Special Article

"Issues in Drug Management"

Part 4

Subcutaneous Infusions for Control of Cancer Symptoms

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Abstract

Continuous subcutaneous infusions offer a safe, simple, effective alternative to intravenous or intramuscular injections when oral medications cannot be used. They are extremely useful for cancer patients suffering from pain, vomiting, seizures, and other symptoms. Hydromorphone or morphine may be combined with metoclopramide, methotrimeprazine, or haloperidol (in D5W only), in the same pump to control both pain and nausea. Seizures can be controlled by subcutaneous infusion of phenobarbital or midazolam. If proper doses are prescribed and skin irritation is watched for, they can be used safely in the patient's home. J Pain Symptom Manage 1990;5:33-41.

Key Words

Subcutaneous infusion, pain, nausea, vomiting, seizures, metoclopramide, haloperidol, methotrimeprazine, midazolam, morphine, hydromorphone

"That nothing can be done to arrest the spread of tumor does not mean that there is nothing to be done at all.1 Control of distressing symptoms such as pain and nausea can allow a cancer patient's final days to be some of his richest. Usually oral medications are effective. When a patient is too weak, nauseated, or somnolent to swallow, buccal/sublingual2 or rectal3 routes are often adequate. The combination of severe symptoms and inability to tolerate oral or sublingual medications can mandate the use of parenteral medications. Frequent intramuscular injections or regularly restarting intravenous infusions can be very painful and distressing—particularly to the cachectic, the very young, and the very ill. The risks and complexity of these regimes often require unwanted and expensive hospitalizations. Subcutaneous infusions can control symptoms as well as or better than4 intramuscular injections or intravenous infusions with much less pain, risk, and expense. They are less invasive and costly than intrathecal or epidural methods.

Russell5 first described the use of subcutaneous infusions for pain control in England in 1979. Its use in England spread rapidly5 and now is common practice in many British hospices.7 It was 1983 before reports of morphine administration by this route began appearing in this country.8,9 At the New Age Hospice of Houston, we have had excellent results and few
problems in the last 3 years in treating a variety of symptoms in over 200 patients by this painless, simple, effective technique.

**Control of Pain**

Oral morphine or other oral analgesics can control pain in the large majority of cancer patients. Fewer than 20% of our hospice patients ever require parenteral narcotics. However, there are times, for a few patients when severe dysphagia, intractable vomiting, complete gastric stasis, bowel obstruction, or other crises prevent adequate absorption of analgesics from the oral or sublingual/buccal routes. Morphine suppositories, although useful, must be inserted every 4 hr and have very limited dosing flexibility. We find virtually 100% patient acceptance of subcutaneous infusions, unlike suppository use, in patients who cannot tolerate oral medications. Morphine levels from subcutaneous infusions are as high as from intravenous infusions—even in hypotensive patients.

A number of narcotic analgesics can be administered subcutaneously, but we have used only morphine and hydromorphone for subcutaneous infusions. Methadone and levorphanol have such long durations of action that they make dosage titration difficult. Butorphanol and pentazocine have a high incidence of psychotomimetic side effects. Meperidine is metabolized to a toxic metabolite, normeperidine, which can accumulate due to its long half-life. Heroin (diamorphine) is highly soluble, but its use remains illegal in the United States.

Hydromorphone is the narcotic we used most frequently for subcutaneous infusions. Hydromorphone is six times as soluble as morphine on a weight per volume basis, and it takes about 7 mg of parenteral morphine to reach the analgesic potency of 1 mg of hydromorphone. Since the subcutaneous tissue has a limited capacity to absorb fluid, hydromorphone has an advantage when there is a need for very high doses of narcotic, or very low volumes of drug (as in multiday infusions). It is available in a concentrated (10 mg/mL) preparation at a reasonable cost. The dose of subcutaneous hydromorphone needed is calculated by determining the optimal total daily dose of oral morphine (4 hourly doses x 6), and then dividing this number by 20 (see Table 1). We rarely need doses of subcutaneous hydromorphone over 200 mg per day, but Bruera and colleagues reported a range of subcutaneous hydromorphone doses from 40 to 4,024 mg per day. Clearly the therapeutic range of narcotics is enormous.

