Preclinical Pharmacology of Arabinosyl-5-azacytidine in Nonhuman Primates

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ABSTRACT

The plasma and cerebrospinal fluid (CSF) pharmacokinetics of arabinosyl-5-azacytidine (AAC) were studied in rhesus monkeys following a 15-min, 1-h, or 12-h i.v. infusion of 200 mg/kg. No clinically significant toxicity was observed with these schedules. The plasma elimination of AAC is rapid and characterized by a triphasic decay with t1/2 = 3.6-5.4 min, t2/3 = 18-24 min, and t»½ = 94-144 min for the above infusion schedules. The CSF penetration of AAC as measured by the CSF/plasma Cmax ratio for the 12-h infusion was 0.15.

The stability of AAC in pooled plasma, phosphate buffered saline, and RPMI 1640 culture media at 37°C was compared with the terminal half-life of AAC observed in vivo. The shorter in vitro AAC half-life in plasma with or without tetrahydrodizine versus that in phosphate buffered saline suggests that the terminal half-life of AAC in vivo is most likely a result of enhanced nucleophilic attack and hydrolytic degradation of the unstable triazine ring in plasma.

A triexponential equation modeling the disappearance of AAC was constructed from the in vivo experimental data. Use of this equation in computer-aided simulations of current Phase I doses and schedules of AAC correctly predicts the human plasma concentrations which have been observed. The preclinical pharmacokinetic data provided here may be useful in helping to develop rational human studies with specific concentration × time goals.

INTRODUCTION

AAC2 (Fazarabine, NSC 281272) is a unique and clinically promising new nucleoside which is currently beginning human Phase I clinical trials. Structurally, AAC is a hybrid molecule which contains elements of both Ara C and 5-AC (Fig. 1) (1). It possesses the arabinosine sugar of Ara C, and its pyrimidine base is the triazine analog of cytosine, identical to that of 5-AC. The resultant molecule is chemically similar to 5-AC in that it rapidly undergoes spontaneous hydrolytic degradation in aqueous solutions and is a poor substrate for cytidine-deoxycytidine deaminase (1-3). However, the biochemical behavior of AAC more closely resembles that of Ara C in that both agents require intracellular activation by deoxycytidine kinase for production of their biologically active nucleotide triphosphates. Like Ara C, AAC inhibits DNA synthesis, and is readily incorporated into DNA in a dose-dependent manner (2, 4). Once incorporated, opening of the unstable triazine base leads to DNA fragmentation and strand breaks (2). While this latter feature appears to be the major cause of AAC cytotoxic effects, this agent is also capable of producing in vitro differentiation of HL-60 promyelocytic leukemia cells, similar to that produced by 5-AC (3).

In preclinical screening of antim tumor activity, AAC demonstrated a much broader spectrum of activity and greater antitumor effects than either Ara C or 5-AC. Significant activity was observed against the murine L-1210 and P-388 leukemias, Lewis lung carcinoma, and B-16 melanoma as well as unusually good activity in the Ara C resistant LX-1 lung and MX-1 mammary human xenografts of the National Cancer Institute preclinical tumor screening panel (1-3). As with many other nucleoside antimitabolites, the antitumor effect of AAC is markedly schedule dependent. Administration every 3 h on Days 1, 5, and 9 was significantly more effective against in vivo L-1210 than once daily for 9 days or less frequent administration (3). Similar observations of schedule dependency have also been made in vitro (4). In preclinical canine toxicology studies, the toxicity of AAC also demonstrated schedule dependency (4).

Because of this schedule dependency, preclinical studies of the pharmacokinetics of AAC may be useful in helping to develop doses and schedules of administration with specific concentration × time goals for human Phase I studies. In an attempt to provide such information, we studied its pharmacokinetics and toxicity in Rhesus monkeys.

MATERIALS AND METHODS

Animals. Seven adult male rhesus monkeys (Macaca mulatta) weighing between 7.7 and 12 kg were used in this study. Animals were housed individually and fed Purina monkey chow and water ad libitum. A silicone Pudenz catheter was surgically placed in the fourth ventricle and attached to an Ommaya reservoir implanted s.c., as previously described (5). This system permits repeated sampling of CSF in unanesthetized animals.

