Cancer Chemother Pharmacol (1986) 16: 264–268

Cancer Chemotherapy and Pharmacology



# Relation between dose, plasma concentration and toxicity in a phase I trial using high dose intermittent administration of an alkylating agent, diacetyldianhydrogalactitol (DADAG)*

**S. Kerpel-Fronius[1], V. Erdélyi-Tóth[1], F. Gyergyay[1], I. Hindy[1], Z. Mechl[2], M. Nekulová[2], S. Somfai-Relle[3], P. Kovács[4], Gy. Ujj[4], B. Kanyár[5], and S. Eckhardt[1]**

[1] National Institute of Oncology, P. O. Box 21, H-1525 Budapest, Hungary
[2] Research Institute of Clinical and Experimental Oncology, 60200 Brno, Czechoslovakia
[3] Research Institute of Oncopathology, H-1525 Budapest, Hungary
[4] Department of Pharmacology, University Medical School of Debrecen, H-4012 Debrecen, Hungary
[5] National Research Institute for Radiobiology and Radiohygiene, H-1089 Budapest, Hungary

**Summary.** Diacetyldianhydrogalactitol (DADAG), a new alkylating sugar alcohol derivative, was administered as single, 30-min infusions in doses ranging from 390 to 1200 mg/m$^2$. The dose-limiting toxicity was myelosuppression. The median times to WBC nadir and regeneration were 16 and 21 days, and to platelet nadir and recovery 20 and 27, respectively. Nausea and vomiting occurred frequently and were of moderate severity. For phase II studies 900 mg/m$^2$ DADAG given every 4–6 weeks is recommended. The area under the plasma concentration time curve (AUC) for DADAG did not increase in proportion with dose escalation; it changed only from 235.5 ± 70.7 to 262.4 ± 71.5 μg h ml$^{-1}$ between doses of 690 and 1050 mg/m$^2$. No correlations between the dose administered and the nadir values for haemoglobin concentration, WBC and platelet counts, or the number of episodes of vomiting were demonstrable in this dose range. Such an association was revealed, however, when the above biological variables were related to the individual AUC for DADAG.

## Introduction

DADAG (1,2:5,6-dianhydro-3,4-diacetyl-galactitol (Fig. 1) is a new alkylating sugar alcohol derivative synthesized in Hungary [10, 16]. Dibromodulcitol was the first substance in this group that was found to be effective against solid tumours. Mammary, head and neck, cervical, bronchial, and brain tumours were found to be especially sensitive [2, 5, 7, 8, 9, 15]. Its pharmacologically most active metabolite, dianhydrogalactitol (DAG), proved to be too toxic in clinical studies [2, 11]. The 3- and 4-substituted analogues of DAG retained the antitumour activity but proved to be less toxic [10]. The most promising member of this series, DADAG, exhibited a higher therapeutic index than either DBD or DAG in Walker tumour and in Harding-Passey and B-16 melanomas [1, 18]. In addition, the drug easily penetrated the blood brain barrier and was effective against intracerebrally inoculated ependymoblastoma according to the data of the EORTC Screening Group [1].

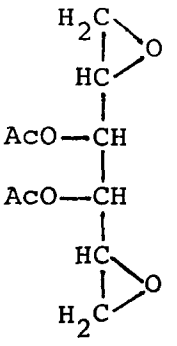


**Fig. 1.** Chemical structure of 1,2:5,6-dianhydro-3,3-diacetyl-galactitol (DADAG)

Bone marrow impairment was recognized as the main toxicity.

A human tolerance study undertaken with low doses administered for 5 consecutive days proved to be well tolerated, but produced an unsightly long-lasting discoloration over the veins used repeatedly for drug infusions. Functional damage was not observed. The dose-limiting toxicity was the inhibition of granulocytopoiesis; in severe cases the nadir and regeneration occurred late, on days 30 and 35, respectively [12].