**Choice of Equipment**

A variety of different pumps can be used, but the standard intravenous (IV) infusion pumps are not ideal. They are generally too complex for families to manage at home, too cumbersome for easy portability in the ambulatory patient, very expensive, and operate at a much higher range of volumes than is useful for subcutaneous infusions.

We have had experience with several different pumps that are much better suited for use with subcutaneous infusions. All of these pumps are easily portable, operate in a low-volume range (2 to 50 cc per day), and can be managed by families at home. The following questions should be asked before choosing an infusion pump for subcutaneous infusions:

1. **Can the infusion rate be changed easily?** Cancer patients often change rapidly and the amount of pain medication needed changes often. Accurate dosing is the key to safe, successful therapy.

2. **Can it deliver "booster" doses?** There are often several times during cancer patients' days when their pain is temporarily greater (moving onto the bedside commode, a visit from a hostile relative, etc.). Booster doses cover these stress periods, thereby optimizing comfort and minimizing side effects for the whole day. With the Graseby MS26 syringe driver, we use about

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<th>Table 1</th>
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<tr>
<td>Approximate Equivalent Doses (in mg)*</td>
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<tr>
<td>Oral</td>
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<tr>
<td>Morphine</td>
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<td>Hydromorphone</td>
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<td>Oxycodone</td>
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<td>Levorphanol</td>
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<td>Methadone</td>
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*Estimates of narcotic bioavailability and potency vary widely among authors. The data above are the closest average of several references and this author's experience.

**The extremely long half-life of these drugs causes accumulation over days of use and makes estimation of potency very imprecise.
1 hr worth of medication for a typical booster, which is administered by pushing a button. These boosts can generally be given safely as often as every 15 min. We consider this feature very valuable for optimal pain control. In our experience, the additional complexity and expense of patient-controlled analgesia pumps are unnecessary and burdensome.

(3) Can the volume of drug remaining be checked visually? All mechanical devices (and the humans operating them) occasionally malfunction. It is important to be able to see how much drug has been infused into the patient.

(4) Can it be loaded and started without much difficulty? In the hospice inpatient unit, a number of different nurses will have to be able to set up the pump. For home use, the family will usually have to be able to reload and check the unit. More difficult loading means more errors, and less pump use.

(5) Can the pump hold 2 or more days' medicine? This capacity greatly reduces the number of nursing visits needed if the family cannot reload the pump.

(6) What extra equipment is needed? In the middle of the night, it is much easier to find 9-volt batteries and syringes than special drug cartridges or lengthy instruction manuals.

(7) Any particular problems? Complexities become simple with practice but cause errors and headaches at first. Syringe drivers are simple but do not restrict the patient's access to the drug (ie, the patient could manually inject himself with an overdose of the drug). This has only happened once in more than 200 patients in our hospice who were treated with a syringe driver type pump (Grasaby MS26). That patient was not harmed by the overdose.

(8) How much does the drug chamber cost? Since usually only 24 hr of drug is loaded at a time, and chambers are rarely refilled, this is the approximate cost per day of operating the pump, in addition to the cost of the parenteral drugs.

(9) How much does the pump cost? The pumps we tried ranged from over $3,000 (Pharmacia/Delteor) to under $800 (Graseby MS26 purchased in London).

Application Technique

An area on the chest, abdomen, upper arms, or thighs is shaved and prepped with providine iodine. The drug is loaded into the pump, and the tubing is flushed. A small-gauge butterfly needle is inserted at an angle under the skin (just as if starting an intravenous [IV] infusion except not in a vein). An adhesive bandage (Band-Aid) may be applied over the plastic butterfly "wings" for stability and padding (the needle insertion site is not covered). The site is covered by a clear adhesive dressing such as Tegaderm or Opsite. For ambulatory patients, a loop of tubing may be secured with adhesive tape. The pump is started and placed in its holster (see Figure 1).

