Morphine Versus Clonidine for Neonatal Abstinence Syndrome

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OBJECTIVE: The study goal was to determine whether clonidine treatment of neonatal abstinence syndrome (NAS) would result in a better neurobehavioral performance compared with morphine.

METHODS: This pilot study prospectively enrolled infants ≥35 weeks’ gestational age admitted for treatment of NAS. After informed consent was obtained, infants were randomized to receive morphine (0.4 mg/kg per day) or clonidine (5 µg/kg per day) divided into 8 doses. A 25% dose escalation every 24 hours was possible per protocol (maximum of 1 mg/kg per day for morphine and 12 µg/kg per day for clonidine). After control of symptoms, the dose was tapered by 10% every other day. Clinical staff monitored infants by using Finnegan scoring. Masked research staff administered the NICU Network Neurobehavioral Scale (NNNS) at 1 week and at 2 to 4 weeks after initiation of treatment and the Bayley Scales III, and Preschool Language Scale IV, at 1-year adjusted age. Analyses included descriptive statistics, repeated measures analysis of variance, and Wilcoxon tests.

RESULTS: Infants treated with morphine (n = 15) versus clonidine (n = 16) did not differ in birth weight or age at treatment. Treatment duration was significantly longer for morphine (median 39 days) than for clonidine (median 28 days; P = .02). NNNS summary scores improved significantly with clonidine but not with morphine. On subsequent assessment, those receiving clonidine had lower height of arousal and excitability (P < .05). One-year motor, cognitive, and language scores did not differ between groups.

CONCLUSIONS: Clonidine may be a favorable alternative to morphine as a single-drug therapy for NAS. A multicenter randomized trial is warranted.

WHAT’S KNOWN ON THIS SUBJECT: Increased central adrenergic activity occurs with opiate withdrawal. Clonidine is an effective drug as an adjunct to morphine in the treatment of neonatal abstinence syndrome. It is unclear whether clonidine is effective as single-drug therapy.

WHAT THIS STUDY ADDS: Clonidine, a α2-adrenergic agonist, seems to be as effective as morphine when used as a single-drug therapy for neonatal abstinence syndrome. Its administration results in improvement in neurobehavioral performance.
The prevalence of nonmedical use of opioid pain relievers is increasing. In the United States, nearly 1% of pregnant women use opiates during pregnancy. Consequently, as the number of infants requiring treatment of neonatal abstinence syndrome (NAS) rises, the health care expenditures associated with hospitalization for clinical monitoring and medical therapy are increasing as well. There is, however, no consensus as to the best single-drug therapy for NAS after failed behavioral intervention. Despite recommendations from the American Academy of Pediatrics that opioids are the first-line therapy for NAS, variation exists among centers in the treatment of NAS. It also remains unclear how opiate treatment of NAS affects children’s long-term outcomes.

Experimental studies reveal concerning data regarding prenatal opiate exposure. Antenatal opiate exposure affects brain development with resulting decreases in corticogenesis, neurogenesis, and synaptogenesis and alterations in the ontogeny of the stress axis and immune response. Human studies also allude to the association of prenatal opiate exposure and small head circumference and decreased brain volumes found on imaging. An additional concern is that infants with NAS receive their pharmacologic treatment during the first few months of life, a period of rapid postnatal brain development. The potential harm of continuing opiate exposure on brain development provides a compelling reason to evaluate the use of a nonopiate drug, such as clonidine, as an alternative to opiate therapy for NAS.

With cessation of the antenatal chronic opiate supply at birth, the opiate inhibitory effect on the fetal noradrenergic neurons is lost, resulting in increased noradrenergic activity. Clonidine, a $\alpha_2$-adrenergic receptor agonist, has inhibitory effects on the release of noradrenaline in the locus coeruleus; its administration decreases noradrenergic neuronal activity, thereby lessening withdrawal manifestations. There have been few reports on clonidine as single-drug therapy for NAS in small numbers of infants. Recent studies found that clonidine was an effective adjunctive treatment when given with morphine or chloral hydrate.

