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Blood Levels of o,p′-DDD Following Administration in Various Vehicles After a Single Dose and During Long-term Treatment

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Summary. *Plasma levels of o,p′-DDD were measured after ingestion of a single oral dose. At the onset of therapy o,p′-DDD was administered as commercially available tablets and granules and in milk, chocolate, and an oil emulsion to 9, 12, 14, 10, and 6 patients, respectively. Following administration in chocolate, emulsion, and milk significantly higher mean plasma levels were recorded in the first 5- and 10-h periods than after tablets. Granules gave significantly lower plasma levels than all other forms.*

Plasma levels were also measured during maintenance therapy, when a total of 200 g o,p′-DDD was administered to 22 patients with adrenocortical carcinoma. The plasma disappearance rate after termination of long-term therapy was found to be between 18 and 159 days.

The recovery of o,p′-DDD from faeces was about five times higher after ingestion of tablets than after administration in oil emulsion and milk.

As far as the rapid increase in plasma levels and patient compliance are concerned, the best results were obtained with the milk powder mixture.

Introduction

2,2-Bis (2-chlorophenyl, 4′-chlorophenyl) 1,1-dichloroethane (o,p′-DDD) was introduced in 1959 by Bergenstal et al. [3] as a chemotherapeutic agent for use in disseminated adrenocortical cancer (ACC).

Several authors have reported varying results with this drug in large series of patients [5, 6]. Temple et al. [14] and Bar-Hay et al. [2] successfully treated patients with pituitary-dependent Cushing's syndrome with commercially available tablets. However, the gastrointestinal side-effects were severe. Luton et al. [7] reported good results and fewer side-effects with enteric-coated, gastric-resistant granules.

Measurement of the plasma levels after the use of o,p′-DDD has seldom been reported. Moolenaar and van Seters [8] found a wide variation in the plasma levels after administration in tablets, and serious central nervous system symptoms when high plasma levels were reached. The side-effects of o,p′-DDD after oral ingestion seem to be partly related to a direct effect on the gastrointestinal tract [4, 7]. Other side-effects, especially the cerebral symptoms, are probably associated with the level of the plasma concentration [8]. Hogan et al. [4] also demonstrated a relation between toxic effects and plasma levels. In one patient, Moy [10] established that the tissue levels of o,p′-DDD were not related to the effect of tumour growth. In our previous study, however, the plasma levels do seem to correlate with the effect of tumour growth [8].

The experiments of Nissen-Meyer and Vogt [11] and Moolenaar and van Seters [8] also indicate that when o,p′-DDD was given as tablets lower plasma levels resulted than when it was administered in oil emulsion. These experiments indicate that the administration of this highly lipophilic drug in a fat-containing vehicle improves resorption. The solubility of o,p′-DDD in water is negligible, while it is about 10% soluble in oil or fat [12]. These facts led us to compare the plasma levels of o,p′-DDD after a standard dose given in various vehicles. We also investigated the plasma levels during long-term treatment. As an additional parameter for resorption we estimated faecal loss of o,p′-DDD after the administration in various forms. We also investigated the effect of the various vehicles on the gastrointestinal side-effects.

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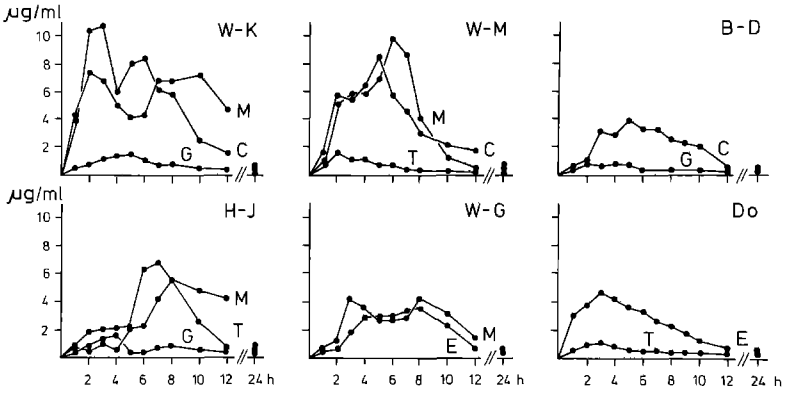

Fig. 1. Plasma o,p'-DDD levels in six patients after one oral dose of 2 g o,p'-DDD in various vehicles. M, milk; C, chocolate; G, granules; T, tablets; E, emulsion

Materials and Methods

All patients had been admitted to the Dept of Endocrinology of the University Hospital, Leiden, for treatment of ACC or pituitary-dependent Cushing's syndrome. The o,p'-DDD levels were estimated according to the method of Moolenaar et al. [9]. The drug was administered as a single dose of 2 g at 8.00 a.m. while the patients were in the fasting state.

