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Prolongation of ifosfamide elimination half-life in obese patients due to altered drug distribution

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Summary. The pharmacokinetics of intravenous ifosfamide were determined in 16 patients with carcinoma of the bronchus. In all 25% (4) of these patients were obese (i.e. >20% over their ideal body weight). The terminal elimination half-life ($t_{1/2}$ β) was found to be higher in the obese group than in the control group (6.36 h, range 5.77–7.45 h) vs 4.95 h, range 1.82–6.48 h) ($P < 0.05$). This prolongation of the elimination half-life was due to an increased volume of distribution ($V_d\beta$) in the obese group (42.81 l, range 35.49–51.90 l) vs 33.70 l range (17.76–50.62 l) ($P < 0.05$). There was therefore no significant difference in total plasma clearance between the obese and normal groups. No correlation of ifosfamide plasma half-life was observed with total body weight (TBW) or ideal body weight (IBW). However, a significant positive correlation was observed between the percentage of IBW and plasma half-life. A strong positive correlation was observed between IBW and the plasma clearance of ifosfamide. The $V_d\beta$ correlated with both TBW and the percentage of IBW, but not with IBW itself. When $V_d\beta$ was normalised for IBW, there was a strong positive correlation with the percentage of IBW, suggesting that ifosfamide distribution into the TBW is higher than that into the IBW.

Introduction

Obesity is a common disorder in the normal population; some 37% of men between the ages of 20–59 years and 49% of women in the same age range carry >20% more than their ideal body weight (IBW) [27]. Furthermore, certain groups of patients suffering from malignant disease demonstrate an even greater degree of obesity. A survey of 836 breast cancer patients from the Mayo clinic revealed that 68% were obese, 53% were severely obese (i.e. >30% above their IBW) and 2% carried >100% more than their IBW [22]. Obesity is known to affect the pharmacokinetics of several drugs [1, 21]. It alters the ratio of adipose tissue to lean body mass, and this can lead to altered drug distribution. Hence, hydrophilic drugs are relatively excluded, whereas lipophilic drugs such as diazepam and theophylline have an increased volume of distribution ($V_d\beta$) [4, 17]. Plasma protein binding and, hence, drug distribution are also known to be altered in obesity [8].

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Renal clearance of drugs may be increased for several reasons, e.g. increased kidney blood flow or increased tubular secretion [7, 26]. Fatty infiltration or hepatic fibrosis associated with obesity may decrease drug oxidation [2, 9, 16]. Phase II metabolism (i.e. drug conjugation) may be increased in obese individuals. Moreover, hepatic blood flow can be altered in obesity, resulting in changes in the pharmacokinetics of drugs whose clearance is dependent on hepatic blood flow [5].

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 before it becomes cytotoxic. Activation occurs mainly in the liver [12] by the action of a mixed-function oxidase, producing the active metabolites 4 hydroxyifosfamide [14] and isophosphoramide mustard [11]. Ifosfamide is less myelosuppressive than cyclophosphamide [10] but is more urotoxic than the latter [28]. However, since the introduction of the uroprotector mesna (Uromitexan) in 1982 [13], this toxicity has now largely become avoidable. Ifosfamide has been shown to be one of the most active drugs in lung cancer treatment [15]. Since such a population of patients may contain a high proportion of obese individuals, we decided to study the effect of obesity on the pharmacokinetics of ifosfamide.

Patients, materials and methods

Patients. A total of 16 patients with advanced non-small-cell lung cancer were intravenously treated with 1.5 g/m^2 ifosfamide (Mitoxana) on days 1–5. The drug was given as a 30-min infusion in 250 ml normal saline. This was followed by a 12-h infusion of 1.5 g/m^2 mesna (Uromitexan) given in 1 l normal saline. The median age of the patients was 59.5 years (range, 40–71 years). All patients had a pretreatment Karnosky performance status of >50 and a pretreatment creatinine clearance of >50 ml/min.

Sample collection. Serial blood samples were collected at 0, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 6, 9 and 24 h after ifosfamide administration on each of the 5 days, in addition to 24-h urine samples. Blood samples were centrifuged immediately; the serum was separated and stored at −20° C. Urine samples were also stored at −20° C.

