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Ambulatory infusion of dacarbazine for metastatic malignant melanoma: A clinical, pharmaceutical and pharmacokinetic case report

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Case Report

Ambulatory infusion of dacarbazine for metastic malignant melanoma: A clinical, pharmaceutical, and pharmacokinetic case report

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Objective. This report describes the development and clinical use of a dacarbazine ambulatory infusion for palliative treatment of metastatic malignant melanoma.

Case Summary. A 39-year-old male with metastatic malignant melanoma received ambulatory infusion of dacarbazine, 2.5 mg/kg/d × 10 days (courses 1 and 2) and 5 mg/kg/d × 10 days (course 3). This was made possible by the development of a modified dacarbazine infusion formulation which increased drug stability. The first two courses were well tolerated and the patient remained independent and active. A pilot pharmacokinetic study was undertaken on the third course to enable comparison of the potential exposure of tissues to dacarbazine between the prolonged infusion and conventional schedules.

Discussion. Under conditions replicating ambulatory infusion (37°C) the modified infusion of dacarbazine was stable for 24 hours (92.4% remaining) compared with a standard infusion in water for injection (89.2% remaining after 8 hours). The patient appeared to benefit from ambulatory treatment, and mild nausea was the only adverse effect recorded during the first two treatment courses. The pharmacokinetic study revealed an average steady-state plasma concentration ($Cpss_{ave}$) and AUC of 243 $ng \cdot mL^{-1}$ and 58.4 $\mu g \cdot h \cdot mL^{-1}$, respectively.

Conclusion. Ambulatory infusion of dacarbazine in the home setting is possible with the modified infusion formulation described in this report.

Key Words: Dacarbazine; ambulatory infusion; stability; pharmacokinetics.

Dacarbazine is a triazene alkylating agent licensed for use in metastatic malignant melanoma, sarcoma, and Hodgkins disease.[1] Standard dose schedules of dacarbazine as single agent are either 2–4.5 mg/kg/d × 10 days at 4-week intervals or 250 $mg/m^2/d$ × 5 days at 3-week intervals.[1] The dose is usually given as a bolus injection or short infusion over 15–30 minutes. Adverse effects include leucopenia, thrombocytopenia, nausea, and vomiting.

Dacarbazine has a short plasma half-life of about 35 minutes, suggesting that proliferative tissues may be exposed to the drug for short periods only.[2] The drug may therefore be a possible candidate for prolonged continuous infusion administration. However, dacarbazine undergoes pH-dependent photolytic and hydrolytic degradation, and, because the commercially available drug is formulated with a citrate buffer (approximately pH 3.5 after reconstitution) to increase drug solubility, the shelf life of reconstituted solution is only 8 hours at room temperature.[2] This would preclude ambulatory continuous infusion where the temperature of drug infusions in a pump worn under the patient's clothing could reach 35–37°C, and the preferred interval between changing pump reservoirs is at least 24 hours.[3]

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CASE REPORT

A 39-year-old male presented for treatment following the diagnosis of metastatic malignant melanoma at an advanced stage. Clinical features included right eye enucleation, pneumothorax, and lumpy mediastinal mass. The patient had heard of the Home Oncology Programme at Exeter[3] and was keen that treatment should not compromise his independence or lifestyle. In accordance with institutional guidelines on nonlicensed routes of administration, dacarbazine, 145 mg over 12 hours × 10 days, was prescribed with the intention of providing fully ambulatory treatment of a palliative nature with the possible reduction of adverse effects.

The issue of dacarbazine stability was immediately addressed by the Pharmacy Department. Previous studies[2] had shown dacarbazine stability was optimal at pH 7, although drug solubility was considerably reduced under these conditions. A modified dacarbazine infusion buffered to pH 7 was prepared (Table 1).

The stability of the modified dacarbazine infusion (Table 1) was compared with a standard dacarbazine infusion (10 mg/mL in water for injection) using a stability-indicating liquid chromatography assay. The results (Table 2) indicated that the modified infusion exhibited improved stability and could be administered as an ambulatory infusion over 24 hours providing it was prepared immediately before use.

The patient received three courses of dacarbazine continuous infusion at 4-week intervals as detailed in Table 3.

Medication reservoirs prefilled with modified dacarbazine infusion were collected by the patient immediately after preparation on a daily basis. A Walkmed 300 ambulatory pump was used to administer the infusion, and both the infusion reservoir and central venous catheter were protected from extraneous light.

The first two courses of chemotherapy were well tolerated. Despite the minor inconvenience of needing to collect his medication daily (the patient's home was near the hospital) the patient enjoyed his independence and remained fully active. The patient experienced only mild nausea of a transient nature and no vomiting. Bone marrow depression was not significant: Prechemotherapy—WBC = 11.7×10^9 liters^{-1}; platelets = 536×10^9 liters^{-1}. 2-week postcourse 1—WBC = 13.0×10^9 liters^{-1}; platelets = 720×10^9 liters^{-1}. 2-week postcourse 2—WBC = 7.7×10^9 liters^{-1}; platelets = 416×10^9 liters^{-1}.