In the toxicological studies carried out according to the guidelines of the CMEA (Council of Mutual Economic Assistance), for cancer cooperation [3], daily doses approximately 2–3 times higher could be administered to both rats and dogs when an intermittent administration schedule was used, with essentially the same side effects [1]. Moreover, antitumour activity was not schedule-dependent. It seemed to be important to study the toxicity and the time course of myelosuppression in humans also with single, high doses. It was hoped that the vascular toxicity could be overcome by decreasing the number of drug infusions. For the new trial the highest tolerable daily dose with the 5-day schedule, 390 mg/m$^2$, was selected as the starting dose [12]. In addition, DADAG and DAG concentrations were measured in several patients, to look for possible correlations between the plasma levels of the parent compound and its main metabolite DAG and also between the pharmacodynamic effects and the AUCs for DADAG and DAG.

* Supported in part by grants from the following organizations: State Office of Technical Development, Medical Research Board, Chinoin Pharmaceutical and Chemical Works

*Offprint requests to:* S. Kerpel-Fronius

## Patients and methods

The phase I study was carried out in close cooperation between the oncologic institutes of Budapest and Brno, according to a protocol accepted by the ethical committees of both. Altogether 25 patients entered the trial, all having histologically verified malignancies. The administration of DADAG was decided upon if no benefit was expected from conventional therapy and at least 1 month had elapsed between the termination of the last radio- or chemotherapy. The patients were all younger than 70 years and had a life expectancy of at least 2 months. Further requirements were the absence of severe cardiorespiratory troubles, and serum bilirubin and creatinine levels lower than 25 and 130 μmol/l, respectively. The WBC and platelet counts were required to be equal to or over $4 \times 10^9$/l and $100 \times 10^9$/l. At least two subjects were examined at each dose. Patients were treated again at the same or a higher dose if they fulfilled the entrance criteria at the start of the new DADAG administration. A minimum of 4 weeks was required to elapse after each cycle before the next. The dose was increased only in 30% increments and the amount of the increment was reduced to 15% if mild or more severe haematotoxicity was encountered in at least two patients at the last evaluated dose.

WBC, platelet and differential counts were performed before the trial, twice weekly in the 1st and 2nd weeks after drug administration, and later once a week. Haemoglobin, haematocrit, serum creatinine, urea nitrogen, bilirubin, transaminases, gamma-glutamyl-transpeptidase (GGTP), alkaline phosphatase (ALP), total protein, calcium, phosphorus, potassium, sodium, and chloride levels were determined before treatment and at the end of the 1st and 2nd weeks. A complete clinical and laboratory check-up was made 4–6 weeks after drug infusion. Performance status and therapeutic and toxic effects were evaluated according to the WHO recommendations [14].

DADAG was made available by the Chinoin Pharmaceutical and Chemical Works as a white, freeze-dried powder. The 50 mg drug contained in each ampoule was dissolved in 10 ml saline and diluted further with 300–500 ml saline, then infused over 30 min. During infusions the patients were connected to cardiac monitors. Measurements of ECG parameters were taken before and after infusion. The severity of nausea and the number of episodes of vomiting were followed on the basis of self-reporting on data sheets given to the patients. At the time of the first exposure to DADAG no antiemetic therapy was given. If the patient had vomited during the first exposure to DADAG, 1 ampoule of Torecan (6.5 mg thioethylperazin) was given before and after drug infusion in subsequent cycles.

