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Moxifloxacin (Avelox[®]) For The Treatment Of Bacterial Skin Infections

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ABSTRACT

Moxifloxacin (Avelox[®], Bayer), which is available for oral administration, is a broad-spectrum synthetic antimicrobial agent with excellent Gram-positive activity and good Gram-negative activity. The US FDA recently approved this drug for the treatment of bacterial skin infections.

Key Words: bacterial skin infections, Gram-positive, Gram-negative, fluoroquinolones, moxifloxacin

Moxifloxacin, also known as Bay12-8039, is a new oral 8-methoxyfluoroquinolone that has significant use in the treatment of bacterial infections of the skin. It differs from the other quinolones by having a methoxy radical at the 8-position, with an S, S-configured diazabicyclonoyl ring moiety at the 7-position, and by having improved anti-bacterial activity over other similar quinolones.^{1, 2, 3}

Mechanism of Action

Moxifloxacin is bactericidal against a range of Gram-positive and Gram-negative organisms. Such activity arises through the inhibition of DNA gyrase (topoisomerase II) and topoisomerase IV, which bacteria require for DNA replication, transcription, repair, and recombination. Moxifloxacin contains the C8-methoxy moiety that augments its antibacterial activity and reduces the possibility of Gram-positive mutations. Because the 8-fluoroquinolones use a different mechanism of action than do the aminoglycosides, beta-lactams, macrolides, or tetracyclines, there has been no known cross-resistance between the quinolones and these antimicrobial agents. While cross-resistance does occur between moxifloxacin and other quinolones with Gram-negative bacteria, moxifloxacin continues to have more activity against most Gram-positive bacteria, particularly those now resistant to other fluoroquinolones.⁴⁻⁷ This agent also shows significant activity against *Mycobacterium leprae*.⁸ (See Table 1)

Pharmacokinetics

Moxifloxacin has a rapid rate of absorption with the majority of the administered dose available systemically within two hours. It is 50% bound to serum proteins, so that tissue levels will often exceed plasma concentrations in the skin, in subcutaneous tissue, and in blister formations. The skin blister concentration/plasma concentration ratio of 1.5 at 24 hours demonstrates that moxifloxacin penetrates well into inflammatory lesions.⁹ There is excellent bioavailability (>85%) and a half-life of 11-14 hours.

This 8-methoxyfluoroquinolone is not affected by, nor does it affect, the cytochrome P450 system. About 45% of the drug is excreted unmetabolized. Thirty-eight percent of the agent is eliminated in the feces with sulfate conjugation, while 14% is converted to a glucuronide conjugate and is excreted in the urine.

Renal and hepatic insufficiency does not affect the pharmacokinetics. Although photosensitivity is a potential unwanted effect with 8-fluoroquinolones, moxifloxacin has not produced UVA or UVB sensitivity. The photosensitivity of lomefloxacin, sparfloxacin, and pefloxacin has limited their usefulness.⁹

Iron and antacids can reduce the bioavailability of all agents in this group, but there are no drug-drug interactions with digoxin, glyburide, probenecid, ranitidine, theophylline, or warfarin. When moxifloxacin was given with a 500-calorie fat meal, there was no decrease in absorption.

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Aerobic Gram-positive bacteria	<i>Staphylococcus aureus</i> (methicillin-susceptible), <i>Staphylococcus epidermidis</i> (methicillin-susceptible), <i>Streptococcus pneumoniae</i> (including penicillin-susceptible/resistant strains), <i>Streptococcus pyogenes</i>
Aerobic Gram-negative bacteria	<i>Escherichia coli</i> , <i>Haemophilus influenzae</i> , <i>Hemophilus parainfluenzae</i> , <i>Klebsiella oxytoca</i> , <i>Klebsiella pneumoniae</i> , <i>Moraxella catarrhalis</i> , <i>Proteus mirabilis</i>
Anaerobic bacteria	<i>Fusobacterium</i> species, <i>Peptostreptococcus</i> species, <i>Prevotella</i> species
Other microorganisms	<i>Chlamydia pneumoniae</i> , <i>Legionella pneumophila</i> , <i>Mycobacterium leprae</i> , <i>Mycoplasma pneumoniae</i>

Table 1: Selected bacteria susceptible to moxifloxacin.

