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Phase I study of the cytotoxic agent *N*-[2-(dimethylamino)ethyl]acridine-4-carboxamide

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Abstract *N*-[2-(Dimethylamino)ethyl]acridine-4-carboxamide (DACA) is a new DNA-intercalating drug with a dual mode of cytotoxic action that is thought to involve topoisomerases I and II. On the basis of novelty of action and promising preclinical activity against solid tumours in mice, DACA was selected for clinical trial under the auspices of the Cancer Research Campaign, United Kingdom. We report the phase I findings of a 3-h infusion regimen, repeated 3-weekly, of escalating doses through 18–1000 mg/m^2 given to 31 patients with solid malignancies. A maximum tolerated dose (MTD) of 750 mg/m^2 was identified, with 3 of 6 cycles being abandoned at 1000 mg/m^2. Dose-limiting toxicity took the form of infusional arm pain, in some cases associated with facial discomfort, that was of rapid onset and subsided quickly on the cessation of infusion. The mechanism is unclear but is modulated to some extent by the rate of drug delivery, and it was unaffected in this study by concurrent anti-inflammatory or opiate medication. No host or tumour anti-proliferative activity was observed at these doses, and only minimal toxicity of any other kind was evident. Animal data suggest that the MTD achieved with this schedule may be sub-therapeutic in humans. It is therefore important that efforts be continued to explore methods of giving higher doses of DACA.

Key words Phase I · Topoisomerase · DACA

Introduction

N-[2-(Dimethylamino)ethyl]acridine-4-carboxamide(DACA) is an acridine-derived DNA-intercalating drug with a dual mode of cytotoxic action thought to involve the cellular enzymes topoisomerase I and II [9]. In vitro the drug has shown a capacity to overcome both classic and atypical multi-drug resistance (MDR) mechanisms [8], and in vivo it is highly active against murine Lewis lung and Colon 38 carcinoma implants [1]. Studies in mice have shown that DACA rapidly crosses the blood-brain barrier [4] yet is readily water-soluble. In plasma it demonstrates linear pharmacokinetics in cytotoxic dose ranges [11].

The maximum tolerated dose of DACA in mice on a 5-day intravenous dosing schedule was 30 mg/kg per day. At this dose, toxicity took the form of sedation and seizures in some animals, occurring soon after drug injection. A reduction in erythrocyte numbers was also evident after 3–6 days, but no appreciable neutropaenia or thrombocytopaenia occurred. Inflammatory changes in the ileum were observed in some animals at necropsy [3].

Two phase I clinical trials were initiated in 1994 under the auspices of the Cancer Research Campaign, United Kingdom (CRC). The first, conducted in the United Kingdom, employed a 3-h infusion given on 3 consecutive days, scheduled 3-weekly (Twelves et al., submitted for publication). The second trial, reported herein, employed a single 3-h infusion scheduled 3-weekly. The starting dose, determined to be one-tenth of the intravenous murine LD_{10} (the dose lethal to 10% of the animals), was 18 mg/m^2. The aim was to escalate the dose for cohorts of three patients until the maximum tolerated dose, as defined below, was reached. Plasma pharmacokinetics and urinary/stool metabolites were investigated and, where possible, tumour response was assessed.

This study was conducted under the auspices of the Cancer Research Campaign's Phase I/II Committee.

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Patients and methods

The protocol was approved by the Phase I/II Committee of the CRC, by the Standing Committee for Therapeutic Trials in New Zealand and by the North Health Ethics Committee, Auckland, New Zealand. All patients were registered with the CRC Data Centre. Eligibility for this study, carried out in the Department of Clinical Oncology, Auckland Hospital, required the histological confirmation of malignancy that was considered refractory to conventional treatment or for which no useful therapy existed. In all instances, patients must have recovered from any previous therapy (interval of 2 weeks after surgery, 4 weeks from the last chemotherapy or radiotherapy, extended to 6 weeks if patients had been exposed to nitrosoureas or mitomycin C) and have adequate renal function (serum creatinine <140 μmol/l) and hepatic function (bilirubin and transaminases $<1.5 \times$ normal, alkaline phosphatase $<2.0 \times$ normal, prothrombin time normal). The minimal requirement for bone marrow function at entry was a neutrophil count of $>2.0 \times 10^9$/l and a platelet count of $>100 \times 10^9$/l. Patients must be aged 18 years or over, be ambulant (Eastern Co-operative Oncology Group performance status 0–2), and be expected to live a further 12 weeks without the co-morbidity of serious infection or cardiac or epileptic conditions. Written, informed consent was required from all patients according to the guidelines of the local ethics committee.