Because of potential deleterious effects of continued postnatal opiate administration on the developing brain, we evaluated the use of clonidine in the treatment of infants with NAS. We tested the hypothesis that clonidine would be better than morphine as a single-drug therapy for NAS as evidenced by improvement in neurobehavior and duration of treatment.

**METHODS**

The study was a pilot randomized, double-blind trial with institutional review board approval. The data safety monitoring board members met every 10 subjects enrolled and submitted the meeting reports to the institutional review board. Research personnel obtained informed consent from parents when the clinical decision was made to start pharmacologic treatment, based on assessments made by using the Finnegan scoring system. Enrollment criteria included: postnatal age < 7 days, gestational age ≥ 35 weeks, known prenatal opiate exposure (maternal history of opiate use and/or positive urine opiate screen during pregnancy or delivery, or infant urine or meconium testing positive for opiate metabolites), no known prenatal cocaine exposure, symptomatic with 3 consecutive Finnegan scores (FS) ≥ 8 assessed 3 hours apart or 2 consecutive FS ≥ 12, no seizures, no major congenital malformations, likely to survive, no blood pressure instability, and no major medical condition in addition to NAS. Infants who did not meet enrollment criteria, including those who developed NAS due to prolonged NICU analgesia and sedation therapy, were excluded.

Nursing personnel had training in assessment of FS, and they performed scoring every 3 hours after nipple feeding (20 kcal/oz) with no volume restriction. All infants received behavioral intervention, including swaddling, rocking, pacifier, dim lighting, and quiet NICU environment. When the FS met criteria for pharmacologic treatment and after consent, the infant received the study drug based on the randomization schedule (4 per block), available only through the investigational drug unit of the Department of Pharmacy. The drugs had identical physical properties (color, volume, clarity, and odor). All clinical and research staff other than the clinical pharmacists were masked to the infant’s study medication. The clinical pharmacists made rounds with the teams, dispensed the study drugs (single dosing), and monitored the physician orders. Doses were prescribed by the medical provider by indicating the infant was to receive study drug at the initial dose per protocol. Any subsequent order was written to maintain dose, increase study drug dose by 25%, decrease dose by 10% from the highest dose, or (in some instances) resume the previous dose.

Infants who were randomized to receive morphine received a starting dose of 0.4 mg/kg per day divided every 3 hours based on the feeding schedule. The dosage was increased by 25% of the initial dose every 24 hours until FS scores were consistently < 8 and symptoms controlled, up to a maximum dose of 1 mg/kg per day. After 48 hours of symptom control (all FS < 8), weaning was begun by decreasing the dose by 10% of the maximum dose.
every other day. If the lowest dose reached < 0.1 mg/kg per day, morphine was discontinued, and the infant was monitored for 48 hours and then discharged. If re-escalation was needed at any time, the previous dose was administered, and weaning was resumed after 48 hours. If no improvement was noted at the maximum dose of 1 mg/kg per day, a second drug was added at the attending physician’s discretion. Those who were randomized to the clonidine group received 5 μg/kg per day divided into 8 doses (0.625 μg/kg per dose every 3 hours). The same procedures as used in the morphine treatment group were followed for dose increases (maximum dose: 12 μg/kg per day), decreases, and re-escalation. In addition, if an infant’s FS was > 8 after the maximum dose, a second drug was initiated at the attending physician’s discretion. Clonidine was discontinued when the dose given was < 1 μg/kg per day. All infants were treated in the NICU. They underwent continuous cardiorespiratory monitoring, and blood pressure measurements were performed every 8 hours. When clinical blood sampling was ordered, extra blood was collected from the enrolled infant; blood samples were processed and stored for later analysis of morphine and clonidine concentrations. Assays for blood concentrations of morphine and clonidine provided a method of confirming that infants received the randomized treatment. The investigator responsible for determination of drug levels was also masked to the treatment assignment. A trained masked examiner assessed the infant’s neurobehavioral performance by using the NICU Network Neurobehavioral Scale (NNNS). The first NNNS administration was at 5 to 7 days after the start of treatment and again at 40 to 44 weeks’ postmenstrual age at discharge or during clinic follow-up. At the attending physician’s discretion and with the institutional emphasis on shortened length of stay, infants completed the drug treatment at home but only after 3 consecutive successful weanings of drug dose. Continuation of therapy postdischarge was possible when the Child Protective Services investigation indicated that infant could be discharged to a safe environment. The clinical pharmacist counseled the child’s caregiver on how to accurately measure and administer the prescribed dose by using a 1-mL oral syringe and how to wean the medication based on the provided calendar. Caregivers were further instructed to bring the labeled medication bottle to any visit with the child’s primary care provider or if seeking care in the emergency department. The caregiver had to satisfactorily demonstrate how to correctly draw up the liquid medication, understand the weaning schedule from the calendar, and identify signs and symptoms of withdrawal and when to seek medical attention. The pharmacist also contacted the primary care physician regarding the child’s treatment and follow-up and faxed a treatment calendar along with the discharge summary. The infants had a clinic visit at 40 to 44 weeks’ postmenstrual age and a developmental follow-up visit at 1-year adjusted age. Assessments included physical and neurologic examinations: the Bayley Scales of Infant and Toddler Development, Edition III, and the Preschool Language Scale, Edition IV.

