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DRUG INTERACTIONS

Three Serious Drug Interactions that Every Dentist Should Know About

Elliot V. Hersh, DMD, MS, PhD; and Paul A. Moore, DMD, PhD, MPH

Abstract: Patients with complex medical and drug histories are becoming more commonplace in dental practice. This article reviews three serious adverse drug interactions that are well supported by the literature and can impact dental practice. Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit the renal excretion of lithium and lead to lithium toxicity. Metronidazole and fluconazole inhibit the metabolism of warfarin by blocking cytochrome P-450 2C9 (CYP-2C9), the major metabolic pathway of warfarin, with the end result being dramatic increases in patients' international normalized ratios (INRs) and potentially fatal bleeding. Propranolol and other nonselective beta-adrenergic blocking agents can inhibit the vasodilatory effect of epinephrine in dental local anesthetic solutions, leading to hypertensive reactions and a concomitant reflex bradycardia. It is important for clinicians to recognize and avoid these serious drug interactions. By doing so, they will provide the safest and best treatment for their patients.

LEARNING OBJECTIVES

- identify three serious drug interactions that impact dental practice
- discuss adverse events related to drug interactions in certain patients, as described in cases and clinical studies
- identify alternative medications that can be employed to avoid these serious drug interactions

Unquestionably, the aging dental patient population is consuming more and more drugs, including a variety of psychotropic medications and cardiovascular drugs.[1] The most common drugs that dentists prescribe or administer include nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and naproxen (Table 1), antibiotics and antifungals such as metronidazole (eg, Flagyl®) and fluconazole (eg, Diflucan®), and local anesthetics containing the vasoconstrictor epinephrine (Table 2). What many clinicians do not realize is that these commonly employed drugs in practice can be involved in serious adverse drug interactions with medications patients are taking for a variety of medical conditions. This article will review three of the serious interactions that can potentially occur within the practice of dentistry.

NSAIDs And Lithium

As illustrated in Table 1, there are a variety of NSAIDs from which dentists can choose to manage odontogenic and postoperative pain. These analgesics represent the first line drugs that should be employed in this situation because of their unique mechanism of action, an inhibition of prostaglandin synthesis at the site of surgical trauma, which renders these drugs highly effective in the treatment of postoperative dental pain.[2,3] There are numerous evidence-based, double-blind, placebo-controlled published studies that demonstrate the overall effectiveness of these drugs after the surgical removal of impacted third molars.[4-11] However, in certain patients, NSAIDs should be avoided or used cautiously because of the possibility of precipitating a serious adverse drug interaction. A comprehensive review of this subject can be found in previous publications.[12,13] One such drug is lithium.[14]

Lithium is a major remedy in the treatment of bipolar depressive disorder.[15] It has a low therapeutic index, which means the difference between effective doses and toxic doses is relatively small. Therefore, plasma levels of lithium must be carefully monitored to ensure therapeutic effectiveness while avoiding toxicity.[15] The NSAIDs inhibit the renal excretion of lithium and can cause plasma lithium to accumulate to toxic levels, potentially leading to renal, gastrointestinal, and central nervous toxicity.[14-18] Both ibuprofen 1800 mg/day and naproxen 750 mg/day for 6 days have been demonstrated to increase previously stable lithium plasma levels, and

TABLE 1

Common NSAIDs Used to Treat Acute Pain

GENERIC NAME	COMMON TRADE NAMES
Ibuprofen	Advil®, Motrin®, Vicoprofen®, Combunox®
Naproxen sodium	Aleve®, Anaprox®
Diflunisal	Dolobid®
Diclofenac	Cataflam®, Zipsor®
Ketoprofen	Orudis®
Etodolac	Lodine®
Meloxicam	Mobic®
Ketorolac	Toradol®, SPRIX®