In subjects treated in Budapest, plasma levels of both DADAG and DAG were determined in samples taken before, immediately after, and then 30, 60, 90, 120, 150, and 180 min and 24 h after the infusion. These time points were necessary to measure the maximum concentrations of both DADAG and DAG, the latter occurring 60–120 min after the termination of DADAG infusion. The value measured at 24 h was regarded as the minimum value, while the average of the maximum and minimum concentrations was called the daily mean plasma concentration. The areas under the curve (AUC) from 0 to 24 h were calculated for both DADAG and DAG by the trapezoidal rule. The analytical method and the pharmacokinetic behaviour of DADAG are described in more detail by Erdélyi-Tóth et al. [6]. In short, 5-ml blood samples were each immediately mixed with 50 μl heparin and 100 μl 100 mg% eserine (Physostigmine, Fluka). The latter was added to block deacetylation of the drug in vitro. DADAG and DAG were trapped on an Amberlite XAD-2 resin (Serva) column and were eluted with ethyl acetate and methanol. DAG was derivatized with *n*-butaneboronic acid. GLC was performed with a CHROM 42 (Kovo) gas chromatograph equipped with FID, on a GAS CHROM Q/SE 30 column. The detection limits were 0.5 μg/ml for DADAG and 0.8–1 μg/ml for DAG. All measurements were done in the linear range. The coefficient of variation was 5%.

For estimation of the sensitivity of GM-$CFU_c$ (granulocyte-macrophage colony-forming cells in cell culture), bone marrow cells of BALB (cxCBA) $F_1$ mice were exposed to the drugs in a liquid medium at 37 °C for 60 min. Surviving GM-$CFU_c$ were estimated in soft agar cultures. Human bone marrow cells were obtained from patients undergoing bone marrow aspiration for diagnostic purposes [19].

The pharmacokinetic and biological parameters measured at the different doses were compared with the Kruskal-Wallis one-way analysis of variance by ranks [17]. Association between these parameters were tested with the Spearman rank correlation test [17]. The difference between related correlations was assayed by the Hotelling *t*-test [20].

## Results

The mean age of the patients in this trial was 50 years, the youngest and oldest being 27 and 68 years old, respectively. Of the 25 patients, 13 were women and 12 were men. The median performance status was 2 (1–4) indicating that the majority of patients spent less than 50% of their waking h in bed. The distribution of cases by tumor type was as follows: 6 melanomas, 5 cervical, 1 ovarian, 2 breast, 2 lung, 1 gallbladder, 1 renal, and 2 embryonal carcinomas, 1 haemangiopericytoma, and 4 sarcomas. Six patients had had no previous treatment, 4 had been irradiated, 1 had received endocrine treatment, and 10, chemotherapy. Combined-modality treatment had been given in 4 cases. None of the subjects had been pretreated with either mitomycin C or nitrosoureas.

The following DADAG doses were studied: 390, 525, 690, 915, 1050, and 1200 mg/$m^2$. Altogether 40 cycles were evaluated. One patient received 4, twelve 2, and all the others, 1 course. The highest cumulative dose of 5185 mg/$m^2$ was reached in a patient whose treatment was started with the daily low-dose schedule.

The main side effect was haematotoxicity (Table 1). Decrease of the red blood cell (RBC) count or haematocrit value together with the haemoglobin level below 6.8 mmol/l was encountered in 19 cycles. The median initial haemoglobin concentration of 7.9 mmol/l (6.8–9.7) fell to 5.9 (3.6–6.6) mmol/l at day 15 (5–24). Recovery time was not calculated since the patients received transfusions as required.

Decrease of WBC count below $4 \times 10^9$/l also occurred in 19 cycles (Table 1). In the clinically relevant dose range between 690 and 1050 mg/$m^2$ the median WBC nadir in these cycles was 2.8 (0.4–3.9) $\times 10^9$/l. Only in 3 cycles were the values below $1 \times 10^9$/l. Nadir and regeneration occurred on days 16 (4–33) and 21 (11–36), respectively.