We planned enrollment of 12 subjects per group, as proposed by Julious32 and Billingham et al.33 An additional 20% (total of 15) was included for each treatment arm, anticipating subject withdrawal or other unforeseen postenrollment exclusions from the study.32,33 Descriptive statistics and the Wilcoxon rank-sum test or Fisher’s exact test were used to compare baseline differences between treatment groups. To compare the NNNS summary scores during the first and second assessments within each group and between treatment groups, a repeated measures analysis of variance was performed. The proportion of infants that completed treatment over time were determined by using the Kaplan-Meier survival analysis,34 and the survival curves were compared by using a log-rank test. To determine the optimal dose given that resulted in control of symptoms until continued weaning of the dose was possible, the receiver-operating characteristic (ROC) curve was determined and the Youden index criteria were used.35–37 Statistical analysis was conducted by using SAS version 9.1 (SAS Institute, Inc, Cary, NC).

RESULTS

Figure 1 displays the flow diagram of the number of subjects screened, excluded, and enrolled. From September 2011 to June 2012, a total of 596 admissions were made to the NICU; of these, 354 were born at ≥ 35 weeks and of those, 88 were opiate exposed. Seventy-four infants needed treatment; 11 had treatment started at a referring hospital, 8 had other medical conditions, and 6 had parents who could not be reached. The parents of 15 infants refused study participation. Thirty-four infants had consent provided and were enrolled in the study. After enrollment, it was determined that 2 infants did not meet the study criteria (cocaine exposure according to meconium drug screen results and chronic hypoxia in utero), and 1 was withdrawn from the study by the attending physician. Fifteen infants were assigned to receive morphine and 16 received clonidine. Table 1 shows the characteristics of the infants according to drug assignment. Those who received morphine were not significantly different from those who received clonidine in terms of birth weight, gestational age, 1- and
5-minute Apgar scores, postnatal age, and FS before and after initiation of treatment. Also listed in Table 1 are the different drugs of exposure, including methadone, buprenorphine, other opiates (hydrocodone, oxycodone), benzodiazepines, or tobacco. Most mothers used multiple drugs.

In our assessment of neurobehavioral performance, no statistically significant differences were noted between the mean ± SD intervals from the initiation of pharmacologic treatment and the first NNNS administration (6.6 ± 1.5 days for the morphine group and 5.5 ± 2.1 days for the clonidine group). There were also no mean between-group significant differences regarding the intervals between the initiation of treatment and the second NNNS (28.5 ± 16.4 days and 24.4 ± 18.9 days, respectively, for the morphine and clonidine groups). Table 2 compares the NNNS summary scores from the first and the second NNNS administration within and between treatment groups. Twelve of 13 summary scores are presented. Habituation procedures were not possible because many infants were not in a sleep state. The neurobehavioral performance did not differ between treatment groups at the first assessment, except for the mean lethargy score, which was higher in the clonidine group (5.13 ± 2.12) compared with the morphine group (3.6 ± 1.6). The morphine-treated infants exhibited no differences in their neurobehavioral performance from the first to the second assessment. However, the clonidine-treated infants showed significant improvements in areas of attention, handling, arousal, excitability, and lethargy. On the second assessment and compared with the morphine-treated infants, the clonidine group had significantly better scores in arousal and excitability.