TABLE 2

Local Anesthetics Containing Epinephrine

GENERIC NAME	COMMON TRADE NAMES
2% lidocaine with 1:50,000 or 1:100,000 epinephrine	Xylocaine®, Octocaine®, Lignospan®
4% articaine with 1:100,000 or 1:200,000 epinephrine	Septocaine®
4% prilocaine with 1:200,000 epinephrine	Citanest® Forte
0.5% bupivacaine with 1:200,000 epinephrine	Marcaine®

the magnitude of this effect varied widely among individuals.[16,17] Ibuprofen produced a mean increase of 34% (range 12% to 66%), while naproxen produced a mean increase of 16% (range 0% to 42%). Individual cases of three- to four-fold increases in lithium blood levels accompanied by stupor, ataxia, confusion, and renal failure have been reported after the use of ibuprofen 1600 mg/day for 1 week to treat shoulder pain.[18] A more recent report describes a 51-year-old patient with a history of bipolar disorder on lithium therapy presenting to an emergency department with confusion, dysarthria, abnormal gait, and diarrhea.[19] He subsequently needed to be intubated before being discharged from the hospital. His symptoms started 2 days after his dentist prescribed ibuprofen 800 mg 3 times daily after extracting an infected molar. His laboratory values were significant for elevated lithium levels of 3 mmol/liter (therapeutic range 0.6 mmol/liter to 1 mmol/liter) and mild renal failure. Another recent report describes a 49-year-old woman with stable lithium concentrations experiencing lethargy, diarrhea, nausea, vomiting, hypersalivation, tremors, muscle weakness, and confusion 3 days after being started on the NSAID meloxicam. Her serum lithium levels were greater than 5 mmol/liter.[20]

It is recommended that before prescribing NSAID analgesics to a patient on lithium therapy, dentists consult with the patient's psychiatrist. More frequent lithium blood level monitoring (every 4 to 5 days) should be initiated, and reductions in the lithium dose may be required.[14] An alternative is to avoid NSAID analgesics altogether in lithium-treated patients and prescribe acetaminophen, or if necessary, an acetaminophen/opioid combination drug such as acetaminophen plus hydrocodone (eg, Vicodin®).

Metronidazole or Fluconazole in Combination with Warfarin

Metronidazole is highly effective against obligate anaerobic bacteria associated with periodontal disease, periapical abscesses, and peri-implantitis.[21-24] Because it has no activity against facultative anaerobic bacteria, which may be part of a flora mixture inhabiting these infected sites, metronidazole frequently is combined with a penicillin or with ciprofloxacin.[21-23] Fluconazole is an antifungal agent that is effective in the treatment of mucosal candidiasis and other candidial infections in the oral cavity.[25]

Warfarin (eg, Coumadin®) is the most frequently prescribed anticoagulant in the world and is employed in preventing myocardial infarctions, pulmonary embolisms, and occlusive strokes in high-risk patients, such as those with atrial fibrillation, heart valve replacement, and deep venous thrombosis.[26,27] Similar to lithium, warfarin has a low therapeutic index, and monthly monitoring of patients' coagulation status is advised to ensure that plasma levels are in the therapeutic range.[12,27] Excessive blood levels of warfarin can lead to internal bleeding, including intracranial bleeding.[28]

Warfarin is mainly metabolized through the intestinal and hepatic cytochrome P-450 system, whose predominant metabolizing isoform is cytochrome P-450 2C9 (CYP 2C9).[29] Metronidazole and fluconazole are potent inhibitors of CYP 2C9; thus, they can block warfarin metabolism and subsequently increase blood levels of warfarin to toxic levels, especially its more potent S(-) isomer.[29-31]

In a study of eight normal volunteers, pretreatment with metronidazole 750 mg/day for 1 week significantly increased plasma levels and half-lives of even a single dose of warfarin compared to taking warfarin alone.[32] This was accompanied by a significant increase in mean prothrombin times.[32] In one case report, a 31-year-old woman who had received 6 years of warfarin therapy without a previous bleeding episode was admitted to a hospital with several ecchymoses of both legs and obvious swelling and hemorrhage into the subcutaneous tissue behind her left knee after completing a 10-day course of metronidazole 750 mg/day for a trichomoniasis infection.[30] Her prothrombin time was 147 seconds; the normal prothrombin time is 17 to 19 seconds. Vitamin K, the antidote for a warfarin overdose, was given and her condition resolved over 1 week.[30] More recently, a 78-year-old woman was started on metronidazole 250 mg every 8 hours for 5 days, and levofloxacin (Levoquin®) 500 mg once a day for 6 days for an upper respiratory tract infection.[33] The patient did not notify any of the healthcare professionals that she was on concomitant warfarin therapy. Her most recent international normalized ratio (INR) reading had been 2.5. Six days after her clinic visit, the patient was admitted to the hospital for a profuse nosebleed and "an unusual headache," and a CAT scan revealed she had a minor hemorrhagic stroke. Her INR had risen to 8.0. After a 1-week hospital stay, which included the administration of vitamin K and a blood transfusion, she was discharged.[33]