Systemic toxicity was monitored on a weekly basis by following plasma hemoglobin, platelet count, white blood cell count, blood urea nitrogen, creatinine, hepatic transaminases, and total bilirubin. In addition, clinical evaluations were performed daily to look for the presence of mucositis and to assess changes in behavior, appetite, or weight.

Drug Formulation and Administration. AAC was obtained from the Pharmaceutical Resources Branch, National Cancer Institute, Bethesda, MD 20892. The drug was supplied in vials containing 250 mg of sterile lyophilized powder. The contents of each vial were dissolved in 4 mL of sterile 70% dimethyl sulfoxide in distilled water which was supplied with the drug. This solution was then diluted with sterile saline to a final dimethyl sulfoxide concentration of 20% prior to administration into a catheterized saphenous vein using a small volume infusion pump.

Three schedules of AAC administration were studied; a 15-min bolus dose (n = 2), a 1-h (n = 3), and a 12-h (n = 2) i.v. infusion. For animals given either the 15-min bolus or 1-h infusion, AAC was given in a dose of 200 mg/kg (4 g/m).3 This dose was chosen as it had been previously shown to be nontoxic in dogs when given at the same schedules (4). In animals given 12-h infusions, the AAC dose was calculated to achieve a steady-state plasma concentration of 30 μg/ml based on pharmacokinetic parameters derived from the bolus and 1-h doses. An initial loading dose of 6.5 mg/kg (130 mg/m) was given as an i.v. bolus and followed by an 8 mg/kg/h (160 mg/m/h) infusion. For these infusions, the initial AAC/70% dimethyl sulfoxide solution was diluted with cold (4°C) sterile 5% dextrose in 0.5 N sodium chloride solution to a final AAC concentration of 20 mg/ml (25% dimethyl sulfoxide). Because the time to 10% loss (t1/2) of AAC in 25% dimethyl sulfoxide is 2.8 h at 24°C, the infusion solution was freshly prepared and replaced every 2 h to insure that spontaneous hydrolytic degradation of AAC would not lead to unacceptable drug loss during the infusion period (6).

1 The Abbreviations used are: AAC, arabinosyl-5-azacytidine; Ara C, arabinosylcytidine; 5-AC, 5-azacytidine; CSF, cerebrospinal fluid; AUC, area under the concentration-time curve.

3 The surface area of adult (8-12 kg) monkeys is calculated on the basis of 20 kg/m.3


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2 The abbreviations used are: AAC, arabinosyl-5-azacytidine; Ara C, arabinosylcytidine; 5-AC, 5-azacytidine; CSF, cerebrospinal fluid; AUC, area under the concentration-time curve.
Fig. 1. Structure of arabinosyl-5-azacytidine and its parental compounds arabinosyl-cytidine and 5-azacytidine.

Assay and Sampling Times. One milliliter of heparinized whole blood, obtained from the saphenous vein on the side opposite that used for AAC delivery, and 0.4 ml of CSF obtained from the Ommaya reservoir were removed for drug analysis at predetermined times. Prior to removing CSF, the reservoir was pumped five times to insure sampling of fresh ventricular CSF.

In animals given either 15-min or 1-h AAC infusions, blood and CSF were obtained at 0, 10, 15, 20, 30, and 45 min and 1, 1.5, 2, 3, 4, 4.5, and 5 h from the start of drug administration. In those animals given 12-h AAC infusions, blood was obtained at times identical to those above for the first 4 h, and then at 6, 8, and 12 h. The CSF samples in these latter animals were taken at 30 min, 1, 2, 4, 6, 8, and 12 h. Whole blood samples were immediately centrifuged at 1100 × g and the plasma removed. An internal standard (10 µl of 2'-deoxyarabinoxy-5-azacytidine, 500 ng/µl) was then added to 0.5 ml of freshly obtained plasma or 0.4 ml of fresh CSF. These spiked samples were then vortexed for 15 s before being frozen at −20°C for later analysis.

