Epidural abscess and subdural empyema

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Epidural abscess and subdural empyema are serious intracranial infections that result in significant morbidity and mortality. Frequently, they are secondary to sinusitis or middle ear disease, and the bacteria involved are inhabitants of the upper respiratory tract. Symptoms may be mild and mimic the symptoms of the underlying infection. However, especially with subdural empyema, alteration in the level of consciousness and focal neurologic deficits are common. Morbidity and mortality are minimized by early diagnosis, which is best made with computed tomography scanning, and proper therapy, which consists of surgical drainage and administration of appropriate antimicrobials. It is important that primary care physicians be aware of the clinical features of these potentially fatal complications of common infections.

"Intracranial suppurations" is an imprecise term that refers to pyogenic infections occurring in or around the brain and its lining structures. Two such processes are cranial epidural abscess and subdural empyema. The clinical features, treatment, and outcome of each is different. Although these secondary infections are uncommon, they occur as complications of common upper respiratory tract infections. Primary care physicians therefore should be aware of their clinical features.

Epidural abscess

Case 1

A previously healthy 13-year-old boy began to experience cough, sneezing, and rhinorrhea 2 weeks prior to admission. He was seen by his family physician, who made a clinical diagnosis of sinusitis and prescribed amoxicillin/clavulanate potassium, which the patient took for the week before admission. The symptoms continued, however, and frontal headache developed. On the day prior to admission, he became febrile and lethargic. He had a generalized tonic-clonic seizure and was brought to the Children's Hospital of Buffalo.

At the time of physical examination, he was afebrile but somnolent. There was mild periorbital edema. The

findings of the remainder of the examination were within normal limits. Laboratory studies revealed a WBC count of 17,400/cu mm, with 68% polymorphonuclear cells, 16% band neutrophils, 10% lymphocytes, 5% monocytes, and 1% eosinophils. The sedimentation rate was 77 mm/h, and urinalysis results and chemistry profile were within normal limits. A computed tomography (CT) scan of the head revealed opacified frontal sinuses and a small frontal epidural abscess.

The patient underwent drainage of the frontal sinus, which yielded *Streptococcus morbillorum* and *Peptostreptococcus micros* on anaerobic culture. Aerobic and fungal cultures were negative. The patient was started on a regimen of chloramphenicol and showed rapid clinical improvement. Repeat CT scan showed no increase in the size of the abscess. The patient was discharged on chloramphenicol therapy. At 6 month follow-up, he was still well.

Discussion

Epidural abscess is a recognized complication of acute or chronic frontal sinusitis¹⁻³ or middle ear disease.⁴⁻⁶ Since epidural abscess is uncommon, it is difficult to determine the actual incidence from the available literature. In two series from university centers that contained sufficient cases to comment on, there was about one case each 3 to 5 years.^{5,7} In contrast, in a medically impoverished population in South Africa, there were 49 cases of epidural abscess discovered among patients attending an ear, nose, and throat outpatient clinic between 1978 and 1983.⁶

The pathogenesis of epidural abscess involves the spread of infection from the sinus or mastoid to the epidural space by way of valveless diploic veins, or less commonly, erosion of the posterior wall of the frontal sinus or the mastoid bone with resultant contiguous spread.^{1,4,8} The infection may spread from the epidural space to the subdural space or the brain parenchyma. This spread may be as a result of destruction of the dura, but the intertwined venous system of these contiguous structures is probably the more likely route.¹

The bacteria that are commonly involved in epidural abscess are listed in Table 1 in approximate order of occurrence. Aerobic streptococci and anaerobic gram-positive cocci and gram-negative bacilli predominate, with a small number of episodes due to staphylococci and *Haemophilus* species. An-

Table 1
Microbiologic Profile in Subdural Empyema and Epidural Abscess*

Bacterial involvement	Percentage of cases
Aerobic streptococci Alpha-hemolytic Beta-hemolytic Pneumococci	30-50
Anaerobes <i>Peptococcus</i> species <i>Peptostreptococcus</i> species <i>Bacteroides</i> species <i>Fusobacterium</i> species	20-40
Staphylococci <i>S aureus</i> <i>S epidermidis</i>	15-25
<i>Haemophilus</i>	5
Aerobic/facultative gram-negative rods	5

*Data derived from references 1,3-5,7-10,16-21.

aerobes may be less common in older studies because of inadequate anaerobic culture techniques.^{9,10}

The clinical presentation of epidural abscess is difficult to distinguish from that of the underlying infection. Patients may complain of fever, headache, upper respiratory tract symptoms, or local tenderness over the sinuses or mastoid. Focal neurologic deficits generally do not occur unless the abscess is large.^{1,6,7}