Cases of cerebral hemorrhage,[34] gastrointestinal bleeds,[35,36] intraocular hemorrhage,[37,38] and significantly elevated INRs[36,39] due to a warfarin–fluconazole interaction have appeared in the literature. In a retrospective cohort study, 22,272 veterans who had been on warfarin therapy for at least 1 month were administered an antimicrobial agent. Among them, 9.7% of those who received fluconazole and 4.9% of those who received metronidazole had INRs that were greater than 6.0 (normal INRs in anticoagulated patients should be between 2.0 and 3.0).[40] Employing US Medicaid data, a case-control study of 308,100 warfarin users demonstrated an elevated risk (odds ratio = 2.09) of gastrointestinal bleeding in warfarin recipients receiving fluconazole compared to those receiving the non-interacting antibiotic cephalexin (Keflex®).[41]

Based on these case reports and clinical studies, the authors recommend that dentists avoid prescribing metronidazole or fluconazole in patients on concomitant warfarin therapy.

Epinephrine with Propranolol

There is probably no area in dental pharmacology that is more highly debated than the use or avoidance of epinephrine-containing local anesthetics in certain medically complex patient populations, including those taking potentially interacting drugs.[12,42-47] In reality, case reports describing adverse drug interactions between vasoconstrictors in dental local anesthetic solutions and potential interacting drugs are extremely rare, partly because epinephrine is currently by far the vasoconstrictor agent most widely used with local anesthetics in dentistry. While epinephrine has alpha-1 adrenergic vasoconstrictive effects on some vascular beds—most notably under the skin and mucous membranes—it also has vasodilatory effects on other vascular beds that contain predominantly beta-2 adrenergic receptors, such as those in skeletal muscle, resulting in vasodilation[48] (Table 3). This opposing vasodilatory property of epinephrine limits the potential pressor effects of the drug compared to other agents like levonordefrin and norepinephrine, which have less, and in the case of norepinephrine, almost no beta-2 adrenergic activity.[44,47,49]

Beta adrenergic–blocking drugs, also known as beta-blockers, are widely used in the treatment of hypertension, angina, cardiac arrhythmias, and migraine headaches.[50] They are classified into two groups: nonselective beta-blockers that block both beta-1 and beta-2 receptors; and cardioselective beta-blockers, which only block beta-1 receptors (Table 4). The cardioselective beta-blockers are more widely prescribed today because their lack of beta-2 adrenergic–blocking activity limits the bronchoconstrictive effects occasionally seen with nonselective beta-blockers.[50] However, the nonselective beta-blocker propranolol is still widely prescribed.[51]

A case series describing severe hypertensive reactions in six patients on chronic propranolol therapy receiving lidocaine with epinephrine for facial plastic surgery procedures has appeared in the literature.[52] In two of the cases, the patients had been administered 10 ml and 12 ml of a 1% lidocaine plus 1:100,000 epinephrine solution, respectively. This translates into the amount of epinephrine in approximately six and seven 1.7-ml dental local anesthetic cartridges. Their blood pressures rose from normal levels (120/80 and 110/70 mm Hg) to acutely hypertensive levels (200/100 and 190/110 mm Hg), with a concomitant reflex bradycardia. In a third case, a patient receiving 13 ml of a 1:200,000 epinephrine solution went into cardiac arrest and had to be resuscitated with emergency treatment, including defibrillation.[52]

There is only a single case report in the dental literature in which a patient, a 32-year-old woman, taking daily propranolol for hypertension and dysrhythmias received 1.5 cartridges of 2% mepivacaine plus 1:20,000 levonordefrin (a vasoconstrictor chemically related to epinephrine).[53] Her systolic and diastolic blood pressures rose by 40 mm Hg and 15 mm Hg, respectively. When two cartridges of 3% mepivacaine plain were used on a subsequent visit, her blood pressure remained stable.