Sample analysis. Sample analyses were carried out using the high-performance liquid chromatographic (HPLC) method of Margison et al. [19].

Pharmacokinetic analysis. The serum concentration profile was fitted to a two-compartment model using the noniterative computer programme MODFIT as described by McIntosh and McIntosh [20]. The intercept and rate constants were used to calculate the half-lives ($t_{1/2}$), area under the curve (AUC^{∞}), and $V_d\beta$. Total body clearance was determined by the formula:

$$Cl_{tot} = D/AUC^{\infty},$$

where D = the dose delivered. By measuring the 24-h urinary excretion of ifosfamide, the renal clearance of the drug was calculated from the formula:

$$Cl_r = Xu/AUC^{\infty},$$

where Cl_r = the renal clearance and Xu, the amount excreted in the urine over 24 h. From Cl_r, the non-renal clearance of the drug could be derived from the equation:

$$Cl_{tot} = Cl_r + Cl_{nr},$$

where Cl_{nr} = the non-renal clearance.

Calculation of IBW. Estimates of the patients' IBWs were obtained from Fogarty tables. The percentage of IBW was calculated from the formula:

$$\% \text{ IBW} = \text{TBW/IBW}$$

where % IBW = the percentage of IBW, IBW = ideal body weight, and TBW = total body weight. Patients with a percentage of IBW of ≥120% were considered to be obese.

Statistical methods. To compare parameters between the normal and obese groups Mann-Whitney tests were used (only pharmacokinetic parameters from day 1 were used).

Results

The results are summarised in Table 1. The median TBW in the obese group was 76.75 kg (range, 47.70–77.00 kg) vs that of 64.15 kg (range, 70.00–86.00 kg) in the control group ($P < 0.05$, Mann-Whitney test). There was no statistically significant difference in IBW between the two groups. The median percentage of IBW in the control group was 102.20% (range, 83.80%–118.50%) vs that of 133.40% (range, 129.70%–150.30%) in the obese group ($P < 0.05$, Mann-Whitney test).

The terminal elimination half-life of ifosfamide was longer in the obese group than in the control group: 6.36 h (range, 5.77–7.45 h) vs 4.95 h (range, 1.82–6.48 h) ($P < 0.05$, Mann-Whitney test). No correlation was observed between half-life and TBW or IBW. However, a statistically significant positive correlation was observed between plasma elimination half-life and the percentage of IBW ($r = 0.52$, $0.01 < P < 0.05$) (Fig. 1).

Total ifosfamide plasma clearance in both groups was the same even when clearance was corrected for TBW or IBW. Total plasma clearance of ifosfamide strongly positively correlated with IBW ($r = 0.70$, $0.001 < P < 0.01$) (Fig. 2).

The median volume of distribution ($V_d\beta$) was higher in the obese group (42.81 l, range 35.49–51.90 l) than in the control group (33.70 l, range (17.76–50.62 l) ($P < 0.05$, Mann-Whitney test). This difference remained even when the $V_d\beta$ was corrected for IBW but not when it was corrected for TBW. There was a positive correlation between the $V_d\beta$ and TBW ($r = 0.61$, $0.01 < P < 0.05$) and between the $V_d\beta$ and the percentage of IBW ($r = 0.61$, $0.01 < P < 0.05$) (Fig. 3). When $V_d\beta$ was normalised to IBW this value strongly correlated positively with the percentage of IBW ($r = 0.76$, $P < 0.001$) (Fig. 4). Non-renal clearance correlated positively with IBW ($r = 0.81$, $P < 0.001$). There was no correlation between renal clearance and TBW, IBW or the percentage of IBW.