**Table 1.** Frequency and severity of toxicity according to dose

| Dose mg/m² | Haemoglobin | | WBC | | Platelets | | Nausea/vomiting | |
|---|---|---|---|---|---|---|---|---|
| 390 | 0/2 | – | 0/2 | – | 0/2 | – | 0/2 | – |
| 525 | 2/5 | 1.5 (1–2) | 2/5 | 1 (1) | 0/5 | – | 3/5 | 2 (1–2) |
| 690 | 5/11 | 2 (1–3) | 5/11 | 2 (1–2) | 3/11 | 2 (2) | 9/11 | 2 (1–3) |
| 915 | 8/13 | 3 (1–4) | 6/13 | 2 (1–4) | 3/13 | 3 (1–4) | 11/13 | 2 (1–4) |
| 1050 | 3/8 | 3 (1–2) | 5/8 | 1 (1–4) | 2/8 | 1 (1–3) | 7/8 | 2 (1–2) |
| 1200 | 1/2 | 1 | 1/1 | 3 | 0/1 | – | 1/1 | 4 |

The number of courses with toxicity divided by all courses evaluated at the given dose level are shown at the left of each column, while on the right the median and the range of the WHO severity scores are given for the toxic cycles

Both granulocytes and lymphocytes were affected by the drug. However, the decrease and regeneration of lymphocyte count occurred before similar changes in the granulocyte series. A decrease of platelet count was seen altogether in 9 cycles (Table 1). In these cycles the median of the nadir was 70 $(20-90) \times 10^9$/l, only 3 values being below $50 \times 10^9$/l. The nadir and regeneration occurred late, on days 20 (12–32) and 27 (23–45), respectively.

Nausea and vomiting of moderate severity (WHO grade 2) occurred in the majority of cycles (Table 1). The median number of episodes of vomiting was 6 (0–25), and the nausea was rated by the patients as moderately intensive. Gastrointestinal disturbances started 2–3 h after the start of the infusion, and lasted for 4–6 h. Torecan given before and after the infusion and then after the start of vomiting was not effective. Diarrhea was noted in 3 cycles at dose levels of 915 and 1050 mg/m². Reversible increases of LDH activity were occasionally measured, while the elevation of hepatic enzyme activities occurred only once. There was bleeding from the tumor in four cases. In one patient decoloration over the vein was seen after the infusion. If extravasation occurred it caused moderate to severe local irritation. ECG and blood pressure did not change, except in one patient after the 5th and 6th cycles, when extrasystoles were seen after infusion, which disappeared without treatment within the next few days. Anorexia and weakness were reported by the patients repeatedly.

Among the 25 cases 1 partial remission of short duration was seen, in a patient suffering from melanoblastoma. Moderate remission (25%–50%) occurred in another patient with hypernephroma, while stabilization of two cases of cervical and one of epidermoid lung cancer was observed.

The plasma concentrations and the AUC of both DADAG and its main metabolite DAG increased only slightly with dose escalation; for example the AUC of DADAG changed only from $235 \pm 70.7$ to $262.4 \pm 71.5$ μg h/ml$^{-1}$ when the dose of DADAG was raised from 690 to 1050 mg/m² (Table 2). Similarly, the alterations in the haemoglobin concentration, WBC and platelet counts, and the number of episodes of vomiting did not follow the rate of dose escalation (Table 2). One-way analysis of variance failed to reveal any significant differences with dose level in any of the pharmacokinetic and biological variables.