The theoretical basis of this serious adverse drug reaction between propranolol and epinephrine is that the former blocks the beta-2 vasodilatory effects of epinephrine, leaving the alpha-1 vasoconstrictive effects functioning unopposed, leading to hypertension with a concomitant reflex bradycardia.[42,43,47] One of the most compelling studies supporting the adverse interaction between propranolol and epinephrine is illustrated in Figure 1 and Figure 2.[54] Five patients being treated for long-standing severe hypertension with either the nonselective beta-adrenergic blocking agent propranolol or the cardioselective beta-adrenergic blocking agent metoprolol took their usual morning dose of their respective beta-adrenergic blocking agent 2 hours prior to undergoing a vasopressor challenge using slow epinephrine infusions of various doses over 8 minutes. After the completion of the first session, these patients were crossed over to the alternative treatment for at least 4 weeks, and the epinephrine challenge was administered

TABLE 3

The Action of Epinephrine at Various Receptors

RECEPTOR SUBTYPE	RECEPTOR ACTIONS
Alpha-1 Adrenergic	Vasoconstriction of blood vessels beneath skin and mucous membranes
Beta-1 Adrenergic	Increased heart rate Increased contraction force
Beta-2 Adrenergic	Bronchodilation Vasodilation of blood vessels in skeletal muscle and internal organs

TABLE 4

Classification of Beta-Adrenergic Blocking Agents with Common Trade Names

NONSELECTIVE BETA-BLOCKERS	CARDIOSELECTIVE BETA-BLOCKERS
Propranolol (Inderal®)	Atenolol (Tenormin®)
Nadolol (Corgard®)	Metoprolol (Lopressor®)
Timolol (Blocadren®)	Acebutolol (Sectral®)
Sotalol (Betapace®)	Betaxolol (Kerlone®)

again. As shown in Figure 1, following the slow infusion of 16 µg (2 µg/min) of epinephrine, which is slightly less than that found in a single 1.7-mL 1:100,000 epinephrine dental cartridge (17 µg or 0.017 mg),[47] the mean increase in systolic blood pressure was about 15 mm Hg in the propranolol group and only 5 mm Hg in the metoprolol group. As shown in Figure 2, the differences in diastolic blood pressure following the 16-µg epinephrine infusion was even more pronounced, increasing only 2 mm Hg in the metoprolol group but 14 mm Hg in the propranolol group. This difference reached the level of statistical significance ($P < 0.05$). When 32 µg of epinephrine was slowly infused, an amount slightly less than two 1.7-mL cartridges of a 1:100,000 solution (34 µg or 0.034 mg),[47] the metoprolol group exhibited a 10-mm Hg increase in mean systolic blood pressure, whereas the propranolol group exhibited a mean systolic blood pressure increase of 33 mm Hg ($P < 0.05$). Diastolic blood pressure remained unchanged in the metoprolol group but increased 21 mm Hg in the propranolol group ($P < 0.05$).[54] Other intravenous infusion studies have reported similar pressor responses when epinephrine was administered to patients on propranolol and other nonselective beta-blockers.[55-57] Although one can argue that intravenous infusions do not resemble typical submucosal dental injections, inadvertent intravascular injections do occur in dental practice, with injection speeds at least eight times more rapid (one cartridge per minute) than the infusion rates in the studies discussed here.[47]

There are two studies in the literature where individuals on nonselective beta-adrenergic blocking agents received dental injections of lidocaine with epinephrine.[58,59] In one study, when normal volunteers were pretreated with a single oral dose of the nonselective beta-adrenergic blocking agent pindolol, small (8 mm Hg to 9 mm Hg) but significant ($P < 0.05$) increases in systolic and diastolic blood pressure and peripheral vascular resistance, with corresponding decreases in heart rate, were observed after the administration of two intraoral injections of 2% lidocaine plus 1:80,000 epinephrine (45 µg or 0.045 mg epinephrine total). When these same individuals were not pretreated with pindolol, the administration of the same dose of local anesthetic solution induced small decreases in systolic and diastolic blood pressure and peripheral vascular resistance.[58] Similar results were reported in dental patients with cardiovascular disease on nonselective beta-blocker therapy who received a single cartridge of 2% lidocaine with 1:80,000 epinephrine (22.5 µg or 0.0225 mg epinephrine).[59]