Baseline investigations included a full history, examination, chest X-ray and electrocardiogram. Tumour dimensions were measured wherever possible and the response on study was recorded using WHO criteria [13]. A full blood count, serum electrolyte, creatinine, urate and liver-function profile was obtained weekly from all patients on study. In patients treated with doses above 575 mg/m^2, electrocardiographic monitoring was undertaken throughout the 3-h infusion.

DACA was supplied as 1- or 2-ml vials containing a 50-mg/ml concentration of the dihydrochloride trihydrate salt in aqueous solution. The dose was diluted in 500 ml of 0.9% sodium chloride and was infused via an IMED pump (IMED Corporation, San Diego, Calif., USA) into a peripheral venous cannula with a target duration of 3 h. Blood pressure, respiratory and heart rate recordings were taken pre-infusion, at 15-min intervals in the 1st h of administration and half-hourly for the remaining 2 h. Plasma drug concentrations were measured in blood drawn from the contralateral arm over 0–72 h [10]. Serum α_1-acid glycoprotein levels were measured in separate samples for each patient prior to infusion and again at 24 h. This acute-phase reactant protein is believed to be responsible for the majority of drug binding and, hence, determines the free fraction of DACA [6]. Urine samples were obtained immediately prior to drug administration, and thereafter, all urine for the next 72 h was collected. A number of these samples were analysed for DACA and its metabolites [12].

The dose level received by the first three patients was 18 mg/m^2, and subsequent cohorts of patients were treated at levels defined by a modified Fibonacci series (Table 1). However, dose escalation could be altered on the basis of pharmacokinetic data in accordance with guidelines accepted by the CRC Phase I/II Trials Committee [5] or through dose levels previously studied and considered safe in the United Kingdom trial centre. Patients could be entered only at a minimal interval of 1 week, and dose escalation was contingent on acceptable levels of toxicity for the preceding group of patients (no escalation was allowed for individuals). The maximum tolerated dose (MTD) was defined as the dose level at which dose-limiting toxicity (DLT) occurred in 33% or more of patients treated at that level, the expectation being that the cohort

Table 1 Patients' data (*ca* carcinoma, *NSC* non-small-cell)

Patient	Histology	Age (years)/sex	Dose level (mg/m^2)	Dose (mg)[a]	Cycles (*n*)
1	Breast	51/F	18	30	1
2	Colon	60/M	18	34	2
3	NSC lung	63/M	18	40	2
4	Breast	42/F	36	55	5
5	Ovary	56/F	36	56	6
6	Colon	49/F	36	60	3
7	Colon	58/F	60	100	2
8	NSC lung	56/F	60	110	3
9	Endometrium	34/F	60	120	5
10	Rectum	46/F	90	160	1
11	Colon	66/M	90	170	2
12	Ovary	52/F	90	165	3
13	Breast	33/F	350	670	2
14	Breast	61/F	350	580	1
15	Ovary	73/F	350	560	2
16	Unknown adenoca	45/M	480	960	2
17	Hepatocellular ca	63/F	480	825	2
18	Ovary	49/F	480	840	2
19	Osteosarcoma	32/M	480	0	0
20	Colon	56/M	480	920	2
21	Pancreas	48/F	575	860	1
22	Unknown adenoca	59/F	575	950	4
23	Renal ca	59/M	575	970	Abandoned
24	Unknown adenoca	64/M	575	1265	4
25	Ovary	51/F	750	1200	2
26	NSC lung	47/M	750	1575	3
27	Rectum	64/M	750	1350	3
28	Liposarcoma	57/F	1000	1400	1
29	Renal ca	67/F	1000	1650	1
30	NSC lung	40/M	1000	1900	1, 2nd abandoned
31	Ovary	67/F	1000	1650	Abandoned
32	Pancreas	45/M	1000	1850	Abandoned

[a] Doses are expressed for DACA as the trihydrated hydrochloride salt

could be expanded to assist with definition of the MTD. DLT, in turn, was defined as (1) a WBC nadir of $< 0.5 \times 10^9$/l or a platelet nadir of $< 50 \times 10^9$/l; (2) failure of the neutrophil count and platelet count to recover to levels at or above 1.5×10^9/l and 100×10^9/l, respectively, by day 35 after the last treatment; and (3) Common Toxicity Criteria grade 4 non-haematological toxicity in any patient that could unequivocally be related to the drug (with the exception of nausea, vomiting and alopecia). Anti-emetics were given only when required.