Table 1. Pharmacokinetic parameters in obese and normal patients receiving 1.5 g/m² intravenous ifosfamide on days 1–5 (values represent medians and ranges)

Parameter[a]	Normal	Obese	P**
Patients (*n*)	12	4	
Total body weight (kg) (range)	64.15 (47.70–77.00)	76.75 (70.00–86.00)	<0.05
Ideal body weight (kg) (range)	64.25 (50.40–77.60)	56.60 (48.90–65.75)	NS
% IBW[b] (range)	102.20 (50.40–118.50)	133.40 (129.70–150.30)	<0.05
$t_{1/2}\beta$[c] (h)	4.95 (1.82–6.48)	6.36 (5.77–7.45)	<0.05
$V_d\beta$[d] (l) (range)	33.70 (17.76–50.62)	42.81 (35.49–51.90)	<0.05
$V_d\beta$/TBW[e] (kg/l) (range)	0.53 (0.27–0.838)	0.55 (0.65–0.84)	NS
$V_d\beta$/IBW[f] (kg/l) (range)	0.54 (0.26–0.74)	0.75 (0.65–0.84)	<0.05
Cl_{tot}[g] (ml/min) (range)	72.240 (53.17–188.83)	76.04 (65.00–91.70)	NS
Cl_{tot}/TBW[h] (ml/min per kg) (range)	1.31 (0.79–3.02)	1.01 (0.88–1.07)	NS
Cl_{tot}/IBW[i] (ml/min per kg) (range)	1.20 (0.94–2.66)	1.36 (1.31–1.40)	NS

[a] Only parameters from day 1 were used in the analysis
[b] % IBW = TBW/IBW
[c] $t_{1/2}\beta$ = elimination half-life
[d] $V_d\beta$ = volume of distribution
[e] $V_d\beta$/TBW = volume of distribution normalised to TBW
[f] $V_d\beta$/IBW = volume of distribution normalised to IBW
[g] Cl_{tot} = total plasma clearance
[h] Cl_{tot}/TBW = total plasma clearance normalised to TBW
[i] Cl_{tot}/IBW = total plasma clearance normalised to IBW
** Mann-Whitney test; NS, not significant

Discussion

These data demonstrate that the elimination half-life of ifosfamide is prolonged in obese patients, apparently due to an increase in the apparent $V_d\beta$ of the drug rather than decreased clearance of ifosfamide. From Fig. 4 would also appear that ifosfamide distributes into body weight above the IBW, implying that the drug can distribute into body fat. Therefore, obese patients have a higher $V_d\beta$ and, as clearance is not affected by obesity, the elimination half-life is prolonged.

These results differ from those of Powis et al. [23], who investigated the pharmacokinetics of cyclophosphamide in

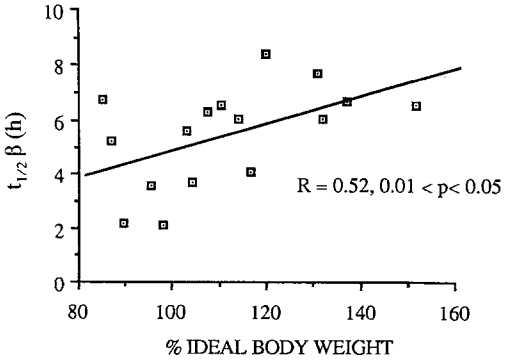

Fig. 1. Correlation between ifosfamide plasma elimination half-life and body weight