In Vivo AAC Stability. Fresh pooled heparinized human plasma (pH 7.6) and phosphate-buffered saline (pH 7.2) or RPMI 1640 tissue culture media (pH 7.4) at 37°C were spiked with either Ara-C or AAC to a final concentration of 5 µg/ml. In a separate set of identically conducted experiments, tetrahydrouridine (final concentration 10⁻⁵ M) was added to pooled plasma or 0.4 ml of fresh CSF. These spiked samples were then vortexed for 15 s before being frozen at −20°C for later analysis. The analysis for AAC content typically followed sample collection within 12–24 h, and was performed using a high-pressure liquid chromatography method with a 100 ng/ml limit of sensitivity in plasma and CSF.

In Vitro AAC Stability. Fresh pooled heparinized human plasma (pH 7.6) and phosphate-buffered saline (pH 7.2) or RPMI 1640 tissue culture media (pH 7.4) at 37°C were spiked with either Ara-C or AAC to a final concentration of 5 µg/ml. In a separate set of identically conducted experiments, tetrahydrouridine (final concentration 10⁻³ M) was added to pooled plasma 5 min prior to either Ara-C or AAC. These solutions were kept at 37°C in an oscillating water bath and aliquots of 1 ml were removed at each concentration after 15 s being frozen at −20°C for later analysis. The analysis for AAC content typically followed sample collection within 12–24 h, and was performed using a high-pressure liquid chromatography method with a 100 ng/ml limit of sensitivity in plasma and CSF.

Pharmacokinetics. Plasma and CSF disappearance curves for AAC were separately constructed for each set (15-min bolus, 1- and 12-h infusions) of experiments. Mean plasma concentration-time data were then fit to triexponential functions of the form

\[ C(t) = \sum_{i=1}^{3} A_i e^{-\lambda_i t} \]

where \( n \) is the administered dose of drug, \( k_0 \) is the infusion rate, and \( T \) is the infusion time (12). These transformed values were then used as the basis for calculating the new intercept values used in each of the simulations. These new intercepts were obtained by assuming that \( A_i \) were linear with respect to AAC dose, and that the quotient, \( "A" \) divided by the total AAC dose in the monkey was directly proportional to that in man on an \( ml^2 \) basis.

RESULTS

Plasma Pharmacokinetics. The disappearance of AAC from plasma was best fit by a triexponential function

\[ C(t) = Ae^{-\alpha t} + Be^{-\beta t} + Ce^{-\gamma t} \]

where \( C(t) \) is the concentration at any time \( t \), \( \alpha, \beta, \) and \( \gamma \) the hybrid rate constants \( (\lambda_i) \), and \( A, B, \) and \( C \) the corresponding time zero AAC concentration intercepts of each phase of elimination \( (A_i) \). The values for \( A, B, C, \alpha, \beta, \) and \( \gamma \) and the mean pharmacokinetic parameters derived for AAC given as a 15-min and 1-h infusion are shown in Table 1. Only 0.3% of the total AAC for the 15-min and 1-h plasma disappearance curves, and 6.6% of the corresponding CSF curves result from extrapolation beyond the last experimentally derived data points. Figs. 2–4 demonstrate the mean plasma and CSF profiles for the 15-min bolus, 1-h, and 12-h infusions of AAC.

Peak plasma levels occurred at the end of drug administration and the drug was eliminated rapidly from plasma. The calculated \( V_{d_m}^{AAC} \) for both the 15-min and 1-h infusion schedules were
Table 1 Mean plasma pharmacokinetic parameters

<table>
<thead>
<tr>
<th>Schedule (dose)</th>
<th>No.</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>Intercept (μM)</th>
<th>Rate constants (min⁻¹)</th>
<th>CI (ml/min/m²)</th>
<th>( V_d ) (liter/m²)</th>
<th>Peak (μM)</th>
<th>AUC (μMh)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 min (200 mg/kg)</td>
<td>2</td>
<td>628</td>
<td>160</td>
<td>0.89</td>
<td>11.7</td>
<td>2.4</td>
<td>0.29</td>
<td>601</td>
<td>16.4</td>
<td>1531</td>
</tr>
<tr>
<td>1 h (200 mg/kg)</td>
<td>3</td>
<td>572</td>
<td>79.1</td>
<td>2.17</td>
<td>7.11</td>
<td>1.77</td>
<td>0.443</td>
<td>743±296</td>
<td>26±20</td>
<td>530±19</td>
</tr>
<tr>
<td>12-h infusion (102.5 mg/kg)</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Numbers in brackets, half-life in min.
* Numbers in parentheses, range.
* Steady state concentration.