Results

Between October 19, 1994, and August 8, 1996, 32 patients were enrolled. In all, 68 cycles were given according to protocol and 4 further cycles were abandoned because of severe arm pain produced by the infusion. Table 1 outlines the patients' characteristics and the doses employed. Altogether, 20 women and 12 men took part (age range 33–73 years, mean 54 years); all but 6 had previously received some form of chemotherapy. Throughout the dose range of DACA given (18–1000 mg/m^2, or (30–1900 mg), no response was observed using WHO criteria [13]. Early progression occurred in 11 cases, 10 had a "best response" described as progression, 5 had static disease during the early cycles of treatment and the remaining 6 patients were non-evaluable, including one patient who was enrolled but subsequently declined treatment and was never exposed to the drug. In those treated patients, no haematological or biochemical disturbance attributable to DACA was seen.

The toxicity profile of DACA was dominated by unusual reversible symptoms of widely varying nature and intensity. Arm pain during the infusion (Table 3); thrombophlebitis (Table 2); discomfort involving the face, mouth and eyes (Table 3); nausea and vomiting (Table 2); and transient skin rashes (for four patients) were described. Vital sign recordings were consistently stable while the infusion was proceeding. The one exception was a patient (patient 24) receiving DACA at a dose of 575 mg/m^2, who developed slow atrial fibrillation in the first 15 min of infusion but reverted spontaneously to sinus rhythm before the administration was complete. It was thought that DACA was not causative because the episode was short-lived and no other episode was recorded in subsequent courses of DACA. The patient's history suggested that similar events had occurred intermittently over the course of several years.

Pain in the arm receiving the infusion was the dose-limiting toxicity. It was seen in its most severe form in three patients treated at 1000 mg/m^2, forcing discontinuation of the infusion only minutes after its start, although one of these patients (patient 30) had previously received a full cycle. The symptom, however, was seen in the very earliest stages of the trial, complicating the treatment of patients at 18 mg/m^2. Figure 1 demonstrates the weak relationship between pain grade and dose level; for example, one patient treated at 1000 mg/m^2 had only minimal discomfort, and patients receiving more than one cycle often experienced markedly different intensities with each infusion. Typically, the sensa-

Table 2 CTC-grade toxicity and number of cycles per dose level (percentage in parentheses)

Dose level	Grade	Neurocortical	Skin	Local thrombophlebitis	Nausea	Vomiting	Diarrhoea
18	0	5 (100%)	5 (100%)	5 (100%)	5 (100%)	5 (100%)	5 (100%)
	I/II	0	0	0	0	0	0
	III/IV	0	0	0	0	0	0
36	0	14 (100%)	14 (100%)	14 (100%)	14 (100%)	14 (100%)	14 (100%)
	I/II	0	0	0	0	0	0
	III/IV	0	0	0	0	0	0
60	0	10 (100%)	10 (100%)	10 (100%)	10 (100%)	10 (100%)	10 (100%)
	I/II	0	0	0	0	0	0
	III/IV	0	0	0	0	0	0
90	0	6 (100%)	6 (100%)	6 (100%)	6 (100%)	6 (100%)	6 (100%)
	I/II	0	0	0	0	0	0
	III/IV	0	0	0	0	0	0
350	0	4 (80%)	5 (100%)	5 (100%)	4 (80%)	3 (60%)	5 (100%)
	I/II	1 (20%)	0	0	1 (20%)	2 (40%)	0
	III/IV	0	0	0	0	0	0
480	0	4 (50%)	7 (88%)	5 (63%)	5 (63%)	5 (63%)	6 (75%)
	I/II	2 (25%)	1 (12%)	3 (37%)	3 (37%)	2 (25%)	2 (25%)
	III/IV	2 (25%)	0	0	0	1 (12%)	0
575	0	10 (100%)	9 (90%)	7 (70%)	8 (80%)	10 (100%)	10 (100%)
	I/II	0	1 (10%)	3 (30%)	2 (20%)	0	0
	III/IV	0	0	0	0	0	0
750	0	7 (88%)	8 (100%)	7 (88%)	6 (75%)	6 (75%)	7 (88%)
	I/II	1 (12%)	0	1 (12%)	2 (25%)	2 (25%)	1 (12%)
	III/IV	0	0	0	0	0	0
1000	0	3 (60%)	3 (60%)	4 (80%)	5 (100%)	3 (60%)	5 (100%)
	I/II	2 (40%)	2 (40%)	1 (20%)	0	2 (40%)	0
	III/IV	0	0	0	0	0	0

