Table 1. Incidence of pleural cancer, Rotterdam area 1987–1989

Men	1987	1988	1989	(*n*)*
Incidence of pleural cancer†	6.1	6.1	6.5	(189)
Histological or cytological verification (%)	90%	87%	86%	(166)
Pathology-based diagnosis of mesothelioma (%)	83%	81%	80%	(153)

Women	1987–1989	(*n*)*
Incidence of pleural cancer†	0.3	(13)

* Number of cases 1987–1989. † Age-standardised to the world standard population.

DISCUSSION

The incidence of pleural cancer in the Rotterdam area is considerably higher than thus far reported by other cancer registries [4]. For the period 1978–1982 the highest rates were those from Western Australia (2.8) and Sweden (2.3). This comparison, however, may not be appropriate due to variation in time periods. Considering the fact that diagnosis of mesothelioma was pathology-based in more than 80% of all patients, misclassification of other primary cancers cannot account for the high incidence.

The high male to female ratio points to an occupational risk factor, in this case presumably crocidolite. Closer study revealed that the incidence of mesothelioma was focused in cities with shipbuilding industry, where crocidolite had been used for insulation purposes. Detailed information on occupational background of the patients is, however, lacking, implying that an effect of chrysotile, the principal type of asbestos used in The Netherlands, cannot be excluded. In view of the fact that the role of chrysotile and other factors is still subject to debate [5, 6], further epidemiological studies regarding the aetiology of mesothelioma should be considered.

Malignant mesothelioma has become an important health problem in the Rotterdam area. At the moment it constitutes almost 1% of overall mortality in men. It is unlikely that the incidence will decrease before the end of this century. Similar clusters of mesothelioma may become apparent in other regions with major shipbuilding or asbestos industries.

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24-Hour Plasma Etoposide Profile After Oral and Intravenous Administration in Children

C.R. Pinkerton, G. Dick and G.W. Aherne

Pharmacokinetic profiles of oral and intravenous etoposide have been compared in 9 children receiving the drug either as a single agent or in combination chemotherapy. The plasma etoposide levels were estimated using a competitive coated antigen ELISA technique. The median bioavailability was 48% and beyond 30 min after either oral or intravenous injection there was little difference in the plasma profile. The duration of plasma concentrations above 1, 5 and 10 μg/ml following either route were compared. It is concluded that unless the height of initial peak concentration is of therapeutic value the oral route should be comparable in children provided that twice the intravenous dose is administered. The short elimination half-life results in low plasma levels beyond 12 h and suggests that a twice daily regimen may be preferable.
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INTRODUCTION

Over the past decade etoposide has found an established role in the management of several childhood cancers. Despite the inconvenience of parenteral administration in almost all paediatric schedules the intravenous (i.v.) route is used. Capsules are difficult for smaller children to tolerate and only recently has the use of oral administration of the i.v. ampoule mixed with a suitable masking agent been adopted. One of the first treatment regimens to use the oral route was the VEEP regimen for Hodgkin's disease, developed by McElwain *et al.* In this regimen 4–5 days of oral etoposide (100 mg/m²/daily) is given. A pilot study showed this method to be feasible in the majority of children [1].

There has recently been particular interest in the oral schedule

because data in adults suggest that prolonged low dose administration is at least as effective as higher doses over a short period and better tolerated [2]. Unless a continuous infusion pump is used, the oral route is mandatory [3]. It has also been suggested that the bioavailability is improved using low dose etoposide compared to higher doses when given by mouth [4, 5] and that prolonged low plasma levels of etoposide may be more cytotoxic [6].

This study analyses plasma etoposide profiles using an enzyme-linked immunosorbent assay (ELISA) with particular attention to the duration of low drug levels following oral compared with i.v. administration in children.

PATIENTS AND METHODS

9 children with cancer were included on study, 6 had soft tissue sarcomas and were receiving either a combination of etoposide and cisplatin or etoposide as a single agent. 2 had Ewing's sarcoma and were receiving etoposide in combination with ifosfamide. One with acute lymphoblastic leukaemia was receiving etoposide in combination with daunorubicin, cytarabine and 6-thioguanine. Ages ranged from 2 to 16 years.