Fig. 2. Mean plasma (○) and CSF (△) AAC concentrations after 15-min infusion of 200 mg/kg in Rhesus monkeys. Solid line connecting the plasma points, computer drawn best fit to a triexponential equation (r² = 0.99).

Fig. 3. Mean plasma (○) and CSF (△) AAC concentration after a 1-h infusion of 200 mg/kg in Rhesus monkeys. Solid line connecting the plasma points, computer drawn best fit to a triexponential equation (r² = 0.99).

Fig. 4. Mean plasma (○) and CSF (△) AAC concentrations after a 12-h infusion of 102.5 mg/kg/h in Rhesus monkeys.

Table 2 Mean CSF pharmacokinetic parameters

<table>
<thead>
<tr>
<th>Schedule</th>
<th>No.</th>
<th>Terminal half-life (min)</th>
<th>Peak (μM)</th>
<th>AUC (μMh)</th>
<th>( \frac{AUC_{CSF}}{AUC_{plasma}} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 min</td>
<td>2</td>
<td>74.5 (40-107)  *</td>
<td>33.5</td>
<td>58</td>
<td>0.14</td>
</tr>
<tr>
<td>1-h infusion</td>
<td>3</td>
<td>47.7 ± 9 (38-56)  *</td>
<td>38 ± 10</td>
<td>71 ± 24</td>
<td>(0.08-0.20)</td>
</tr>
<tr>
<td>12-h infusion</td>
<td>2</td>
<td>5* (2-8)  *</td>
<td>71 ± 24</td>
<td>71 ± 24</td>
<td>(0.07-0.41)</td>
</tr>
</tbody>
</table>

* Numbers in parentheses, range.
* Steady state concentration.
* \( C_{\text{plasma}} \).

Using the 1-h infusion value for clearance, a \( C_{\text{plasma}} \) of 30 μM was predicted to occur with an AAC infusion rate of 8 mg/kg/h (160 mg/m²/h). In two animals given a 6.5 mg/kg (130 mg/m²) loading dose of AAC followed by the above infusion rate, the mean \( C_{\text{plasma}} \) was 31 μM. Fig. 4 demonstrates the mean plasma and corresponding CSF steady-state profiles for the 12-h AAC infusions.

CSF Pharmacokinetics. The CSF kinetics of AAC are presented in Table 2. Peak CSF AAC concentrations occurred shortly after those in plasma and its elimination from CSF was slower than in the plasma as evidenced by the fact that CSF AAC concentration exceeds that in plasma at the later time points (Figs. 2 and 3). The CSF:plasma AUC ratios in Table 2 show the mean CSF penetration of AAC to be 0.14 and 0.22 for the bolus and 1-h infusions. For the 12-h infusions, the mean CSF:plasma AUC and \( C_{\text{plasma}} \) ratios were 0.11 and 0.15, respectively.

In Vitro Stability. The disappearance of AAC in these in vitro experiments was first-order. The half-life of AAC in fresh pooled human plasma (\( n = 3 \), in RPMI 1640 (\( n = 3 \), and in phosphate-buffered saline (\( n = 3 \)) at 37°C was 175 ± 32, 235 ± 27, and 422 ± 37 min, respectively. The half-life of AAC in plasma with tetrahydrouridine (\( n = 2 \)) was 150 ± 12 min. The stability of the positive control, Ara-C, in tetrahydrouridine-treated fresh plasma (\( n = 2 \)) was identical to that observed in phosphate-buffered saline (\( n = 2 \), there being no apparent loss of parent compound, while the half-life in untreated plasma was 107 min.
Toxicity. In animals given 15-min or 1-h infusions of AAC, no hematological or systemic toxicity was observed for up to 4 weeks. In the two animals given 12-h drug infusions, only mild and clinically insignificant hematological toxicity was apparent (Fig. 5). The nadir in the blood counts occurred between Days 9 and 15, with rapid recovery to pretreatment levels occurring shortly thereafter. No other manifestation of systemic toxicity, such as mucositis, weight loss, loss of appetite, or behavioral changes were noted in any animal given AAC.