Table 3 Non-CTC-grade toxicity and number of cycles per dose level (percentage)

Dose level	Grade[a]	Arm pain	Mouth/Facial	Ocular	Flushing
18	I	3 (60%)	0	0	0
	II	0	0	0	0
	III	0	0	0	0
36	I	3 (21%)	0	0	0
	II	11 (79%)	0	0	0
	III	0	0	0	0
60	I	6 (60%)	0	0	0
	II	0	0	0	0
	III	1 (10%)	0	0	0
90	I	1 (17%)	0	0	0
	II	3 (50%)	0	0	0
	III	1 (17%)	0	0	0
350	I	4 (80%)	0	0	0
	II	1 (20%)	0	0	0
	III	0	0	0	0
480	I	3 (38%)	4 (50%)	0	0
	II	3 (38%)	2 (25%)	1 (13%)	0
	III	2 (25%)	0	1 (13%)	0
575	I	3 (30%)	7 (78%)	3 (33%)	1 (11%)
	II	6 (60%)	0	0	0
	III	1 (10%)	0	0	0
750	I	1 (13%)	6 (75%)	5 (63%)	2 (25%)
	II	3 (38%)	0	0	0
	III	4 (50%)	1 (13%)	0	0
1000	I	1 (17%)	0	2 (66%)	1 (33%)
	II	2 (33%)	2 (66%)	0	0
	III	3 (50%)	0	0	0

[a] Grades: I = mild, II = moderate, III = severe
Specifically for arm pain, I = slight, not uncomfortable
mouth/facial: II = uncomfortable but no compulsion to stop infusion
III = infusion requires cessation to control discomfort
ocular: I = suffusion, red eye, not uncomfortable
II = symptomatic, gritty feeling, lacrimation
III = marked lacrimation

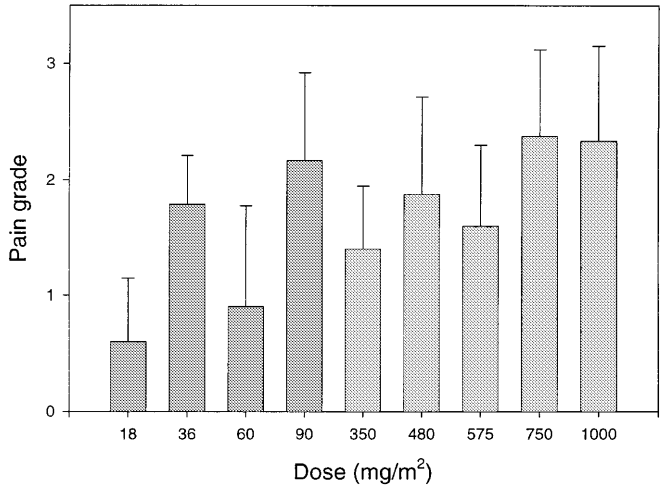

Fig. 1 Mean grade of arm pain (± SD) recorded for treatment cycles within each DACA dose level (data from Table 3)

tion was a burning or squeezing discomfort a matter of centimetres away from the intravenous access site, beginning within minutes of the initiation of infusion. It would then spread up the arm toward the shoulder over a period of 10–15 min before starting to fade. For most patients the discomfort would linger for the remainder of the 3-h infusion, waxing and waning unpredictably but not approaching the initial intensity. As soon as the DACA dose was complete, the pain as reported by patients would subside immediately. When the infusion was briefly stopped and re-started again to allow the pain to disappear, the remainder of the dose could usually be infused without the discomfort reaching the same intensity. Despite this manoeuvre, one patient (patient 23) refused to complete an infusion at 575 mg/m^2 because of pain. He had indicated that he would not tolerate any discomfort, and the level of intensity experienced was relatively low. Accordingly, the cohort at this dose level was not expanded. The three cycles abandoned at 1000 mg/m^2 were noteworthy for their severity (only one patient wished to re-start the infusion before it was again stopped and the drug, withdrawn), for the slowness of the pain to settle (30 min) and for the observation that <20 mg of the drug had entered the vein.