**Table 2.** Toxic parameters, DADAG and DAG plasma values according to dose (Means ± SD)

| Dose mg/m² | | 525 | 690 | 915 | 1050 |
|---|---|---|---|---|---|
| Number of cycles | | 1 | 6 | 8 | 5 |
| DADAG[a] | | | | | |
| Maximum concentration | (μg/ml) | 62.7 | 54.4 ± 11.3 | 43.8 ± 12.4 | 66.6 ± 13.0 |
| Mean daily concentration | (μg/ml) | 33.3 | 30.4 ± 6.2 | 25.2 ± 6.6 | 37.3 ± 6.7 |
| AUC | (μg h$^{-1}$ ml$^{-1}$) | 97 | 235.5 ± 70.7 | 224.3 ± 87.0 | 262.4 ± 71.5 |
| DAG[a] | | | | | |
| Maximum concentration | (μg/ml) | 3.6 | 4.1 ± 2.2 | 3.4 ± 1.9 | 4.5 ± 1.6 |
| Mean daily concentration | (μg/ml) | 2.1 | 2.8 ± 1.2 | 2.1 ± 1.3 | 3.2 ± 0.5 |
| AUC | (μg h$^{-1}$ ml$^{-1}$) | 22 | 32.7 ± 11.2 | 34.0 ± 18.9 | 39.4 ± 9.5 |
| Nadir of haemoglobin concentration[b] | (mmol/l) | 4.6 | 7.9 ± 1.2 | 6.1 ± 1.3 | 7.5 ± 1.2 |
| Nadir of WBC count[b] | ($\times 10^9$/l) | 4.2 | 3.5 ± 1.3 | 2.9 ± 1.7 | 4.0 ± 1.2 |
| Nadir of platelet count[b] | ($\times 10^9$/l) | 160 | 130.0 ± 71.3 | 146.3 ± 82.6 | 124.0 ± 58.6 |
| Number of episodes of vomiting | | 5 | 10.7 ± 9.3 | 7.9 ± 7.6 | 4.0 ± 4.0 |

[a] Daily maximum and minimum concentrations of DADAG are those measured immediately and 24 h after the termination of the infusion; their average is referred to as the mean daily concentration. For DAG the maximum was selected from serial measurements

[b] The lowest values observed for haemoglobin concentration and WBC and platelet counts during the cycle were given irrespective of whether they were above or below the WHO specified toxicity threshold. Only those cycles were considered for which all the listed parameters were available