During the treatment period the patient received 4 units of packed cells and 1 unit of blood to compensate for disease-related internal bleeding. Assessment of response after the second course of treatment revealed stable tumor mass at main sites with evidence of minor regression.

Table 1. Modified Dacarbazine Infusion (pH 7)

Dacarbazine (10 mg/mL)*	15 mL
Sodium phosphates 2.6% injection†	10 mL
Water for injection	to 100 mL

**Dacarbazine (DTIC-DOME, Bayer UK) reconstituted with water for injection. †$Na_2HPO_4 \cdot 12H_2O$, 58.74 g, $NaH_2PO_4 \cdot 2H_2O$, 7.60 g, water for injection to 250 mL. Packed into 10-mL type 1 glass ampoules and sterilized at 115°C for 30 minutes.*

Table 2. Stability of Standard and Modified Dacarbazine Infusions at 37°C

	Dacarbazine (% of initial concentration)	
Time (h)	Standard	Modified
0	100	100
8	89.2	
18		97.8
24		92.4

Table 3. Chemotherapy Schedules and Doses

Course	Dose and schedule
1	2.5 mg/kg/d = 145 mg over 12 h × 10 days
2	2.5 mg/kg/d = 145 mg over 12 h × 10 days
3	5 mg/kg/d = 270 mg over 24 h × 10 days

For the third course of chemotherapy the dose was increased to 5 mg/kg/d × 10 days, which required an infusion of 270 mg over 24 hours × 10 days. The volumes for the components of the modified infusion (Table 1) were doubled to give a slight overage, and the infusion was presented as a 24-hour dose in a 250-mL medication reservoir. On completing the third course, there was no bone marrow depression but the patient reported fatigue and increased nausea compared with the previous courses.

One month after completing the third course, the patient's condition declined significantly (blood vomitus, weight loss, appetite loss). Elevated liver function test levels (alkaline phosphatase > 1500 IU/L, γ-GT = 1197 IU/L) indicated extensive liver disease, and gastroscopy revealed an invasive fungating necrotic tumor in the duodenum. Dacarbazine was discontinued and after one further course of multiple agent chemotherapy the focus switched to pain control and supportive therapy only.

In order to establish that the prolonged infusion schedule of dacarbazine provided tissue exposure to drug comparable with conventional schedules, a pilot pharmacokinetic study was conducted during the third

Table 4. Pharmacokinetic Data for Dacarbazine Infusion, 270 mg/d (Infused Over 24 h) × 10 Days

Infusion time (h)	Plasma dacarbazine ($ng \cdot ml^{-1}$)
0	0
24	154
48	296
72	202
96	232
120	328
144	240
168	277
192	221
216	269
240	208

$Cpss_{ave}$ = 243 $ng \cdot ml^{-1}$; AUC = 58.4 $\mu g \cdot h \cdot ml^{-1}$.

treatment course. Patient and Ethics Committee approval was obtained and blood samples were taken at 24-hour intervals over the course of the infusion (the contribution of run-up and run-down phases of the plasma concentration/time plot were considered negligible). Extracted plasma samples were assayed using a validated LC method, and from the time course plot the average steady-state plasma concentration of dacarbazine ($Cpss_{ave}$) was determined and the AUC was calculated using a computer model (Statis III, Clydesoft UK). These data are presented in Table 4.

DISCUSSION

This case study demonstrates that with considerable pharmaceutical input, it was possible to facilitate the ambulatory administration of a relatively unstable drug in the home setting. The modified infusion was stable for 24 hours under "in-use" conditions (Table 2), whereas the maximum infusion time for standard dacarbazine infusion would have been less than 8 hours.

The need for the infusion to be prepared on a daily basis and the larger infusion volumes resulting from reduced dacarbazine solubility at the modified pH were not significant issues in this case. Ambulatory infusion of dacarbazine was well tolerated over the first two courses. The patient, clinician, and pharmacist considered this approach to be worthwhile given that the objective of therapy was palliation. Increased toxicity during the third course, where the dose was increased from 2.5 to 5 mg/kg was not unexpected and may, in part have been associated with the advanced stage of the disease before treatment commenced.

Pharmacokinetic studies on the third treatment course were not intended to be definitive. However the AUC of 58.4 $\mu g \cdot h \cdot mL^{-1}$ (Table 4) obtained with the new schedule, which delivered a total dose of 2.7 g of dacarbazine, compares favorably with an AUC of 71 $\mu g \cdot h \cdot mL^{-1}$ obtained with a 30-minute infusion of 1.65 g/m^2 (total dose, 3.1 g).[4] These data also lend support to the functionality of the modified formulation and ambulatory delivery system.

We have demonstrated that a modified dacarbazine formulation is suitable for prolonged ambulatory infusion in the domicillary setting. We hope this work will facilitate larger studies to compare the efficacy, toxicity, and quality of life achieved by prolonged infusion with conventional dacarbazine regimens.

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