DISCUSSION

Preclinical pharmacokinetic studies in animals may be useful in providing early insight into the disposition of an agent, and such information can subsequently be applied to the design of human trials. The ability to correctly predict the kinetics of drugs which are highly schedule dependent, such as AAC, allows the clinician to devise doses and schedules of administration which meet specific safety and therapeutic goals.

From the data of the 1-h infusion experiments in the monkey, we have constructed a pharmacokinetic model which can reasonably predict the plasma AAC concentration in humans. Applying the model equation

$$C(t) = 572.4 e^{-0.01t} + 79.1 e^{-0.5t} + 2.17 e^{-2.5t}$$

to the doses and schedules of AAC beginning to be investigated in Phase I trials, we can calculate peak and $C_m$ µg/ml levels as well as simulate the plasma concentration profiles which are likely to be observed. Fig. 6 demonstrates the approximate plasma profiles derived from the above simulations.

In two patients given AAC at a dose of 20/mg/m²/h for 24 h in our ongoing pediatric Phase I trial, a $C_m$ of 1.85 and 2.1 µM has been observed. This compares favorably to the 2.6 µM levels predicted by the model.

At an AAC dose of 72 mg/m² given as a 1-h infusion (for five consecutive days) in adult patients, the peak daily plasma concentration predicted by the model is 8.8 µM (2.13 µg/ml).

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![Fig. 6. Semilogarithmic plots of expected AAC plasma concentration in current Phase I trials derived from computer-aided simulations. A, 72 mg/m² × 1-h infusion; B, 20 mg/m²/h × 24-h infusion; C, 1 mg/m²/h × 72-h infusion; D, 0.2 mg/m²/h × 72-h infusion.](image)

Fig. 6. Semilogarithmic plots of expected AAC plasma concentration in current Phase I trials derived from computer-aided simulations. A, 72 mg/m² × 1-h infusion; B, 20 mg/m²/h × 24-h infusion; C, 1 mg/m²/h × 72-h infusion; D, 0.2 mg/m²/h × 72-h infusion.

Preliminary results in three adult patients who have been treated with this dose and schedule at Ohio State University reveal peak levels to be 7.5-10 µM (1.8-2.4 µg/ml) at the end of the infusion. In another ongoing AAC Phase I trial being conducted by the National Cancer Institute, the starting dose was 0.2 mg/m²/h for 72 h. At this dose our primate model would predict that AAC would be undetectable ($C_m = 0.02$ µM or 6 ng/ml), and that a clinically detectable $C_m$ of 0.4 µM (100 ng/ml) would not be achieved until a dose of 3 mg/m²/h had been given. In fact, at dose levels of up to 1.0 mg/m²/h for 72 h so far administered, plasma levels of AAC have not been detectable.

As the half-lives of the $\alpha$ and $\beta$ elimination phases still reflect a significant effect of drug distribution, the $\gamma$ phase may be the best place to look for evidence of any in vivo metabolic processes which act in concert with the spontaneous hydrolysis of the AAC triazine ring to affect its overall clearance. The 144-min $\gamma$ half-life of AAC in vivo observed in the 1-h infusion experiment is not significantly different than the 150- and 175-min half-life values we have observed in vitro in fresh human plasma at 37°C with and without tetrahydrouridine. However, these values are significantly ($P < 0.02$) less than the 422-min half-life for AAC in phosphate-buffered saline at 37°C. As expected, tetrahydrouridine had no effect on the rate of decay of AAC in plasma, indicating that cytidine deaminase is not catabolizing this drug as occurs with Ara C. These data suggest that the short in vivo and in vitro half-life of AAC in plasma and RPMI 1640 may be a result of greater hydrolytic degradation in more complex aqueous solutions such as plasma and RPMI 1640 than is known to occur in water and other buffered aqueous solutions (1, 6). Such an occurrence is probably mediated through enhanced nucleophilic attack at the C-6 position of the AAC triazine ring from dipolar amino acids and other organic nucleophiles present at physiological pH in plasma and RPMI 1640 as compared with phosphate-buffered saline. Since the ring-open hydrolytic decomposition products of 5-AC appear to have no inherent toxicity or antitumor activity in mice (13), similar AAC products are also likely to be nontoxic. If, as suggested above, the major pathway for AAC elimination is nonenzymatic and its degradation products have no adverse biological activity, it is possible that major dose reductions of AAC may not be necessary in patients with hepatic or renal dysfunction.