Control of Nausea and Vomiting

Like pain, nausea and vomiting can have many causes. Some of them, such as constipation, hypercalcemia, or raised intracranial pressure, have specific treatments. When antiemetics are needed, and oral tablets cannot be tolerated, the standard rectal suppository preparations of prochlorperazine, promethazine, or chlorpromazine often provide relief. If the patient cannot be given suppositories, good results can be obtained in some patients with sublingual/buccal administration of concentrated solutions of haloperidol (2 mg/mL) or chlorpromazine (100 mg/mL but sometimes requires dilution to prevent mucosal irritation). Unfortunately, many patients who are nauseated cannot tolerate strong-tasting medications sublingually. As with analgesic suppositories, limited dosage flexibility and frequent turning limit the usefulness of suppositories for the severely or chronically nauseated patient. Subcutaneous infusions have been extremely useful for these problems.

Chlorpromazine and prochlorperazine are too irritating to the subcutaneous tissues to allow them to be used for continuous subcutaneous infusions.17 Fortunately, five antiemetics not available in suppository form are extremely useful when administered in this fashion (see Table 2).

(1) Haloperidol is a dopamine antagonist and is one of the most potent suppressors of the medullary chemoreceptor trigger zone. It has been found to be more effective than prochlorperazine for chemotherapy-induced vomiting and is much less sedating than chlorpromazine in comparable doses.18 It causes little if any skin irritation. It has been extremely effective in doses from 5 to 20 mg/day and remains our antiemetic of choice in most situations.
Fig. 1. Subcutaneous infusion application technique: (A) Assemble materials. (B) Load syringe driver and flush line. (C) Clean skin with alcohol. (D) Disinfect skin with iodine. (E) Insert butterfly needle. (F) Stabilize needle with adhesive strip. (G) Cover with transparent dressing.

(2) Metoclopramide is a procainamide derivative that both increases the motility of the gastrointestinal tract and blocks dopamine receptors in the chemoreceptor trigger zone. Its effectiveness in suppressing chemotherapy-induced nausea and vomiting are well known. Metoclopramide has been reported as effective for the chronic nausea of terminal cancer when
Table 2
Subcutaneous Infusion Medication List

- Atropine
- Calcitonin
- Cyclizine
- Dexamethasone
- Haloperidol
- Heparin
- Hydromorphone
- Hydroxyzine
- Methotrimeprazine
- Metoclopramide
- Midazolam
- Morphine
- Phenobarbital
- Scopolamine

given by continuous subcutaneous infusion with a Travenol infuser pump, in doses from 60 to 90 mg/day. It is compatible with morphine or hydromorphone in a high concentration (15 mg/mL) at refrigerator temperature for over 1 wk, so it is ideal for homecare applications. Baines and colleagues found that metoclopramide should not be used for patients with bowel obstruction because it tends to increase the colic. We have found metoclopramide a useful second antiemetic when haloperidol alone was not effective in unobstructed patients. It is the agent of choice when gastric stasis complicates nausea, as in the “squashed stomach syndrome” common with severe hepatomegaly.

(3) **Metotrimeprazine** (levomepromazine) is a phenothiazine with potent analgesic, antiemetic, and anxiolytic properties. By injection, methotrimeprazine 20 mg and morphine 10 mg are equally analgesic. There is no antagonism by naloxone, so its site of action is different than morphine. It is also a potent sedative. It is very useful, in combination with a narcotic, for pain control in patients who are extremely anxious. At St. Christopher's Hospice, it is the strong antiemetic of choice for subcutaneous infusions in patients with intractable vomiting and the sedative of choice for patients with terminal restlessness. It can cause orthostatic hypotension and skin irritation at the injection site in the higher-dosage ranges. Its package insert in the United States warns against subcutaneous administration, but the manufacturer sends the same preparation to the United Kingdom, where it is given routinely by subcutaneous infusion. This author has had excellent results with doses of 50 to 300 mg/24 hr. Needle sites should be closely watched and changed at the first signs of inflammation. Subcutaneous irritation can progress in rare cases to painful abscess formation.