Various approaches were used in an attempt to ameliorate particularly uncomfortable episodes. The use of brief cessation of infusion to reduce pain was successful in six patients (patients 9, 12, 17, 18, 25 and 26). Doubling of the vehicle volume to 1000 ml (given over the customary 3 h) was unsuccessfully employed in one patient (patient 32). On occasion, in some cases it was found that elevation of the limb would reduce pain, whereas inflation of a blood-pressure cuff on the infusion arm would aggravate it.

Specific premedication was given only to two patients (patients 13 and 32) in the form of opiate and steroid medication, respectively, with no observed benefit. There was no evidence in this study that patients receiving concurrent anti-inflammatory medication, amitriptylene, opiates or benzodiazepines had any protection against the intensity of pain, although other investigators have achieved benefit with opiate premedication (Xenova Ltd., personal communication).

Thrombophlebitis complicated eight cycles but was usually mild. One patient (patient 21) had an ascending thrombosis extending from the access site in the left arm into the brachiocephalic vein that developed within 1 week of a dose of DACA. This patient had pancreatic cancer, which may have been contributory. Thrombophlebitis episodes were not encountered in patients who received ≤350 mg/m^2 and only complicated cycles where some degree of arm discomfort had occurred.

Another prominent symptom with a threshold dose level was the mouth/facial discomfort seen in patients treated with doses of ≥480 mg/m^2. Typically it would appear 30–90 min into the infusion as a feeling of tingling or warmth in the lips, spread back into the mouth (especially the hard palate area) as a "hot curry" or "peppery" sensation, and sometimes spread across maxillary skin. Like the arm pain, it would disappear almost immediately on cessation of the infusion, which was used to control the discomfort on one occasion (patient 26). Injected red conjunctivae were seen in 12 cycles at or above 350 mg/m^2, with subjective sensation being limited to a feeling of grittiness or lacrimation. It was not necessarily associated with the other facial or oral symptoms. Lacrimation was particularly marked in one patient (patient 16) for 2 successive cycles at 480 mg/m^2. He used two boxes of tissue paper during the course of each infusion. There was no ocular sequela.

At 350 mg/m^2, one patient (patient 14) experienced a transient feeling of word-finding difficulty during the infusion. A further two patients (patients 16 and 17) treated at 480 mg/m^2 were noticeably sedated, although they would rouse in response to a raised voice. Because of this event an extra patient was entered at this level, but no sedation was observed. At 575 mg/m^2, patient 25 became mildly drowsy, but there was no further problem of this kind at this or higher dose levels (Table 2). At 1000 mg/m^2 an episode of restless legs occurred during infusion (patient 28) and a second patient (patient 30) noted a brief "funny feeling in the head". No confusion or disorientation was seen. These events did not outlast the duration of the infusion.

Nausea and vomiting were seen at doses of ≥350 mg/m^2 (Table 2) but were readily controlled with standard anti-emetics. Facial flushing was experienced by four patients (patients 21, 22, 27 and 28) for a matter of minutes during DACA treatment at doses of 575, 750 and 1000 mg/m^2. Skin rashes were observed during administration of DACA on four occasions as faint maculopapular asymptomatic changes that resolved within minutes. Only one case appeared to be generalised, being more prominent on the flexor surfaces of both arms. No treatment was required.

A constellation of unusual symptoms accompanied the arm pain in one patient (patient 31, 1000 mg/m^2), forcing the abandonment of this dose. The patient started to cough and described a feeling of constriction in the throat "as if the pain went from the arm into the neck". It settled over a period of 30 min without any treatment save cessation of the DACA infusion. There was no evidence of bronchospasm. She insisted on rechallenge and within 7 min, exactly the same symptoms recurred.