The dose of etoposide varied from 100 to 150 mg/m^2 given daily for 3–5 days. These children were on standard treatment regimens and in order not to risk compromising efficacy an oral dose twice that given i.v. was used in all cases, based on studies in adults suggesting 50% bioavailability. Etoposide was administered either i.v. as a 60-min infusion and orally in the form of capsules or as the i.v. solution diluted in orange juice.

Blood plasma samples were taken prior to etoposide administration and at approximately 0.5, 1, 1.5, 2, 4, 8, 12, 18 and 24 h following drug administration. The plasma was stored at −20°C until assayed using a competitive coated antigen ELISA previously described [7]. Samples were assayed at two dilutions (1/250 and 1/1000) in duplicate and all samples from one study day were analysed on the same microtitre plate. Between assay variation of two control plasma samples included in each microtitre plate was 25.7% (CV) at 0.7 μg/ml and 28.8% (CV) at 4.5 μg/ml (n = 20).

The study was approved by the Ethics Committee of the Royal Marsden Hospital and informed parental consent was obtained in all cases.

RESULTS

The median maximum plasma concentrations achieved at 30 min following an i.v. dose or after an oral dose were 22 and 21.4 μg/ml, respectively. Following the oral administration the median time to maximum plasma concentration was 1.25 h. There was no significant difference in the elimination half life of the drug after either route, median $t_{\frac{1}{2}}$ 4.2 and 5.3 h, respectively, for the i.v. and oral route. The median bioavailability was 48% (Table 1 and Fig. 1).

There were essentially no differences between the plasma profiles after either route, although a trend towards a longer elimination $t_{\frac{1}{2}}$ was seen after the oral route. This was not statistically significant.

The duration of plasma concentrations above 1, 5 and 10 μg/ml following either route of administration are shown in Table 1 after either route. Levels > 10 μg/ml were achieved for only a short period of around 3 h. After these single doses of etoposide plasma levels over 1 μg/ml were achieved for 12–24 h in the majority of patients but in a number for less than 12 h.

Table 1. Pharmacokinetic data and duration of plasma concentrations after i.v. and oral administration

		Oral	i.v.
C_{max}		15.5–28.4 μg/ml (μ = 21.4)	79.4–80.1 μg/ml (μ = 22)
t_{max}		0.5–1.5 h (μ = 1.25)	—
$t_{\frac{1}{2}}$		2.3–6.2 h (μ = 5.3)	3.3–8.8 (μ = 4.2)
Bioavailability		35–88% (μ = 48)	
Duration of concentration (μg/ml)	> 1	8–24 h (μ = 14.7)	8–24 h (μ = 14.7)
	> 5	3–11 h (μ = 8.5)	6–17 h (μ = 7.7)
	> 10	0.5–4.3 h (μ = 3.3)	1.5–6.4 h (μ = 2.5)

DISCUSSION

This study was designed to compare plasma etoposide profiles after standard dose administration using the i.v. and oral routes in children. The aim was to confirm studies in adults demonstrating an approximately 50% bioavailability and to document the 24 h serum level profile in children, which may be of relevance with regard to timing of drug administration or the use of repeated low dose daily administration.