Clinical Profile

Moxifloxacin, given once daily as a 400mg tablet, is useful in treating uncomplicated skin infections of bacterial origin. In a study of 351 patients with such infections,⁷ moxifloxacin (400mg, daily) administered orally for 7 days was compared with cephalexin (500mg, tid).¹⁰ Moxifloxacin was 90% successful clinically, compared to 91% for the cephalosporin. Both eradicated *Staphylococcus aureus* (moxifloxacin 92%, cephalexin 93%), with moxifloxacin eradicating more of the *Streptococcus* species (90% to 82%).

Adverse Events

Drug related adverse events caused discontinuation in 3% of the moxifloxacin patients, while 4% of the cephalexin treated patients stopped treatment. The unwanted reactions most commonly found included nausea (8%), diarrhea (6%), headache (2%), abdominal pain (2%), vomiting (2%), taste perversion (1%), and dyspepsia (1%). Abnormal liver function studies (elevated bilirubin levels) occurred in 1% of the study group.

When compared to other available fluoroquinolones, moxifloxacin receives a high rating. There is no interference with the QTc interval. It has a favorable safety profile. The dosage is not dependent upon creatinine levels, as is the case with ofloxacin and levofloxacin. Headaches and dizziness are uncommon, contrary to the experience with trovafloxacin.

Conclusions

Many clinicians may select a macrolide or a cephalosporin as their first choice for treating bacterial skin infections. However, the excellent penetration of the quinolones and their broader antibacterial spectrum make them an integral part of the dermatologic armamentarium.¹¹ The safety profile of moxifloxacin, its bactericidal activity, and its once daily dosage highlight its attributes. (See Table 2.)

Moxifloxacin has an excellent safety and efficacy profile and can be used in dermatologic practice as part of the antimicrobial armamentarium to treat bacterial skin and skin structure infections.¹²

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Treatment of Hemangiomas in Children

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ABSTRACT

Although hemangiomas are frequently encountered in pediatric practice, their management has been controversial because they are notoriously unpredictable, especially in early infancy. In the past, clinicians believed that infant and childhood hemangiomas were best left untreated, due to spontaneous involution and the adverse effects of treatments such as radiotherapy and surgery.¹ However, today there is an increased awareness of both the physical and psychological sequelae associated with hemangiomas, a small percentage of which can be life threatening and this has resulted in a renewed push to treat them. Furthermore, therapeutic advances have been made, and new therapies are on the horizon.

Key Words: active non-intervention, hemangiomas, PHACES Syndrome

Hemangiomas, benign tumors of infancy, occur in 1-2% of newborns and up to 10% of children aged ≥ 1 year.² Fifty five percent present at birth, while the rest develop within the first few weeks of life. They are more commonly found in premature infants weighing less than 1500gm,² and a female's chance of being affected is three times greater than a male's.³

Typically, hemangiomas begin as pale blue-red macules with superficial telangiectases. Over the next 8-14 months they proliferate rapidly into bright red elevated plaques if they are superficial. If they lie deeper within the skin they appear as a bluish nodule. They are most commonly a combination of both.^{3,4} The proliferative phase is followed by slow involution, and almost all hemangiomas resolve spontaneously over time. By 5 years of age, 50% of hemangiomas involute, 70% by age 7, and 90% by age 9.^{2,3} Approximately 20-40% leave residual changes in the skin, which can have a lasting psychological effect. Approximately 10% require treatment, and less than 1% are life threatening. Hemangiomas are usually solitary, but up to 20% of affected children have multiple lesions.³

Past and Current Therapies

Historically, the treatment of hemangiomas usually involved surgical excision or radiation. Today, while it is recognized that most hemangiomas do not need treatment, 'active non-intervention', rather than 'benign neglect' is advised.¹ Before and after photographs are extremely helpful in reassuring parents of the natural involution of this phenomenon.³

Hemangiomas that threaten life or an important bodily function, such as vision or the airway, do require intervention. Recognizing high risk hemangiomas and being aware of all possible associated malformations, e.g., PHACES syndrome (P_{osterior} fossa malformations, H_{emangiomas} of the cervicofacial region, A_{rterial} anomalies, C_{ardiac} anomalies, E_{ye} anomalies and S_{ternal} or abdominal clefting or ectopia cordis), is essential to ensure the patient receives the most appropriate treatment and to reduce sequelae. For example, midline hemangiomas can be markers for occult spinal malformations, and anomalies of the anorectal and urogenital regions. Consequently, spinal imaging should be done.³

For management, a multidisciplinary approach is best, including dermatology, pediatrics, plastics and radiology.² In the more

severe cases, psychological and social support services can also be helpful. Essentially, the type and location of hemangioma, the associated complications, as well as the patient's age should guide the treatment.