Pharmacokinetic data were obtained for 33 cycles, including 2 consecutive cycles for 5 patients, and a detailed appraisal has been reported elsewhere [10]. The area under the concentration-time curve (AUC) ranged from 0.79 to 75.6 μ*M* h in a linear fashion with respect to dose as compared with the AUC reported for mice receiving the maximum tolerable intraperitoneal dose (410 μmol/kg) of 23.4 μ*M* h [7]. However, when free-drug AUC values were compared, the highest human value (1.25 μ*M* h) was barely one-third of that obtained in mice (3.50 μ*M* h). The overall mean volume of distribution at steady state (Vss) for all doses given was 1.75 l/kg, and the data fitted a two compartment model ($t_{1/2}1$ = 0.28 h, $t_{1/2}2$ = 2.04 h), with the overall mean clearance being 1.0 l^1 h^{-1} kg^{-1}. There was no correlation between the arm pain experienced by patients and the individual pharmacokinetic parameters. Approximately 45% of the dose was recoverable in the urine, the vast majority in the form of N-oxide DACA acridone. Only 2% of the DACA dose was excreted unchanged by the kidneys. A detailed analysis of urinary metabolites has been reported elsewhere [12].

Discussion

Using a 3-h intravenous infusion of DACA given every 3 weeks up to a dose of 1000 mg/m^2, we observed no anti-proliferative activity against tumour or host tissues. Using a murine model, extrapolation of AUC values corrected for protein-binding differences between the species indicates that such activity might require doses of approximately 3000 mg/m^2 [10]. If this is so, the arm pain prevented the delivery of potentially therapeutic doses of DACA in this schedule.

The cause of the dose-limiting pain is still not understood. The observations that the pain in the arm was worse in the initial 10–15 min of the drug infusion and that it was ameliorated by cessation and re-starting of the infusion suggest that the mechanism is receptor-mediated, with a saturation effect (desensitisation) occurring. The slow migration of the pain up the infusion arm raises the possibility of a vascular effect, and the frequency of thrombophlebitis suggests some form of damage or inflammation of the vein wall. If the drug delayed its own egress from the limb by constricting capillary beds in an ascending fashion, it might intensify

any local irritant effect until the vessels dilated or collaterals opened. However, no obvious sign of cutaneous vasoconstriction was seen during infusion, and it is unlikely that vasoconstriction alone could be responsible for the arm pain syndrome. Reduction of pain by elevation of the limb as well as exacerbation of pain during the inflation of a blood-pressure cuff on the infusion arm suggest that the rate of drug entry into the vein (rather than the drug concentration in the infusion solution) and the rate of venous "run-off" may be factors modulating the intensity of the pain.

The lacrimation experienced by some patients suggests that a DACA metabolite may be a lacrimate. It is interesting that acridine-4-carboxylic acid, an intermediate in DACA synthesis, is an extremely potent lacrimate (G.J. Atwell, personal communication). However, there is currently no evidence to support the hypothesis that this compound might be produced in vivo by metabolism of DACA.

Since the limiting toxicity of arm pain is to some extent dependent on the infusion rate (Fig. 1), one approach to reducing pain would be to increase the infusion time. It is a matter of concern that one patient (patient 4) experienced significant discomfort at a low infusion rate ($36\ mg^{-1}\ m^{-2}\ h^{-1}$). It remains to be seen whether prolongation of the infusion time will alleviate the problem in all patients or whether further strategies will be required.

Central venous access for DACA offers the potential advantage of improved flow rates through a large-calibre vessel, thus reducing the chance of local vessel irritation. It was not utilised in this study because of concern that the pain might simply be transferred to the chest and that thrombophlebitis, a peripheral complication, might also affect the great intrathoracic veins. In the CRC study in the United Kingdom this approach was tried in one patient, who developed chest pain during the infusion that was accompanied by ECG changes suggesting possible myocardial ischaemia (Twelves et al., submitted for publication). The patient had no history of angina or cardiac disease. The pain and electrical abnormalities resolved on the cessation of infusion.

In conclusion, DACA is a novel drug with a mechanism of action that is distinguishable from that of all clinically available cytotoxic agents. However, it also produces unusual and unpredictable side effects during intravenous infusion, which manifest in the form of arm and facial discomfort. Elucidation of the underlying mechanisms of these side effects would provide the best approach to ameliorating them, and in this regard the development of appropriate animal or tissue-culture models would be of enormous assistance. The present study demonstrates that arm pain limits the maximum tolerated dose for DACA given as a 3-h intravenous infusion every 3 weeks to $750\ mg/m^2$. Predictions based on murine models [10] suggest that this dose is subtherapeutic. Arm pain is therefore a major hurdle to the peripheral intravenous delivery of an effective dose of this drug. Subsequent phase I investigation has shown that higher doses of DACA can be given for longer infusion periods via central lines [14].

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