Based on the case reports in the plastic surgery literature and the results of the clinical studies presented above, the following recommendations are made. In patients requiring simple restorative dentistry procedures who are on propranolol or other nonselective beta-adrenergic blocking agents, complete avoidance of local anesthetic solutions containing epinephrine, such as employing 3% mepivacaine or 4% prilocaine plain, appears prudent. In patients requiring hemostasis for dental surgical procedures or a longer duration of action, an absolute maximum of 0.034 mg of epinephrine (two cartridges of a 1:100,000 solution or four cartridges of a 1:200,000) solution is advised. Proper aspirating technique is mandatory to avoid inadvertent intravascular injections, and very slow injections rates are recommended. Before administering additional cartridges of local anesthetic solution, blood pressure and heart rate should be taken to ensure that these vital signs remain stable. The use of 1:50,000 epinephrine

FIG 1.

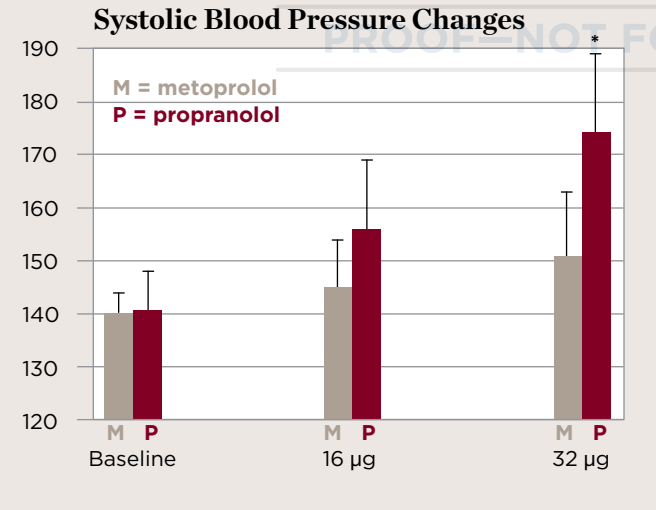

Fig 1. Systolic blood pressure recordings (mean ± SEM) at baseline and at the end of 16-µg and 32-µg epinephrine infusions in five hypertensive patients on long-term metoprolol or propranolol therapy. The study was a crossover design. (* $P < 0.05$ versus metoprolol pretreatment.)
(Data from Houben H, Thien T, van't Laar A. Effect of low-dose epinephrine infusion on hemodynamics after selective and nonselective beta-blockade in hypertension. *Clin Pharmacol Ther.* 1982;31[6]:685-690. Redrawn and used with permission from Hersh EV, Giannakopoulos H. Beta-adrenergic blocking agents and dental vasoconstrictors. *Dent Clin North Am.* 2010;54[4]:687-696.)

FIG 2.

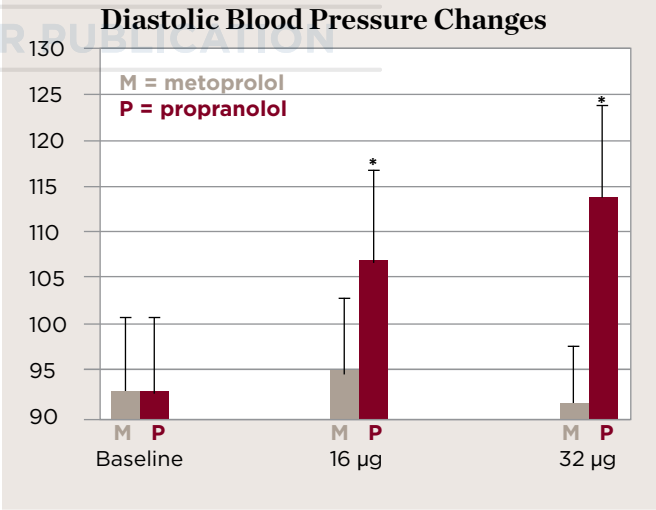

Fig 2. Diastolic blood pressure recordings (mean ± SEM) at baseline and at the end of 16-µg and 32-µg epinephrine infusions in five hypertensive patients on long-term metoprolol or propranolol therapy. The study was a crossover design. (* $P < 0.05$ versus metoprolol pretreatment.)
(Data from Houben H, Thien T, van't Laar A. Effect of low-dose epinephrine infusion on hemodynamics after selective and nonselective beta-blockade in hypertension. *Clin Pharmacol Ther.* 1982;31[6]:685-690. Redrawn and used with permission from Hersh EV, Giannakopoulos H. Beta-adrenergic blocking agents and dental vasoconstrictors. *Dent Clin North Am.* 2010;54[4]:687-696.)