Hemangiomas That Require Treatment

Lesions that require treatment include:

- life and function threatening hemangiomas, e.g., those causing impairment of vision, Kasabach-Merritt coagulopathy, respiratory compromise, congestive heart failure, hepatic involvement
- hemangiomas in certain anatomic locations that often leave permanent scars or deformity, especially the nose, lip, ear, and glabellar area
- large facial hemangiomas, especially those with a prominent dermal component (more likely to leave permanent scarring)
- smaller visible hemangiomas, (e.g., the face and hands) may be considered for treatment with modalities unlikely to cause scarring or significant side effects
- ulcerated hemangiomas
- pedunculated hemangiomas (likely to leave significant fibrofatty tissue after involution)
- hemangiomas that are psychologically disturbing, such as lesions on the face, hands and feet.²

Treatment

Corticosteroids

While the mechanism of action for corticosteroids is unknown, there are data to suggest that vasoconstriction of arterioles and precapillaries may be responsible, and it has been suggested that steroid therapy works by increasing the sensitivity of arterioles and precapillaries to other, physiologically occurring vasoconstrictive agents.⁵ Certain steroids inhibit angiogenesis in the presence of a fragment of heparin. Triamcinolone reduced the transcription of the growth factors, PDGF-A and -B, IL-6, TGF- β 1 and - β 3. Furthermore, there was up-regulation of the mitochondrial cytochrome *b* gene expression.⁶

Superficial hemangiomas requiring treatment, with the exception of those affecting vision or causing respiratory distress, are generally treated with either localized use of corticosteroids (potent topical or intralesional) or with pulsed dye laser.¹

Complication	Type/Occurrence	Comments
Ulceration	<ul style="list-style-type: none"> • results from necrosis • typically occurs in deep, rapidly enlarging hemangiomas • when at the anogenital region, there is a high risk of ulceration 	<ul style="list-style-type: none"> • most frequent complication • can be excruciatingly painful • can cause infection, hemorrhage and scarring
Astigmatism	at periorbital and periocular regions	<ul style="list-style-type: none"> • should be carefully monitored • should be evaluated by ophthalmologist
Otitis; decrease in auditory conduction	when involving the ear, may obstruct the external auditory canal	may delay speech development
Visceral hemangiomas	may be associated with diffuse or multiple cutaneous hemangiomas, and large facial hemangiomas	<ul style="list-style-type: none"> • have a much higher morbidity and mortality rate (40-80%) • lesions with a high flow pattern may cause high-output cardiac failure and anemia (e.g., liver, which typically involves both lobes)
Airway obstruction or associated airway involvement	cutaneous hemangiomas that involve the chin, lips, mandibular region, "beard distribution" area and neck at greatest risk for this complication	<ul style="list-style-type: none"> • may be life threatening • may progress rapidly to respiratory failure
Hoarseness and stridor	subglottic hemangiomas	may progress rapidly to respiratory failure
Kasabach-Merritt phenomenon (KMS)	kaposiform hemangioendotheliomas or tufted angiomas	does not have typical hemangiomas. KMS can lead to significant morbidity and bleeding, but this is not a complication of true hemangiomas, as was previously believed.

Table 1: Possible complications caused by hemangiomas.³

The use of triamcinolone, 20mg/ml, can be used as intralesional corticosteroid therapy for any small, bossed, facial hemangioma. The drug should be injected at low pressure, using a 3ml syringe and 25-gauge needle.⁷ The dose should not exceed 3-5mg/kg per procedure. Treatment in the periocular region is contraindicated except by an experienced ophthalmologist, as there is a risk of embolic occlusion of the retinal artery or oculomotor nerve palsy.³

During the injection of any facial lesion, the surrounding tissue should be compressed, either digitally or with the finger ring of an instrument. Usually three to five injections are needed, given at 6-8 week intervals. The response rate is similar to that for systemic corticosteroids. If there is necrotic tissue and/or secondary infection, the injections should not be undertaken.⁷