The duration of treatment significantly differed between the morphine group and the clonidine group (median [range]: 39 [26–89] days vs 27.5 [18–107] days; P = .02). Figure 2 displays the Kaplan-Meier survival curve. One clonidine-treated infant (an outlier) was excluded from this analysis; the infant’s prolonged treatment was due to the clinical team’s decision to wean the dose every 5 days, which was a deviation from the protocol. Two morphine-treated infants completed therapy before discharge (41 and 31 treatment days); the remaining infants continued their treatment at home. The median (range) duration of home treatment was 13.5 (6–71) days for the clonidine group, which was significantly shorter than for the morphine group (26 [16–57] days) (Table 1). No infant received a second drug.

Because some infants required a dosage increase of either morphine or clonidine to achieve control of symptoms, the ROC curve was determined for each drug (Fig 3). For morphine, the optimal dose was 0.5 mg/kg per day (equivalent to 0.0625 mg/kg per dose given every 3 hours). For clonidine, the optimal dose was 7.5 μg/kg per day (~1 μg/kg per dose every 3 hours). This dose of clonidine is also consistent with
published population pharmacokinetics in newborn infants.\textsuperscript{38} Because blood sampling was not performed in prescribed intervals, kinetic studies were not possible. However, assays revealed that infants received the assigned drug.

Twelve children in each treatment arm were evaluated at the 1-year follow-up visit completed in September 2013. The morphine-treated infants were comparable to those who received clonidine in terms of their cognitive, motor, and language scores (Table 3). For 3 subjects, the language score of the Bayley Scales of Infant and Toddler Development, Edition III, was included in the analyses because the Preschool Language Scale, Edition IV, score was not available. Table 3 also presents the growth measures; these also did not differ between groups.

**DISCUSSION**

To our knowledge, this study is the first randomized trial comparing morphine versus clonidine as a single-drug therapy for NAS. Results of this pilot study are promising and suggest that clonidine is comparable to morphine in the treatment of NAS, specifically in terms of infants’ neurobehavioral performance. Those treated with clonidine exhibited significant improvement in some measures of neurobehavior, whereas those treated with morphine demonstrated no significant change in their neurobehavioral function even after a few weeks of pharmacologic treatment.

Clonidine, a $\alpha_2$-adrenergic agent, acts on the central sympathetic activity, which has been shown to be increased with opiate withdrawal. Prolonged opiate exposure results in activation of opiate receptors in the locus coeruleus, which contains clusters of noradrenergic cells. Opiate exposure decreases adenylate cyclase activity, reducing cyclic adenosine monophosphate levels.\textsuperscript{39–41} This effect on cyclic adenosine monophosphate results in increases in potassium efflux with associated decreases in calcium influx; these processes are inhibitory to brain noradrenergic activity.\textsuperscript{42,43} Cessation