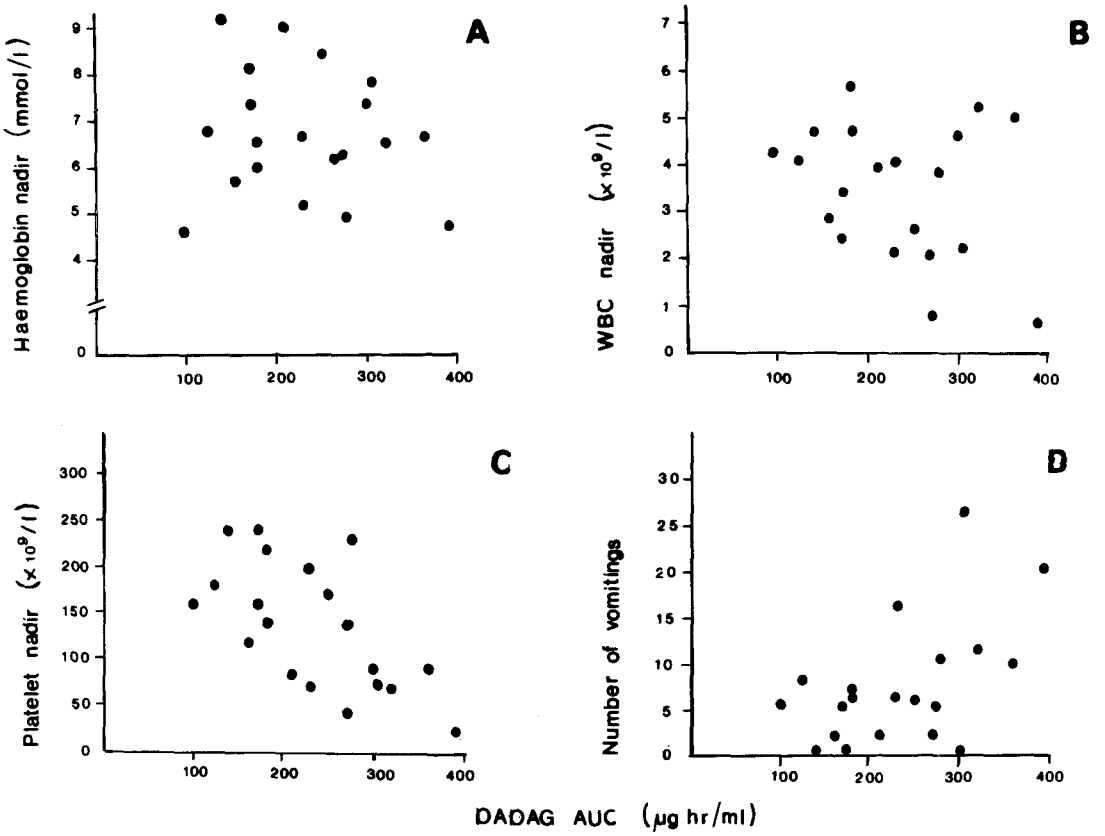


**Fig. 2 A–D.** The distribution of toxicity parameters according to the AUC of DADAG. The Spearman rank correlation coefficient ($R_s$) and the level of significance are given for each panel. **A** nadir of hemoglobin concentration, $R_s = -0.17$, not significant. **B** nadir of WBC count, $R_s = -0.19$, not significant. **C** nadir of platelet count, $R_s = -0.594$, $P < 0.01$. **D** number of episodes of vomiting, $R_s = 0.51$, $P < 0.05$

Because of the wide personal variations we attempted to correlate the toxicity and drug levels in individual patients irrespective of the dose given (Fig. 2). The severity of all side effects became more pronounced with increasing AUC of DADAG, but the Spearman rank correlation was only significant in the cases of the platelet nadir ($R_s = -0.594$, $P < 0.01$) and the number of episodes of vomiting ($R_s = 0.51$, $P < 0.05$). The relation between the AUC of DADAG and DAG was also significant ($R_s = 0.46$, $P < 0.05$). Consequently it is not surprising that there were no statistical differences between the correlations relating the toxic effects to the AUC of DADAG and those established between the same pharmacodynamic effects and the AUC of DAG. Finally, similar correlations were obtained when the daily mean plasma level of either DADAG or DAG was used as reference instead of the AUC.

## Discussion

In this study the maximum tolerated dose with predictable, severe toxicity was not reached. Several considerations prompted us to decide against further dose escalation. First of all, the myelotoxicity seems to be cumulative. One of the patients developed a life-threatening drop of both WBC and platelet counts after a cumulative dose of 5815 mg/m$^2$. It was even more disturbing that in two patients, who entered the trial without pretreatment at 1050 mg/m$^2$, WBC nadirs of $2 \times 10^9$/l and $3 \times 10^9$/l were seen after the second cycle. A third, heavily pretreated woman required WBC and platelet transfusions for a prolonged period even after the first infusion of 1050 mg/m$^2$ DADAG. The only patient to whom 1200 mg/m$^2$ was infused, who died shortly thereafter, had a WBC count of $1.8 \times 10^9$/l. It is evident that with 900–1000 mg/m$^2$ a dose range of crucial importance was reached, where differences in drug metabolism, bone marrow reserve, etc. might cause serious toxicity. The correctness of our decision was proven in the course of our ongoing therapeutic trial, in which up to ten infusions of 900 mg/m$^2$ could be successfully given with acceptable side effects.

The dose acceptable for clinical practice turned out to be higher than expected. In rats and dogs cumulative doses three to five times higher could be given when they were divided over 5 consecutive days [1]. Similar findings were reported by Kovács et al. [13], who found that in mice the exponential part of the dose response curves relating the surviving fraction of GM-CFU$_c$ to DADAG or DAG doses decreased more rapidly after single than after repeated in vivo administrations. Consequently, when divided doses were given over 5 consecutive days approximately three times more drug was needed to decrease the GM-CFU$_c$ content of the bone marrow by 50%. In humans, the maximum tolerated daily dose with the 5-day schedule was 390 mg/m$^2$, giving a total dose per cycle of 1950 mg/m$^2$ [12]. Consequently, the tolerated daily dose with high-dose intermittent administration was calculated at 600–700 mg/m$^2$. This assumption was further supported by the steep dose response curve of the in vitro-treated human GM-CFU$_c$ [19]. Fifty percent inhibition of colony forming was caused even by as little as 25 µg/ml DADAG,