Resulting complications have been few, although serious consequences may result. Shorr and Seiff⁸ reported a case of central retinal artery occlusion due to retrograde blood flow. This resulted from the force of injection or digital pressure, which in turn propelled steroid suspension particles into the central retinal artery. Full thickness eyelid necrosis may be related to spontaneous thrombosis within the lesion. Linear subcutaneous fat atrophy following lymphatic channels has been reported, but remits spontaneously.⁹

As a mainstay of treatment for serious cases, the most common choice is oral prednisone, at a dosage of 2-4mg/kg/day given

either in a single morning dose or divided doses in emergent cases. Within days approximately 1/3 of affected infants exhibit dramatic shrinkage of the hemangioma. Stabilization of growth without measurable shrinkage can be seen in another third, and minimal or no effect in the final third. Increasing the dosage does not enhance results in situations where there is poor response. If effective, corticosteroids must be continued for the entire anticipated proliferative phase or regrowth will occur.^{1,3,4}

Infants treated with systemic corticosteroids need to be observed for adverse effects such as growth retardation, blood pressure elevation, insulin resistance, and immunosuppression. Moon facies have been recorded as a side effect of prednisone. However, they disappear shortly after treatment is completed.⁵

Interferon Alpha

Although interferon alpha has shown very promising results, there have been reports of neurotoxicity,⁴ and it should be reserved for use only in life threatening cases where high-dose corticosteroid treatment has failed.³ It has a limited role in treating subglottic hemangiomas.

Both interferon alpha-2a and alpha-2b are usually administered as a subcutaneous (SC) injection of 3 million U/m² of body-surface area per day.³ Regular neurological monitoring before and during treatment is mandatory.⁴ For high-risk hemangiomas SC interferon alpha-2a should be given, at an initial dose of 1 million U/m²/day,

which is then increased to 3 million U/m²/day if tolerated.²

Common side effects, including irritability, neutropenia, liver enzyme abnormalities, and spastic diplegia, were recently reported in 20% of patients.³

Pulsed Dyed Laser

Flash-lamp-pumped pulsed dye laser works well for small, superficial lesions and for some large, plaque-like lesions. However, there is only a brief window of opportunity during infancy when hemangiomas are thin enough to be effectively treated with this laser, because its penetration is limited to approximately 1.2mm. It can improve residual telangiectases after involution. Though it has not been proven reliable in eliminating ulcerated hemangiomas, this treatment can result in reduced pain and prompt reepithelialization.¹

Rarely, laser treatments can induce ulceration, and shallow scars may develop, even at relatively low fluences. For unknown reasons, this type of scarring seems to occur more commonly in infants with hemangiomas than in infants with port wine stains.¹

Intralesional Laser Therapy

In one study the ND:YAG laser was reported to be useful for treating large capillary/cavernous hemangiomas, often rendering an inoperable lesion safely resectable, or markedly decreasing the size and functional impact of the lesion.¹⁰

Surgical Excision

The benefits and risks of surgery must be weighed carefully, since the scar may be worse than the results of spontaneous regression.³ Generally, it is recommended that a re-evaluation be done when the child is 4 years old, in order to assess the potential benefit of excision. Factors such as the extent of residual hemangiomas must be considered if:

- the involution is slow
- there is post ulcerative scarring, unalterably expanded skin, or a high probability of fibrofatty residuum
- surgery is likely to have a good result.¹

Surgery is especially good for small, pedunculated hemangiomas and occasionally, in cases where there may be functional impairment. It is usually used to repair residual cosmetic deformities.³ Nasal and labial hemangiomas seem to involute more slowly. In the case of nasal tip hemangioma, the tumor can be debulked using unilateral/bilateral rim incisions, which allow the skin to contract by whatever elasticity remains.⁷ General anesthesia is usually required for children younger than 10 years of age, but older patients can sometimes be managed with local anesthesia.⁷

Other treatment modalities

In exceptional cases, when earlier therapies have failed cyclophosphamide, embolization, radiotherapy, and sclerotherapy may be considered. A recent study evaluated the use of sclerotherapy for treating hemangiomas over a period of 20 years (1975-1995). A total of 157 patients found it to be a relatively simple, inexpensive, and effective form of therapy. In the study, sclerotherapy with polidocanol was carried out on monstrous or rapidly growing cavernous hemangiomas that were

mainly localized on the face. The results showed that one to three injections were sufficient to maintain the sclerosis effect and long-term aesthetic results were encouraging. No severe complications were observed.¹¹ Evolving therapies include leuprolide acetate, a GnRH agonist with antiproliferative effects, ketotifen (Zaditor[®], Zaditen[®], Ciba Visions/Novartis), new selective lasers, and new angiogenesis inhibitors.²