and the use of epinephrine-impregnated gingival retraction cord that contains 0.5 mg to 1 mg of racemic epinephrine per 2.5 cm,[60] should be absolutely avoided.[47,61]

Conclusion

With an aging dental patient population using an increasing amount of drugs, practitioners must be cognizant of adverse drug interactions that can potentially endanger their patients. Three such serious interactions have been reviewed. NSAIDS, which are highly effective in the treatment of postoperative pain, should be avoided or used cautiously in lithium-treated patients. Prescribing either metronidazole, an effective drug against anaerobic bacteria, or the antifungal agent fluconazole should be avoided in patients who are on concomitant warfarin therapy. Finally, for patients on propranolol, epinephrine-containing local anesthetics should be avoided in patients undergoing restorative procedures of short duration and used cautiously (no more than 0.034 mg) in patients requiring hemostasis or longer duration dental procedures.

DISCLOSURE

Within the past five years, Dr. Moore has served as medical director and/or a research consultant to several pharmaceutical companies marketing local anesthetic products, including DENTSPLY Pharmaceutical Division, Kodak Dental Systems, Septodont USA, St. Renatus, and Novocol of Canada Inc. His consultations have involved pharmacovigilance of marketed products as well as protocol development of new anesthetics for dentistry. Dr. Hersh had no disclosures to report.

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QUIZ

Three Serious Drug Interactions that Every Dentist Should Know About

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1. **Lithium is a major remedy in the treatment of:**
   A. atrial fibrillation.
   B. bipolar depressive order.
   C. hypertension.
   D. anxiety.

2. **Cases of increases in lithium blood levels accompanied by stupor, ataxia, confusion, and renal failure have been reported after the use of:**
   A. ibuprofen.
   B. penicillin.
   C. diazepam.
   D. hydrocodone.

3. **Fluconazole is an antifungal agent that is effective in the treatment of:**
   A. anaerobic bacterial infections.
   B. aerobic bacterial infections.
   C. facultative anaerobic bacterial infections.
   D. mucosal candidiasis and other candidial infections in the oral cavity.

4. **Warfarin is employed in high-risk patients, including those with:**
   A. atrial fibrillation.
   B. heart valve replacement.
   C. deep venous thrombosis.
   D. all of the above

5. **As potent inhibitors of CYP 2C9, metronidazole and fluconazole can block the metabolism of:**
   A. warfarin.
   B. hydrocodone.
   C. naproxen.
   D. none of the above

6. **The antidote for a warfarin overdose is:**
   A. naloxone.
   B. vitamin K.
   C. ibuprofen.
   D. lidocaine.

7. **For certain medically complex patients, perhaps no area in dental pharmacology is more debated than the use or avoidance of local anesthetics containing:**
   A. ketorolac.
   B. fluconazole.
   C. epinephrine.
   D. ibuprofen.

8. **Beta adrenergic–blocking drugs, also known as beta-blockers, are widely used in the treatment of:**
   A. hypertension.
   B. angina.
   C. migraine headaches.
   D. all of the above

9. **Theoretically, propranolol blocks the beta-2 vasodilatory effects of epinephrine, leaving the alpha-1 vasoconstrictive effects functioning unopposed, which leads to:**
   A. angioedema.
   B. stomach ulcers.
   C. hypertension.
   D. tachycardia.

10. **In patients requiring hemostasis for dental surgical procedures who are on propranolol, a maximum of how much epinephrine is advised?**
    A. 0.034 mg (34 µg)
    B. 0.054 mg (54 µg)
    C. 0.068 mg (68 µg)
    D. 0.108 mg (108 µg)

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