which corresponded to the daily mean plasma concentration measured after the administration of 390 mg/m$^2$ DADAG [12]. Doubling this concentration decreased the number of surviving precursor cells to about 5%. It was thus surprising to find that following an almost threefold increase of the daily dose the frequency and severity of myelotoxicity changed only slightly.

The explanation was offered by the plasma level measurements. In spite of the considerable individual variations in drug metabolism, which must be expected in an unselected group of patients receiving various supportive medication, it is clearly evident that neither the plasma concentrations nor the AUC of DAG and DAG increased in parallel with the dose escalation. The drug shows dose-dependent pharmacokinetics over a daily dose of 300–400 mg/m$^2$, as described in the companion paper to this [6]. In the dose range of 690–1050 mg/m$^2$, which was studied extensively in this trial, the individual plasma concentration differences measured after the same DADAG dose were larger than those related to dose escalation. Therefore, it is not surprising that no significant differences could be revealed between the biological effects of the various doses. Nevertheless, the pharmacologic effects are related to the plasma concentration of the drug, as proven by the significant correlation of the AUC of both DADAG and DAG with the nadir of the platelet count and the number of episodes of vomiting. The weaker correlation with the haemoglobin and WBC nadirs can probably be explained by the interference of steroid therapy and transfusions.

DADAG concentrations equal to the daily mean plasma concentration range ($30.4 \pm 6.2$ to $37.3 \pm 6.7$ μg/ml) measured after the administration of 690–1050 mg/m$^2$ DADAG caused a 70%–80% decrease in the surviving fraction of GM-CFU$_c$ if added to human bone marrow cells in vitro for 60 min. The concentration corresponding to the maximum plasma level reduced the surviving fraction to less than 5% [19]. Under similar in vitro conditions the concentrations equal to the mean and peak plasma levels of DAG reduced the surviving fraction of human GM-CFU$_c$ to about 30% and 70%, respectively. The maximum DAG levels measured in our study are very close to those reported by Eagen et al. [4], who administered two split DAG doses in the range of 60–72.5 mg/m$^2$ 1 h apart, i.e., 120–145 mg/m$^2$ total dose. As in our results, myelotoxicity was the dose-limiting toxicity and there was no correlation between the dose and the plasma concentration of DAG. Since both DADAG and DAG plasma levels show the same degree of correlation with toxicity and both are active in vitro against human bone marrow cells, it is not apparent whether DADAG alone, DAG alone, or the combination of the two is responsible for the pharmacodynamic events. Moreover, it is not known how accurately the intracellular concentrations of DADAG and DAG are reflected by the plasma level measurements.

In view of the pharmacodynamic and pharmacokinetic properties of DADAG, a dose of 900 mg/m$^2$ infused over 30 min is recommended for phase II studies. Drug doses should be separated by intervals of at least 4 weeks, because of the slow regeneration of the bone marrow. If this regeneration is not complete by the time the next dose is due, further drug administration should be delayed until the whole dose can be given. Dose reduction to 690 mg/m$^2$ is not recommended because of the lack of correlation between the dose given and the plasma concentration of the drug.

*Acknowledgements.* The authors wish to express their deep gratitude for the devoted technical and secretarial work of Mrs. J. Bódi, J. Kudász, E. Marik, E. Rozsnyai-Czapkó, and K. Szigeti.