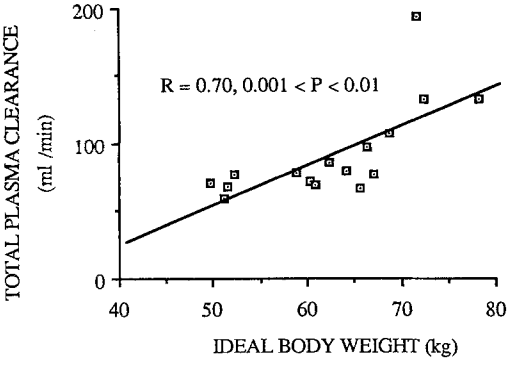

Fig. 2. Correlation of ifosfamide plasma clearance with ideal body weight

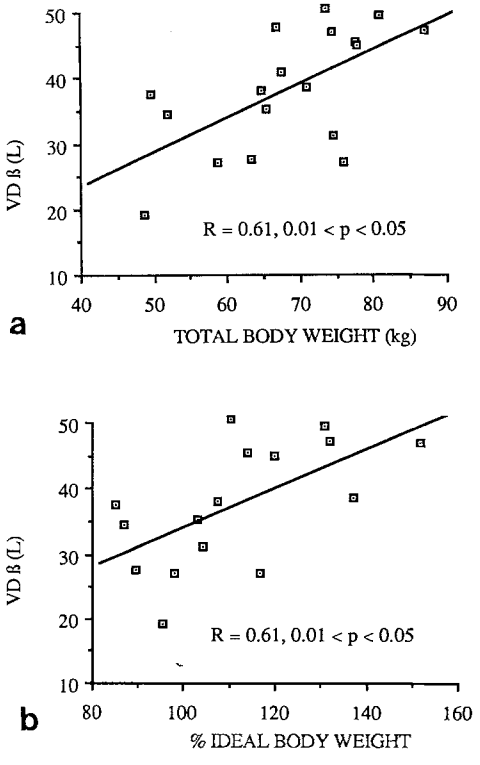

Fig. 3. Correlation of ifosfamide volume of distribution with total body weight and the percentage of ideal body weight

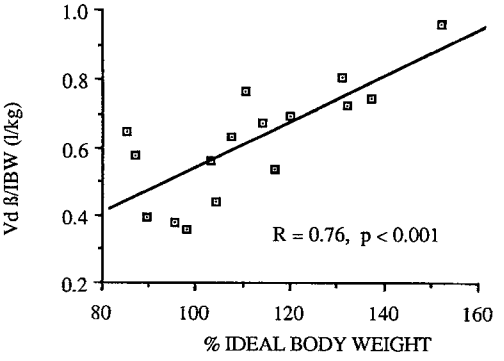

Fig. 4. Correlation of ifosfamide volume of distribution normalised to ideal body weight with the percentage of ideal body weight

16 female patients with carcinoma of the breast. This work demonstrated a positive correlation between TBW and plasma half-life and a negative one between cyclophosphamide clearance normalised to surface area and body weight. However, no correlation of pharmacokinetic parameters with the percentage of IBW was observed. These authors concluded that their observations might have been due to decreased hepatic oxidation of cyclophosphamide, as the clearance of certain drugs undergoing hepatic oxidation is known to be reduced in obese patients [3, 6, 25]. The cause of the disparity between our results and those of Powis et al. is not clear; physiochemical differences between ifosfamide and cyclophosphamide may account for this difference [9].

The pharmacokinetics of other anticancer agents have been demonstrated to be abnormal in obese individuals. Rodvold et al. [24] have demonstrated that doxorubicin clearance is reduced in the obese, leading to a prolonged half-life and increased AUC value. These authors also observed lower levels of aglycone metabolites in obese patients receiving doxorubicin, suggesting impaired cytochrome P450 function in obesity.

In summary, the half-life of ifosfamide is increased in obese patients due to an increased volume of distribution. Although studies to date have failed to correlate ifosfamide pharmacokinetics with toxicity and/or response [18], it is not inconceivable from the present data that toxicity might be expected to be worse in obese patients. Clearly, further studies are required to address this problem. In addition, there may be other anticancer agents whose pharmacokinetics and pharmacodynamics may be altered by obesity.

References

1. Abernethy DR, Greenblatt DJ (1982) Pharmacokinetics of drugs in obesity. Clin Pharmacokinet 7: 108–124
2. Abernethy DR, Greenblatt DJ (1985) Ibuprofen disposition in obese individuals. Arthritis Rheum 28: 1117–1121
3. Abernethy DR, Greenblatt DJ (1986) Drug disposition in obese humans, an update. Clin Pharmacokinet 11: 199–213
4. Abernethy DR, Greenblatt DJ, Divoll M, Harmatz JS, Shader RI (1981) Alterations in drug distribution and clearance due to obesity. J Pharm Exp Ther 217: 681–685
5. Abernethy DR, Greenblatt DJ, Divoll M, Shader RI (1983) Enhanced glucuronide conjugation of drugs in obesity; studies of lorazepam, oxazepam and acetaminophen. J Lab Clin Med 101: 873–880