**TABLE 1** Characteristics and Response to Treatment of Morphine- and Clonidine-Treated Infants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Morphine ($n = 15$)</th>
<th>Clonidine ($n = 16$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight, g</td>
<td>3024.6 ± 463</td>
<td>2763.9 ± 427</td>
</tr>
<tr>
<td>Gestational age, wk</td>
<td>37.8 ± 1.8</td>
<td>37.8 ± 1.4</td>
</tr>
<tr>
<td>Apgar score, median (range)</td>
<td>1 min 8 (7–9)</td>
<td>8 (3–9)</td>
</tr>
<tr>
<td></td>
<td>5 min 9 (8–10)</td>
<td>9 (5–10)</td>
</tr>
<tr>
<td>Male/female</td>
<td>7/8</td>
<td>6/10</td>
</tr>
<tr>
<td>Prenatal exposures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methadone</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Oxycodeone, hydrocodone</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Benzo diazepines</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Tobacco</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Age at treatment, d</td>
<td>2 ± 1</td>
<td>3 ± 1</td>
</tr>
<tr>
<td>FS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before treatment</td>
<td>13.5 ± 1.1</td>
<td>12.4 ± 1.4</td>
</tr>
<tr>
<td>At 48 h</td>
<td>7.4 ± 0.35</td>
<td>8.5 ± 0.30</td>
</tr>
<tr>
<td>At 7 d</td>
<td>6.6 ± 0.65</td>
<td>5.7 ± 0.44</td>
</tr>
<tr>
<td>At 14 d</td>
<td>7.1 ± 1.1</td>
<td>6.7 ± 0.98</td>
</tr>
<tr>
<td>Total length of treatment, d</td>
<td>42.7 ± 17.8</td>
<td>32 ± 20.4</td>
</tr>
<tr>
<td>Length of hospital stay, d</td>
<td>21 ± 12.3</td>
<td>14.9 ± 6.0</td>
</tr>
<tr>
<td>Length of treatment postdischarge, d</td>
<td>25 ± 11.06</td>
<td>18 ± 15.06</td>
</tr>
</tbody>
</table>

$P > 0.05$ for all comparisons according to the Wilcoxon rank-sum test except total length of treatment ($P = 0.02$) and duration of postdischarge treatment ($P = 0.005$). Unless otherwise noted, data are presented as mean ± SD.

**TABLE 2** NNNS Summary Scores of Morphine-Treated Versus Clonidine-Treated Newborns During the First and Second Assessments

<table>
<thead>
<tr>
<th>Behavior Scales (Summary Items)</th>
<th>NNNS Time 1</th>
<th>NNNS Time 2</th>
<th>Time 1 Versus Time 2</th>
<th>Time 1 Versus Time 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Morphine ($n = 15$)</td>
<td>Clonidine ($n = 16$)</td>
<td>Morphine ($n = 13$)</td>
<td>Clonidine ($n = 14$)</td>
</tr>
<tr>
<td>Attention</td>
<td>5.06 ± 0.27</td>
<td>4.51 ± 0.263</td>
<td>5.20 ± 0.27</td>
<td>5.39 ± 0.26</td>
</tr>
<tr>
<td>Handing</td>
<td>0.38 ± 0.06</td>
<td>0.42 ± 0.06</td>
<td>0.34 ± 0.06</td>
<td>0.18 ± 0.06</td>
</tr>
<tr>
<td>Quality of movement</td>
<td>5.2 ± 0.18</td>
<td>5.26 ± 0.17</td>
<td>5.05 ± 0.19</td>
<td>5.56 ± 0.18</td>
</tr>
<tr>
<td>Regulation</td>
<td>3.73 ± 0.42</td>
<td>4.15 ± 0.40</td>
<td>4.15 ± 0.44</td>
<td>3.55 ± 0.43</td>
</tr>
<tr>
<td>Nonoptimal reflexes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymmetric reflexes</td>
<td>0.20 ± 0.14</td>
<td>0.00 ± 0.14</td>
<td>0.46 ± 0.15</td>
<td>0.07 ± 0.15</td>
</tr>
<tr>
<td>Stress/abstinence</td>
<td>0.07 ± 0.01</td>
<td>0.08 ± 0.01</td>
<td>0.08 ± 0.01</td>
<td>0.05 ± 0.01</td>
</tr>
<tr>
<td>Arousal</td>
<td>3.91 ± 0.13</td>
<td>3.95 ± 0.13</td>
<td>4.02 ± 0.15</td>
<td>3.54 ± 0.14</td>
</tr>
<tr>
<td>Hypertonicity</td>
<td>0.40 ± 0.25</td>
<td>0.25 ± 0.24</td>
<td>0.77 ± 0.27</td>
<td>0.07 ± 0.26</td>
</tr>
<tr>
<td>Hypotonicity</td>
<td>0.13 ± 0.13</td>
<td>0.19 ± 0.13</td>
<td>0.23 ± 0.14</td>
<td>0.37 ± 0.13</td>
</tr>
<tr>
<td>Excitability</td>
<td>2.6 ± 0.53</td>
<td>2.38 ± 0.51</td>
<td>2.94 ± 0.56</td>
<td>0.84 ± 0.54</td>
</tr>
<tr>
<td>Lethargy</td>
<td>3.6 ± 0.50</td>
<td>5.13 ± 0.49</td>
<td>2.65 ± 0.54</td>
<td>3.70 ± 0.52</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SE.
of chronic opiate supply results in increases in noradrenergic activity. With the inhibitory effects of clonidine on noradrenaline release in the locus coeruleus, the noradrenergic neuronal activity decreases, resulting in a decrease in withdrawal manifestations.