Blood samples were taken frequently via an indwelling needle for the first 10 h, and also at 12 and 24 h after administration. Five vehicles were used: commercially available tablets (Mitotane; referred to below as tablets); enteric-coated gastric-resistant granules in capsules (gift of Roussel, France, granules); a mixture of powdered Mitotane tablets and a powder composed of 70% vegetable fat and 30% fat-free milk powder (D.V.M. Veghel, Holland), administered in water (milk); a mixture of 1 g o,p'-DDD (Sigma) and 9 g melted chocolate (Callabaut, Belgium) (Chocolate); and 12 g peanut oil and 15 g water emulsified with arabic gum (emulsion). The various batches of o,p'-DDD were checked for purity.

In total 19 patients were included in the study, and ten patients received o,p'-DDD in two or more forms. The numbers of patients receiving tablets, granules, milk, chocolate, and emulsion were, respectively, 9, 12, 14, 10, and 6. In the long-term study we compared the plasma values in 22 patients after a total dose of 200 g o,p'-DDD in tablets, emulsion, and milk, administered over 30–60 days. These patients were often part of the same group as was used for the one-dose experiments. Samples were obtained at least 12 h after the preceding dose.

Faeces was collected in 4 to 7-day periods during maintenance therapy. The individual daily dose was between 1.75 and 4 g o,p'-DDD. Faecal recovery of o,p'-DDD was calculated as a percentage of the daily dose. All patients gave oral consent for their inclusion in this study. Statistical analysis was performed according to the multiple comparison method as described by Armitage [1].

Results

In Fig. 1, the plasma levels of o,p'-DDD are shown for the six patients who received it in different forms. Maximum o,p'-DDD plasma levels, varying between 1.5 and 11.5 µg/ml, were reached between 2 and 8 h after oral ingestion of the drug. Most of the curves showed more than one maximum.

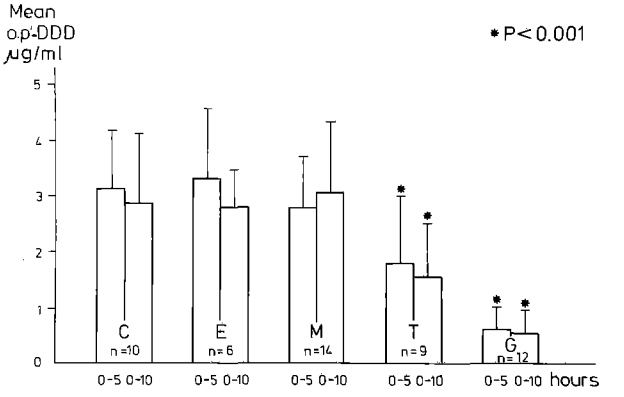

Fig. 2. Mean plasma levels (± S. D.) in the first 5- and 10-h periods after one oral dose of 2 g o,p'-DDD in various vehicles. M, milk; C, chocolate; G, granules; T, tablets; E, emulsion. G* < T* < C, E, and M

To compare the plasma levels obtained after administration of o,p'-DDD in various vehicles, we calculated the mean plasma levels for the first 5- and 10-h periods by estimation of the surface under the plasma curves (Fig. 2). These values were not significantly different for chocolate, emulsion, and milk. The values for tablets were significantly lower than those for chocolate, emulsion, and milk ($p < 0.001$), but higher than those for granules ($p < 0.001$). After granules, plasma levels were significantly lower than after the other application forms ($p < 0.001$). After this single dose of o,p'-DDD, patients complained of nausea and borborygmus when the drug was administered in chocolate or emulsion. These complaints were not observed when the other vehicles were used.