## References

1. Chinoin Documentation (1979) Preclinical pharmacologic and toxicologic documentation of diacetyl-dianhydrogalactitol
2. Chiuten DF, Rosencweig M, Von Hoff DD, Muggia FM (1981) Clinical trials with the hexitol derivatives in the US. Cancer 47: 442
3. CMEA (1976) Recommended documentation on new cytostatic agents for joint CMEA clinical trials (1976) Antitumour Drug Therapy Reports 2: 143
4. Eagen RT, Ames MM, Powis G, Kovach JS (1982) Clinical and pharmacologic evaluation of split-dose intermittent therapy with dianhydrogalactitol. Cancer Treat Rep 66: 283
5. Eckhardt S, Hindy I (1982) Clinical investigations. In: Eckhardt S (ed) Dibromodulcitol. Medicina, Budapest, p 167
6. Erdélyi-Tóth V, Kerpel-Fronius S, Kanyár B, Eckhardt S (1985) Pharmacokinetic study in a phase I trial with an alkylating agent, diacetyldianhydrogalactitol (DADAG) Cancer Chemother Pharmacol (in press)
7. Hindy I, Szándó J, Bodrogi I, Farkas E, Eckhardt S (1980) Forms and results of Mitolactol therapy. Oncology 37 [Suppl 1]: 115
8. Horváth IP (1982) The pharmacokinetics and metabolism of dibromodulcitol. In: Eckhardt S (ed) Dibromodulcitol. Medicina, Budapest, p 131
9. Horváth IP, Cseténvi J, Hindy I, Kerpel-Fronius S, Institóris L, Hegedüs L, Eckhardt S (1982) Metabolism and pharmacokinetics of dibromodulcitol (DBD, NSC-104800) in man: II. Pharmacokinetics of DBD. Eur J Cancer Clin Oncol 18: 1211
10. Institóris L (1982) Chemical consideration in the research of DBD. In: Eckhardt S (ed) Dibromodulcitol. Medicina, Budapest, p 11
11. Kerpel-Fronius S (1982) Hungarian anticancer drugs. Ther Hung 30: 110
12. Kerpel-Fronius S, Erdélyi-Tóth V, Gyergyay F, Baki M, Hindy I, Kanyár B, Eckhardt S (1983) Phase I study of diacetyldianhydrogalactitol (DADAG) with two administration schedules. 2nd European Conference on Clinical Oncology and Cancer Nursing. Amsterdam 06–36, p 67
13. Kovács P, Ujj Gy, Hernádi F, Institóris L, Institóris L Jr, Kerpel-Fronius S (1981) Effect of cytostatic hexitols on murine granulocyte-macrophage colony forming cells (CFU$_c$): comparison of dose effect curves. Exp Hematol 9 [Suppl 9]: 137
14. Miller AB, Hoogstraten B, Staquet M, Winkler A (1981) Reporting results of cancer treatment. Cancer 47: 207
15. Mischler NE, Earhart RH, Carr B, Tormey DC (1979) Dibromodulcitol: A review. Cancer Treat Rev 6: 191
16. Sellei C, Eckhardt S, Németh L (1970) Chemotherapy of neoplastic diseases. Akadémiai Kiadó, Budapest
17. Siegel S (1956) Nonparametric statistics for the behavioral sciences. McGraw-Hill Kogakusha, Tokyo
18. Somfai-Relle S, Gáti E, Bencze J, Gál F (1978) New derivatives of dianhydrogalactitol (NSC-132313) with significant antitumour activity. In: Siegenthaler W, Lüthy R (eds) Current chemotherapy, vol II. American Society of Microbiologists, Washington, p 1302
19. Ujj Gy, Kovács P, Kiss A, Hernádi F, Rák K (1983) The effect of dianhydrodulcitol and diacetyl-dianhydrodulcitol on the granulopoietic progenitor cells of human bone marrow. (In Hungarian) Magyar Onkológia 27: 81
20. Van Tassel D (1981) Basic-pack statistics programs for small computers. Prentice-Hall, Englewood Cliffs

Received June 13, 1985/Accepted August 21, 1985