(4) **Cyclizine** is an antihistamine with antiemetic activity in vestibular disturbances such as motion sickness. Since it affects the vomiting centers of the brain by a different route than the chemoreceptor trigger zone, it is a logical addition to one of the other antiemetics in cases of intractable vomiting. At St. Christopher’s Hospice, cyclizine commonly is administered to patients requiring antiemetics by subcutaneous infusion in doses from 75 to 100 mg/24 hr. At Sir Michael Sobell House (Oxford), the same type of skin irritation has been noted with higher doses of cyclizine as with methotrimeprazine, and the clinicians there suggest using concentrations of cyclizine below 25 mg/mL to prevent drug precipitation.

(5) **Hydroxyzine** is an anxiolytic sedative with antispasmodic, antipruritic, and antiemetic properties. In postoperative patients, 100 mg intramuscularly (IM) has the analgesic potency of 8 mg of morphine and provides additive analgesia when given together with morphine. In a second postoperative study, intramuscular morphine 5 mg and hydroxyzine 100 mg gave relief comparable to morphine 10 mg alone. We have found this drug useful as a coanalgesic and sedative. Like cyclizine, it might be useful as a second antiemetic. Its antipruritic effects have also been very useful in doses from 75 to 150 mg per day.

**Narcotic-Antiemetic Stability Study**

Many times, the reason patients cannot tolerate oral analgesics is because of persistent nausea and vomiting. Thus, the simultaneous administration of a parenteral narcotic and antiemetic is often needed. At St. Christopher’s Hospice in 1983, 5% (34) of the admissions required subcutaneous infusions, and by far the most frequent indication (74%) was for vomiting. Our experience has been similar, and yet the use of combinations of narcotics and antiemetics for subcutaneous infusion has not yet been reported, to our knowledge, on this side of the Atlantic. In the United Kingdom, heroin (diamorphine) is considered the narcotic of choice for subcutaneous infusions because of its solubility. Heroin is routinely mixed with the...
above-mentioned antiemetics and scopolamine (hyoscine) hydrobromide without compatibility problems, although Badger and Regnard warn against precipitation problems with higher concentrations of heroin and either haloperidol or cyclazine.

Limited data are available on the compatibility of morphine or hydromorphone with these antiemetics, necessitating the high-performance liquid chromatography (HPLC) study we have recently undertaken. Solutions of morphine sulfate (morphine sulfate, Merck and Company, West Point, PA; morphine sulfate–metoclopramide (metoclopramide, Reglan, A.H. Robins Company, Richmond, VA; morphine sulfate–haloperidol (haloperidol, Haldol, McNeil Pharmaceutical, McNeilab, Inc., Spring House, PA); hydromorphone HCL (hydromorphone HCL, Dilaudid, Knoll Pharmaceutical Company, Whippany, NJ); and hydromorphone HCL–metoclopramide, hydromorphone HCL-haloperidol, and hydromorphone HCL–methotrimeprazine (methotrimeprazine, Levo–promer, Lederle Parenterals, Inc., Carolina, PR) were quantitatively prepared in deionized and distilled water. Samples were examined against light and dark backgrounds for visible precipitation and measured with the use of HPLC.