Comparable cytotoxic effect can be achieved either by

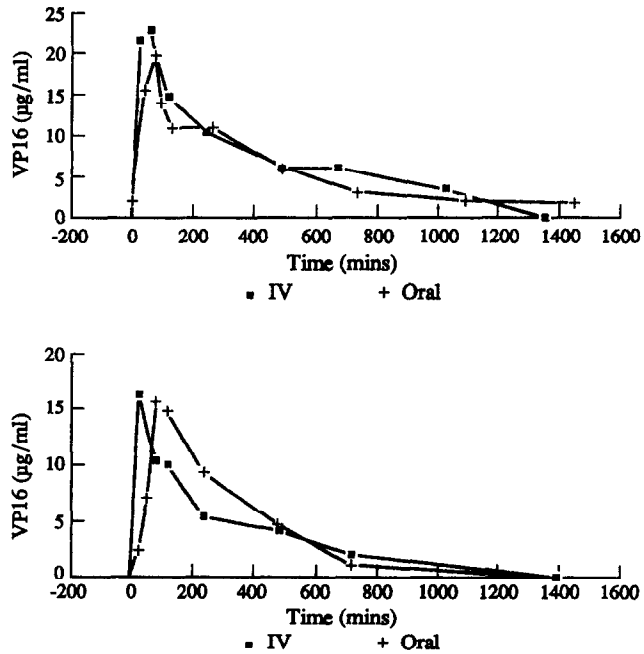

Fig. 1. Plasma etoposide profiles in 2 children after i.v. and oral doses of 150 and 300 mg/m^2, respectively.

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exposure of tumour cells for short duration at high dose drug levels or prolonged exposure at low levels. The critical factor in clinical practice would, therefore, be the comparable toxicity. Clinical studies have suggested that divided dose regimens in small cell lung cancer are of superior efficacy to single high dose administration and the studies of Slevin *et al.* have shown that in small cell lung cancer maintenance of low plasma concentrations of drug is a major factor in efficacy [2, 8, 9].

In attempting to design optimal schedules for etoposide in children it is clearly necessary to obtain baseline pharmacokinetic data using both the parenteral and enteral routes. A small number of previous studies have reported results in children similar to those seen in adults [10–12]. A two compartment first order pharmacokinetic profile is described with an elimination half-life of 5.8 h, volume of distribution of 3.1 l and serum clearance rate of 19.5 ml/min/m^2 [10]. It has been suggested that in children the elimination half-life may be shorter than in adults. This would be consistent with a trend towards higher EDTA clerance in this age group, which has been shown to correlate with etoposide clearance [13]. The elimination half-lives of 5.3 h orally and 4.2 h i.v. in the present study are consistent with previous reports. EDTA clearance was not performed on these children so no comment can be made on the influence of renal function.

A median bioavailability of 48% (range 35–88%) is also consistent with reports in adults. It seems likely that the marked inter and intra patient variability described in adults would also apply in children, making inconsistencies probable with repeated administration [14]. An inverse relationship between dose and bioavailability has been reported suggesting saturability of the absorption mechanism at comparatively low doses. A mean oral bioavailability of around 50% could only be assumed at a total oral dose of less than 300 mg [5] and at 100 mg doses a mean absorption of 86% was found, compared with 45% at 400 mg [4]. Absorption using the i.v. ampoule is reported to be higher than using the oral capsule, although because of the intra patient variability these differences are probably not of clinical relevance. In the paediatric population the use of the i.v. ampoule preparation is preferable as the large capsule is often unpalatable. Moreover, with the i.v. ampoule a more accurate dose in relation to body size can be administered.

The only accurate way of determining the importance of specific plasma drug profiles in paediatric tumours would be to repeat the studies done in small cell lung cancer where different schedules were compared in a randomised fashion and drug levels prospectively determined [15]. From the present study it seems clear that because of the short half-life in children a single daily dose using either oral or i.v. route is unlikely to maintain significant drug levels beyond 12 h in many patients. Unless single very high dose therapy is being given then a twice daily schedule would appear to be advisable.

At the present time the United Kingdom Children's Cancer Study Group is performing a phase II study of 21 day oral low dose etoposide giving 25 mg/m^2 twice daily for 3 weeks. This regimen is designed to achieve consistent low plasma levels above 1 μg/ml, thus mirroring the optimal schedules reported in small cell lung cancer. The present study failed to show any significant difference in the maintenance of serum levels between 1 and 10 μg/ml when either the oral or i.v. route was used. A small number of patients will be too young to tolerate the oral route and repeated i.v. drug administration using 50% of the recommended oral dose is an alternative. Continuous low dose infusion is an alternative, although the volume of fluid required for solubility may make this less practical.

In conclusion, this study has demonstrated comparable serum profiles when etoposide is given orally at twice the i.v. dose. Further large studies are required to clarify the importance of serum drug profiles in paediatric tumours either at very high dose, conventional dose or prolonged low oral doses.

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