Major goals of treatment

When treating a hemangioma, the major goals should include:

- prevention or reversal of any life-threatening or function-threatening complications
- prevention of permanent disfigurement left by residual skin changes after involution
- minimization of psychosocial distress from the presence of hemangiomas for the patient and his/her family
- avoidance of aggressive, potentially scarring procedures for treatment of those hemangiomas likely to have an excellent prognosis without therapy
- prevention or adequate treatment of ulcerated hemangiomas to minimize scarring, infection, and pain.²

Conclusion

Most hemangiomas require no treatment. However, active non-intervention is recommended in order to recognize those that may require treatment quickly. When treatment is undertaken, it is important that it be customized to the individual patient, and that the possible physical, and psychological complications be discussed in advance. Often, a multidisciplinary approach is recommended. In cases where treatment must be undertaken, it is important that it not be delayed. Rapid tapering or discontinuation of treatment in the proliferative phase should be avoided.

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Update on Drugs

Class	Name/Company	Approval Dates and Comments
<i>Antiviral Agents</i>	Valacyclovir HCl Valtrex® GlaxoSmithKline	The US FDA approved a shorter course of therapy for this antiherpes drug in July 2001. Instead of taking Valtrex® tablets twice/day for five days, the new 500mg. caplets can now be prescribed as a 3-day course administered twice daily.
<i>Anti-acne Agents</i>	Tretinoin Gel Retin-A® Micro® Microsphere AP Phrama/Johnson & Johnson Canada	TPP – Canada approved this gel for marketing in Canada in July 2001, for the treatment of acne.
<i>Oral Contraceptive</i>	Drospirenone/Ethinyl Estradiol Yasmin® Berlex	The US FDA approved this low-dose monophasic, oral contraceptive in July 2001. It is the first and only birth control pill that contains the progestin drospirenone, which exhibits antimineralocorticoid activity and influences water and electrolyte balance. As a result, Yasmin® reduces sebum output and does not cause the weight gain that other contraceptives do. Women with kidney, liver or adrenal disease should be cautioned against taking this product.
<i>Enzyme Replacement Therapy</i>	Agalsidase Beta Fabrazyme™ Genzyme	The European Commission of the European Union granted marketing authorization to this product in July 2001, for long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry disease.
Drug News		
<i>Antibacterial Agents</i>	In a double-blind, placebo-controlled trial, recently reported in the <i>New England Journal of Medicine</i> *, the administration of a single 200mg dose of doxycycline within 72 hours after a tick bite from <i>Ixodes scapularis</i> was more effective than placebo in preventing the development of Lyme disease. *Nadelman RB, et al. <i>N Engl J Med</i> 345(2):79 (2001 July 12)	
<i>Immuno-suppressors</i>	Rapamune® (Sirolimus, Wyeth-Ayerst Laboratories), a transplant immunosuppressant, became available in August 2001, as a 1mg tablet for the US market in addition to the oral solution. This product is indicated for the prevention of acute organ rejection in kidney transplant patients and is recommended for use in a regimen that includes cyclosporine and corticosteroids.	
<i>Herbal Preparations</i>	In an article published in the <i>Journal of the American Medical Association</i> *, Ang-Lee, et al, reviewed the literature on commonly used herbal medications in the context of the perioperative period. The authors found that complications can arise from direct effects, pharmacodynamic effects, and from pharmacokinetic effects. Direct effects include bleeding (garlic, ginkgo, ginseng), cardiovascular instability (ephedra), and hypoglycemia (ginseng). Pharmacodynamic herb-drug interactions include potentiation of the sedative effect of anesthetics by kava and valerian and pharmacokinetic herb-drug interactions include increased metabolism of many drugs used in the perioperative period by St. John's wort. The authors conclude that physicians should explicitly elicit and document a history of herbal medication use and be familiar with the potential perioperative effects of these commonly used herbal medications. * <i>JAMA</i> 286(2):208-16 (2001 Jul 11).	



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