During long-term treatment with a total dose of 200 g o,p'-DDD, plasma levels for milk were not significantly higher than those for emulsion. The levels for tablets were again significantly lower than those for emulsion and milk (Fig. 3) ($p < 0.01$ and $p = 0.02$). Calculation of the plasma disappearance

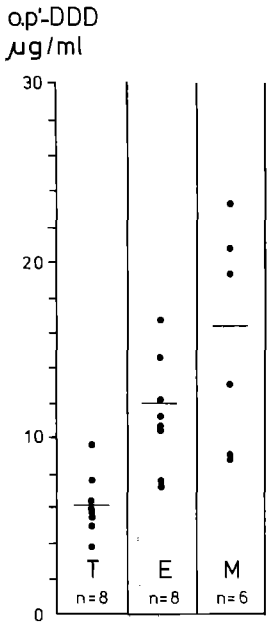

Fig. 3. Plasma levels reached after a total dose of 200 g o,p'-DDD in various vehicles. M, milk; T, tablets; E, emulsion. T < E ($P < 0.01$) E < M($P = 0.02$)

Table 1. Plasma disappearance rate (T_L ½) after withdrawal of o,p'-DDD medication in seven patients

Patient	Day of drug withdrawal	r	n[a]	T_L ½ (days)
1	48	−0.9787	5	18
2	260	−0.9961	5	40
3	93	−0.9693	17	48
4	70	−0.9784	11	53
5	190	−0.9963	6	60
6	160	−0.9409	6	81
7	241	−0.9716	9	159

[a] n, number of o,p'-DDD estimations

Table 2. Recovery of o,p'-DDD from faeces during long-term medication at a constant dose level of o,p'-DDD in various vehicles

n	Vehicle	Recovery in faeces (% of dose)	
		Individual data	Mean ± SD
9	Emulsion	6.7-8.7-4.1-7.5-5.1 8.6-3.3-4.1-9.0	6.1 ± 2.1
6	Tablets	37-40-36-58-48-29	41.3 ± 9.3
5	Milk	33[a]-2-1-3-4	8.6 ± 12.2

[a] Diarrhoea during collection period

rate after one dose on o,p'-DDD (T_S½) is complicated by the presence of more than one maximum, probably caused by delayed emptying of the stomach. T_S½ was found to be approximately 120–180 min.

In seven patients the plasma disappearance rate after withdrawal of o,p'-DDD medication (T_L½) could be measured (Table 1). We found a T_L½ between 18 and 159 days (Table 1). In Table 2 the faecal excretion of o,p'-DDD after ingestion in various vehicles is presented. With tablets, about 40% of the ingested dose could be recovered from the faeces, whereas following in milk and emulsion the o,p'-DDD excretion was less than 10%.

Discussion

The results described in the literature for o,p'-DDD treatment patients with ACC are difficult to compare, due to the variation in natural history of the tumour, lack of knowledge regarding the effective doses of o,p'-DDD, and low patient compliance to the drug. Because of the irregular individual plasma curves, the mean plasma levels over the first 5- and 10-h periods were computed. According to this criterion, significant differences existed among chocolate, emulsion, and milk. Tablets did not lead to significantly lower levels as a result of a lower absorption from the gut (Table 2). However, our gas chromatographic method does not allow us to exclude faecal loss of dechlorinated or methylated metabolites [13]. After granules lower values were obtained than after tablets. When patients were studied after ingestion of a total dose of 200 g o,p'-DDD, the plasma levels reached after tablets, emulsion, and milk differed. The highest values were reached after milk and the lowest after tablets. An explanation for the discrepancy from the results of short-term studies can be found in the better patient compliance and fewer complaints of diarrhoea when the vehicle is milk rather than emulsion.

The results represented in Table 2 indicate that there is hardly any difference in resorption of o,p'-DDD between emulsion and milk. Some patients suffered continuously from severe gastrointestinal side-effects resulting in low therapy compliance and poor resorption of o,p'-DDD due to diarrhoea (see footnote to Table 2).

In these patients high levels could not be obtained in spite of good initial resorption. Because the highest levels of o,p'-DDD were found after administration of the drug in milk powder and the side-effects when this vehicle was used were acceptable, we recommend

the following schedule to saturate the adipose tissue depots as soon as possible:

The therapy is started with 4–10 g o,p'-DDD per day in three or four equal doses administered as a milk powder mixture. When the plasma level exceeds 20 μg/ml a higher frequency of administration and a lower daily dose may prevent toxic peak levels.

The drug can be made more palatable by mixing the milk powder with a flavour such as lemonade. Sometimes it is practical to prescribe the chocolate formula as an alternative. For long-term therapy tablets can be used as well as granules and milk powder.

During maintenance therapy the plasma levels of o,p'-DDD should be monitored regularly, to avoid both over- and undertreatment.

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