Most studies evaluated clonidine as an adjunct to morphine or chloral hydrate for the treatment of NAS. Clonidine as adjunctive therapy for NAS was associated with a decrease in the number of morphine doses, duration of treatment, or length of hospital stay. From a recent randomized trial, clonidine given with morphine resulted in a shorter duration of therapy compared with the morphine and phenobarbital combination. However, these studies combined clonidine with morphine, and the concern for potential detrimental effects of continuing postnatal opiate exposure remains.

We observed a longer duration of treatment than those reported in combination therapy; this outcome may be related to the single-drug therapy. In addition, the dose for this study is at the lower end reported in the literature, especially for clonidine. A higher initial dose for morphine and clonidine is suggested from the ROC curves in our study. We also used a slow weaning schedule, being careful to monitor and avoid potential adverse effects from clonidine administration. In the NICU, infants had routine cardiovascular and respiratory monitoring. We found no significant fluctuation in blood pressure (ie, decreases with initiation of dose or with dose increases, increases in blood pressure when doses were decreased). Other investigators found no significant blood pressure changes with clonidine doses higher than used in our study.

Our research protocol did not dictate that treatment be completed before discharge; thus, infants were discharged to continue treatment at home. The length of stay is often emphasized as a benchmark of efficient care. However, multiple, complex issues, such as family involvement with child protective services, ensuring infant’s discharge to a safe home, and assisting the mother to access treatment programs are considerations in the evaluation of length of hospital stay.

Coyle et al evaluated the neurobehavior of infants born to mothers on methadone or buprenorphine; 69% were treated with morphine. Overall, their infants’ scores for attention, quality of movement, and self-regulation increased over days while scores for handling, arousal, excitability, depression, and hypertonia decreased with time. We found similar changes between the first and second assessments in our study but more so among the infants treated with clonidine. With our randomization schedule, an unbalanced distribution.
of prenatal exposure to methadone was noted. It is interesting that the infants with methadone exposure had better scores with clonidine treatment compared with those with no methadone exposure treated with morphine. The significant improvement of infants in some areas of neurobehavioral performance especially with clonidine is a pertinent consideration for long-term outcomes. Investigators have reported that the behavior profile from the NNNS of drug-exposed children predicted later childhood cognitive and behavior outcomes.48

The masking of clinical and research personnel, except for the clinical pharmacists for the duration of hospital stay was feasible. Masking of examiners was also feasible during the NNNS administration and long-term follow-up.

There are limitations to the present study. It was a pilot study with a small sample. The small number precluded a meaningful analysis as to which of the drugs predicted the highest FS to initiate pharmacologic treatment. We did not systematically determine prenatal drug exposure by using meconium assays. The nursing personnel had training in assessing FS, but we did not assess interobserver reliability. In addition, we did not include a protocol for adjunctive treatment. We continued treatment postdischarge, but this resulted in unmasking of the caretaker and the primary care physician. Although the caretaker had instructions to administer the medication with the dosing schedule noted on a calendar, concern still remains regarding caretaker’s competence to recognize changes in the child’s withdrawal manifestations and thus close outpatient follow-up is needed. Lastly, our preliminary findings are not generalizable.

CONCLUSIONS

Our findings suggest that clonidine may be as effective as morphine as a single-drug therapy for NAS. A randomized multicenter trial with long-term follow-up is warranted while considering other prenatal exposures, including nonopiate drugs. Longitudinal studies suggest that changes in behavioral outcomes occur after prenatal opiate exposure.49,50

The effects of NAS or its treatment on later development remain unclear.

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