6. Abernethy DR, Todd EL, Schwartz JB (1985) Caffeine disposition in obesity. Br J Clin Pharmacol 20: 61–66
7. Bauer LA, Wareing-Tran MS, Drew Edwards WA, Raisys V, Jack R, Dellinger P, Simonowitz D (1985) Cimetidine clearance in the obese. Clin Pharmacol Ther 37: 426–430
8. Benedek IH, Fiske WD, Griffen WO, Bell RM, Blouin RA, McNamara PJ (1983) Serum alpha-1-acid glycoprotein and the binding of drugs in obesity. Br J Clin Pharmacol 16: 751–754
9. Brade WP, Herdrich K, Varini M (1985) Ifosfamide – pharmacology, safety and therapeutic potential. Cancer Treat Rev 12: 1–47
10. Brade W, Seeber S, Herdrich K (1986) Comparative activity of cyclophosphamide and ifosfamide. Cancer Chemother Pharmacol 18 [Suppl 2]: 1–9
11. Brock N (1983) The oxazaphosphorines. Cancer Treat Rev 10 [Suppl A]: 3–15
12. Brock N, Hohrst H-J (1963) Über die Aktivierung von Cyclophosphamid in vivo und in vitro. Arzneim Forsch 13: 1021–1031
13. Bryant BM, Jarman M, Ford HT, Smith IE (1980) Prevention of isophosphamide-induced urothelial toxicity with 2-mercaptoethane sulphonate sodium (mesnum) in patients with advanced carcinoma. Lancet II: 657–659
14. Connors TA, Cox PJ, Farmer PB, Foster AB, Jarman M (1974) Some studies of the active intermediates formed in the microsomal metabolism of cyclophosphamide and isophosphamide. Biochem Pharmacol 23: 115–129
15. Costanzi JJ, Gagliano R, Loukas D, Panettiere FJ, Hokanson JA (1978) Ifosfamide in the treatment of recurrent or disseminated lung cancer. A phase II study of two dose schedules. Cancer 41: 1715–1719
16. Dunkelman SS, Fairhurst B, Plager J (1964) Cortisol metabolism in obesity. J Clin Endocrinol Metab 24: 832–841
17. Gal P, Jusko WJ, Yurchak AM, Franklin BA (1978) Theophylline disposition in obesity. Clin Pharmacol Ther 23: 438–444
18. Lind MJ, Margison JM, Cerny T, Thatcher N, Wilkinson PM (1989) Comparative pharmacokinetics and alkylating activity of fractionated oral and intravenous ifosfamide in patients with bronchogenic carcinoma. Cancer Res 49: 753–757
19. Margison JM, Cerny T, Thatcher N, Wilkinson PM (1986) A simple quantitative HPLC assay for ifosfamide in biological fluids. Biomed Chromatogr 1(3): 101–103
20. McIntosh JEA, McIntosh RP (1980) Mathematical modeling and computing in endocrinology. Springer, Berlin Heidelberg New York
21. Milsap RL, Plaisance KI, Jusko WJ (1984) Prednisolone disposition in obese men. Clin Pharmacol Ther 36: 824–831
22. Powis G (1983) Effects of disease states on pharmacokinetics of anticancer drugs. In: Ames MM, Powis G, Kovach JS (eds) Pharmacokinetics of anticancer agents in humans. Elsevier, Amsterdam, p 63
23. Powis G, Reece P, Ahmann DL, Ingle JN (1987) Effect of body weight on the pharmacokinetics of cyclophosphamide in breast cancer patients. Cancer Chemother Pharmacol 20: 219–222
24. Rodvold KA, Rushing DA, Tewksbury DA (1988) Doxorubicin clearance in the obese. J Clin Oncol 6: 1321–1327
25. Rohrbaugh TM, Danish M, Ragni MC, Yaffe (1982) The effect of obesity on the apparent volume of distribution of theophylline. Pediatr Pharmacol 2: 75–83
26. Sketris I, Lesar T, Zaske DE, Cipolle RJ (1981) Effect of obesity on gentamicin pharmacokinetics. J Clin Pharmacol 21: 288–293
27. Silverstone JT, Gordon RP, Stunkard AJ (1969) Social factors in obesity in London. Practitioner 202: 682
28. Teufel G, Pfleiderer A (1986) Ifosfamid im Vergleich zu Endoxan bei fortgeschrittenen Ovarialkarzinomen. Geburtshilfe Frauenheilkd 36: 274

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