5 From adult AAC Phase I trial of 72 mg/m²/day for 5 days at Ohio State University. Data obtained and quoted with permission of Dr. L. Malaspie.

6 Data obtained and quoted with permission of Dr. J. A. Kelley.

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dysfunction unless some specific toxicity to these organs is identified for AAC in Phase I trials.

In spite of what appears to be significantly different modes of degradation for Ara C and AAC, the in vivo pharmacokinetics of AAC and Ara C in nonhuman primates and humans are remarkably similar. In the rhesus monkey, AAC demonstrated a triphasic elimination and rapid clearance. The mean half-life and clearance values for AAC listed in Table 1 are similar to the α and β half-life and clearance values of 2–4.5 min, 7–20 min, and 400–1100 ml/min/m² reported for similar doses of Ara C (14–18). Further, the long terminal half-life of AAC in this study is closely analogous to the 156-min γ phase of Ara-C (16, 17). Triphasic elimination kinetics for AAC have also been observed in preclinical studies with AAC in the murine model (19). Also, as might be expected, AAC shows a Vd, which is close to that of its parental nucleosides Ara C (17 liters/m² mean) and 5-AC (18-33 liters/m²), suggesting drug distribution in total body water (19, 20).

As in plasma, the CSF kinetics of AAC (Table 2) resemble those of Ara C. The reported 50–60-min half-life of CSF Ara C after intraventricular bolus doses in nonhuman primates is similar to the terminal half-life which we have observed for CSF AAC after peripheral infusions (8, 14). Additionally, when the relative CSF penetration of these nucleosides are compared, the mean CSF:plasma AUC and Cm ratios are analogous to those (0.03–0.16) reported for similar doses and delivery rates of Ara C in humans (15, 17, 18). As can be seen in Fig. 2, the disappearance curve of AAC in CSF crosses that of plasma so that CSF concentrations are actually higher than concurrent plasma concentrations at time points beyond 2 h. This phenomenon may be a reflection of the previously noted greater stability of AAC in simple aqueous solutions such as CSF as compared with plasma.

The toxicity of AAC is highly schedule dependent, similar to that of other antimetabolites such as Ara C. Preclinical toxicology studies of AAC revealed that doses of 333 mg/m²/h, producing a Cm of 119–139 μM for up to 12 h, and 108 mg/m²/h, leading to Cm of 41 μM for up to 24 h, were unassociated with toxicity in dogs (4). Our studies in primates demonstrate that 160-mg/m²/h infusions of AAC for 12 h (producing a Cm of 31 μM) are likewise unassociated with any clinical or laboratory evidence of toxicity. This Cm is well within the 4.1–41 μM levels which have been reported to inhibit clonogenic survival of L1210 and Molt-4 cells in vitro (2, 19).

In summary, AAC appears to display pharmacokinetics which are generally similar to those of Ara C. The broader spectrum of preclinical in vitro and in vivo antitumor activity observed for AAC combined with its favorable plasma and CSF kinetics suggests that it may have significant clinical utility for systemic, meningeval, and perhaps parenchymal central nervous system malignancy. Indeed, AAC has already been demonstrated to possess excellent activity against intracranially implanted L1210 and P388 leukemia in mice, often producing survivals equivalent to those seen with the positive control drug 1,3-bis(2-chloroethyl)nitrosourea (22).

The pharmacokinetic parameters derived from our experiments differ greatly from those reported in mice and dogs (4) and underscore the utility of preclinical studies in the nonhuman primate. The model presented here should be useful in the design of human studies with specific drug concentration × time goals and may also help to predict the toxicity of such treatments in humans.

REFERENCES

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