(HPLC Instrumentation and Conditions: hydromorphone HCL-methotrimeprazine admixtures were chromatographed on a Hewlett-Packard 1090 liquid chromatograph, C-18 hypersil ODS column, 5 μm packing, 10-cm length. Isocratic conditions were maintained at .75 mL/min of 60/20/20 of .1% H3PO4/Acetonitrile/Methanol. Ultraviolet [UV] detection was obtained at 254 nm. Peak areas were integrated with a Hewlett-Packard 5392A integrator. All other admixtures were chromatographed on a Perkin-Elmer Series 4LC, C-18 FX Ultrasphere ODS column, 5 μm packing, 25-cm length. Isocratic conditions were maintained at 1.2 mL/min of 60/20/20 of .1% H3PO4/Acetonitrile/Methanol. Ultraviolet detection was employed with an Altex Model 153 detector at 254 nm. Peak areas were integrated with the Perkin-Elmer 5600 Data Station and Chromatographics Intelligent Terminal. LC runs were performed in triplicate, samples were stored in 25 mL clear glass scintillation flasks.) Visual examination and HPLC were performed immediately after sample preparation and after storage of 1, 4, and 7 days at refrigerator temperature (8°C). The concentrations used and results obtained are summarized in Table 3.

Injectable haloperidol is commercially available at a concentration of 5 mg/mL in a lactate buffer. When the solution is diluted to 2 mg/mL with a solution of morphine or hydromorphone in distilled water, a white crystalline precipitate forms. This precipitate was collected, washed, redissolved, and analyzed by HPLC as described above. It proved to be pure haloperidol.

At the New Age Hospice of Houston, we occasionally noted a white crystalline precipitate when haloperidol was diluted to 1 to 3 mg/mL with hydromorphone 10 mg/mL (Dilaudid HP) or normal saline. We noted that this precipitate was more common with bacteriostatic saline than with preservative-free saline.

At M.D. Anderson Cancer Center, they confirmed our observations that haloperidol forms a precipitate when diluted with normal saline. They pointed out that haloperidol 1 mg/mL in 5% dextrose has been shown to be stable in glass or plastic for 38 days at 24 degrees C. They tested haloperidol at concentrations of 1 to 3 mg/mL in 5% dextrose for precipitate formation. No precipitate was found in samples stored at room temperature (25°C), in the refrigerator (8°C), and the freezer (−70°C). They regularly dilute haloperidol with 5% dextrose for intravenous use with no apparent problems. At the New Age Hospice, we now use 5% dextrose as the diluent for all our subcutaneous infusions. No increase in skin reactions

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<tr>
<td>Results: Narcotic-Antiemetic Stability Study, 7 Days at 8°C in Distilled Water</td>
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<th>Stable (&gt;90% of active drug remains in solution)</th>
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<tr>
<td>Morphine sulfate (25 mg/mL)</td>
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<td>Hydromorphone HCL (20 mg/mL)</td>
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<th>Stable and compatible (&gt;90% of both drugs remain in solution)</th>
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<tr>
<td>Morphine sulfate (25 mg/mL) + metoclopramide (15 mg/mL)</td>
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<tr>
<td>Hydromorphone HCL (10 and 20 mg/mL) + metoclopramide (15 mg/mL)</td>
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<tr>
<td>Hydromorphone HCL (10 mg/mL) + methotrimeprazine (10 mg/mL)</td>
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<th>Instabilities indicated (precipitate formation)</th>
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<tr>
<td>Morphine sulfate (20 mg/mL) + haloperidol (15 mg/mL)</td>
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<tr>
<td>Hydromorphone HCL (15 and 10 mg/mL) + haloperidol (2 mg/mL)</td>
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has been noted, and haloperidol precipitation has only rarely been observed.

**Medical Management of Bowel Obstruction**

A distressingly frequent complication of abdominal cancer is inoperable obstruction of the bowel. Chronic nasogastric suction and intravenous fluids are uncomfortable at best and extremely difficult to manage at home. Baines and colleagues\(^1\) have reported a remarkable advance in control of symptoms in these patients, using oral medications, rectal suppositories, or subcutaneous infusions of diamorphine (heroin) and antiemetics (methotrimeprazine 50 to 150 mg/day, haloperidol 5 to 10 mg/day, and/or cyclizine 150 mg/day).\(^2\) They reported a series of 40 consecutive patients with bowel obstruction (18 confirmed by autopsy) in which 38 were managed without further surgery, without an intravenous line or nasogastric tube, and with excellent symptom control (only 10% had more than one vomit per day). Patients were encouraged to eat and drink freely. The mean survival was 3.7 mo with 7 patients living for 7 mo or more. We have had good results with continuous subcutaneous infusions of hydromorphine and haloperidol or methotrimeprazine for control of symptoms in several patients with malignant bowel obstructions. Transdermal or subcutaneous scopolamine has been helpful for control of colic. We consider our results in this area extremely encouraging.

