, 1989). The clinical relevance of these findings may not at first be obvious as the pharmacokinetic parameters for ifosfamide do not affect the drug's pharmacodynamics (Lind *et al.*, 1989) and there was no relationship between total metabolite alkylating activity in those patients over the age of 60 years and those under 60 years of age. It must be remembered that use of the NBP test to assay ifosfamide metabolites is very non specific. Several of the metabolites of ifosfamide will react positively in the NBP reaction (Roberts *et al.*, 1988) and thus patients

with similar levels of alkylating activity in the serum might have quite different profiles of ifosfamide metabolites. The half-life of the two principal metabolites of cyclophosphamide, 4-hydroxycyclophosphamide and phosphoramide mustard, have been shown to correlate with that of the parent drug (Sladek *et al.*, 1984). Thus, a prolongation in cyclophosphamide elimination half-life will result in a prolongation of the apparent half-life of phosphoramide mustard and probably more importantly that of 4-hydroxycyclophosphamide. Wagner *et al.* (1981) has shown that the apparent half-life of 4-hydroxyifosfamide is approximately 6 h and it would therefore seem likely that the half-life of this metabolite is dependent on the half-life of the parent drug. Thus alteration of the elimination of the half-life of ifosfamide with age may alter the plasma concentration-time profile of the principal metabolite 4-hydroxyifosfamide. Klein *et al.* (1984) have demonstrated that fractionation of ifosfamide dosage over several days leads to an improved therapeutic index. Thus prolonged administration of ifosfamide may alter the toxicity and/or responsiveness to the drug. One possible explanation of this finding is that a prolonged exposure to low levels of the 4-hydroxy metabolite may be less toxic than a relatively short exposure to high concentrations of this metabolite. Therefore alterations in the half-life of the active metabolites of ifosfamide by altering the shape of the plasma metabolite concentration profile curve may change both the efficacy and toxicity of the drug.

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