**Control of Seizures**

Seizures from cerebral metastases can be controlled with oral anticonvulsants until the patient can no longer swallow medication. Phenytin is extremely irritating to peripheral veins and is not absorbed from rectal suppositories (no detectable levels from 250-mg suppositories made from cocoa butter or suppositrine).\(^3\) Carbamazepine is absorbed from rectal suppositories, but 660 mg to 1,800 mg per day may be required.\(^4\) A simple, painless, and effective method of controlling this distressing symptom is a continuous subcutaneous infusion of phenobarbital (150 to 260 mg/day). A loading dose of 65 to 130 mg can be pushed through the subcutaneous butterfly before the infusion is started.

Midazolam, a new, water-soluble benzodiazepine, is also proving useful for this purpose. Unlike phenobarbital and diazepam, it is compatible with narcotics and has a short duration of action. It seems to be as effective as diazepam for controlling seizures,\(^5\) anxiety, and dyspnea but is less irritating to subcutaneous tissues. Since it is several times as potent as diazepam, starting doses should be low and the responses, particularly respiratory rate, carefully monitored. We have found 2 to 10 mg/day to be safe and effective in most patients, but others have reported good results with much higher doses (36 to 60 mg/day).\(^6\)

**Control of Bronchial Secretions and Intestinal Colic**

The anticholinergic agents atropine or scopolamine (hyoscine) can be added to narcotic and antiemetic infusions. At doses of 0.8 to 2.0 mg/day they are often very effective.

**Precautions**

Once familiarity with a pump is gained, problems diminish. The most common adverse effect of this technique (and any method of continuous infusion) is drug overdose or underdose. We begin the large majority of patients on infusions in our inpatient unit where the patient’s response to therapy is closely monitored. Infusion rate corrections are made frequently. We also closely observe the infusion site in patients requiring high doses or combinations of antiemetics. Irritation at the infusion site often occurs under these circumstances, and the infusion site may need to be changed as often as once a day. In narcotic-only or phenobarbital infusions, the needle can usually be left in one position for 1 to 3 wk (a range of 2 to 31 days in one recent study).\(^7\)

**Conclusion**

As the number of patients with terminal illnesses grows and funds available for health care shrink, the need for cost-effective palliative care increases. Continuous subcutaneous infusions offer a safe, simple, cost-effective alternative to intravenous or intramuscular injections when oral medications cannot be used. They are extremely useful in cancer patients suffering from pain, nausea, seizures, and other symptoms. If drug dosage and skin irritation are monitored,
they can be safely used in a patient's home. Thus, patient, physician, and society can all benefit from increased utilization of this technique. By making use of all the skills, techniques, and wisdom available to make the cancer patient's body a comfortable place to live, we can make it possible for the final days to be a time of spiritual and emotional healing.

Acknowledgments
The authors thank Dr. Garold Yost, College of Pharmacology and Toxicology, University of Utah, for advice and assistance in obtaining the necessary drugs, and thank Sonja Chandler, MS, RPh, at M.D. Anderson Cancer Center for testing haloperidol in 5% dextrose for drug precipitation, and Mildred Duebberg for taking the photos. The authors also acknowledge Lederle Pharmaceuticals, Inc., A.H. Robins Co., Knoll Pharmaceutical Co., McNeil Pharmaceutical, and McNeillab, Inc., for their contribution of the pharmaceuticals used in this study.

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