Presurgical diagnosis was possible only with arteriography in the past.¹¹ Computed tomography scanning appears to have supplanted arteriography, and it should be possible to localize the abscess prior to surgery in most cases.¹²⁻¹⁴ Epidural abscess is described as showing an extradural mass with a thick, dense ring of enhancement when contrast is administered.¹²⁻¹⁴ However, the ring may not be distinct early in the course of infection, and it may persist for up to 2 weeks postoperatively.¹³ There is concern over reports of false-negative scans⁷⁻⁸; however, newer generation scanners may alleviate this problem.⁸

Treatment usually consists of antimicrobial therapy and surgical drainage of the abscess and the affected sinus or mastoid.^{1,7} The patient in case 1 responded to a less aggressive approach, probably because the epidural abscess was small and centrally located, and his level of consciousness was

not significantly depressed. Appropriate antibiotic therapy should be administered early and continued for a prolonged period of time, particularly if there is associated osteomyelitis or residual fluid collection.

On the basis of the bacteriologic picture described heretofore, appropriate empiric therapy should include coverage of aerobic and anaerobic upper airway flora. Penicillin may be adequate in this regard. However, concern about penicillin resistance among some upper airway anaerobes has been expressed.⁹ In this latter situation it would be reasonable to use metronidazole or chloramphenicol in addition to penicillin. In children, *Haemophilus* coverage should be included, which can be accomplished with ampicillin, chloramphenicol, cefuroxime, or a third-generation cephalosporin. It also may be necessary to add antistaphylococcal coverage. Empiric therapy may be modified on the basis of results of Gram's staining of specimens obtained at the time of surgery. Ultimately, therapy should be based on the results of properly obtained aerobic and anaerobic cultures of abscess material.⁸ The prognosis of this disease is good, with low morbidity and mortality when managed appropriately.^{6,7}

This case of epidural abscess is typical of many cases described in the literature. The patient had a clinical picture that suggested sinusitis without any evidence of neurologic impairment, but appropriate therapy did not resolve his symptoms. The subsequent development of headache and seizure led to the diagnostic CT scan. The patient underwent drainage of the frontal sinuses and received a prolonged course of antibiotics, resulting in cure. In an analogous case, nonsurgical treatment of a small, intrahemispheric subdural empyema has been reported.¹⁵ This should not be construed as a "trend," but there may be a subset of neurologically intact patients with small epidural collections of pus who may be cured with medical therapy alone.

Subdural empyema

Case 2

A 45-year-old man with a history of chronic alcoholism was brought to the Emergency Department at the Buffalo Veterans Administration Medical Center after suffering a partial, complex, left-sided seizure that progressed to a generalized tonic-clonic seizure. A small, chronic, right parietal, subdural hematoma had been diagnosed 6 months before admission. His medical history was also positive for alcoholic liver disease, seizure disorder, hypertension, and Wernicke's encephalopathy.

On admission, he was unarousable and restless. Vital signs were normal and he was afebrile. Left-sided facial palsy was evident. There were no spontaneous or purposeful movements on the left side of his body; toes were upgoing bilaterally, and no left-sided deep tendon reflexes could be elicited. Routine admitting laboratory studies yielded essentially normal results except for a WBC count of 18,400/cu mm with a normal differential count.

The patient was taken to the operating room on the night of admission for anticipated drainage of a subdural hematoma. Right occipital bur holes were placed with subsequent drainage of 200 mL of thick, purulent material from the epidural and subdural spaces. This material yielded growth of *Streptococcus pneumoniae*. Chloramphenicol (500 mg IV q6h) and penicillin (4 million units q4h) treatment was started and the latter regimen was continued once culture results were known.

Later in the hospitalization, a CT scan of the mastoids showed opacification of the right mastoid air cells, sclerosis of the tip of the right mastoid, and an old fracture of the right occipital bone. Tympanometry showed decreased motion of the right tympanic membrane, and the patient later underwent insertion of a tympanostomy tube on the right with drainage of sterile fluid.

The patient recovered from surgery, and he remained without sequelae when seen at 18-month follow-up. He received a total of 6 weeks of parenteral penicillin treatment.

Case 3

A 59-year-old woman was referred by her family physician at the Buffalo General Hospital with a 7- to 10-day history of watery diarrhea and progressive generalized weakness. She denied any history of headache, focal neurologic deficit, or sinus disease. The remainder of her past history was noncontributory.

At the time of admission, the patient was afebrile and vital signs were normal. Except for bilateral periorbital edema, the findings of physical examination were within normal limits. Laboratory studies on admission revealed a WBC count of 19,800/cu mm with 61% polymorphonuclear neutrophil leukocytes, and 22% band neutrophils. Serum values were as follows: sodium, 125 mEq/L; potassium, 3.0 mEq/L; chloride, 91 mEq/L; and bicarbonate, 31 mEq/L.

The patient was given intravenous fluids, and a workup for the diarrhea was started. Soon after admission, headache and fever developed. A spinal tap revealed a WBC count of 1000/cu mm, 78% of which were neutrophils. The CSF glucose level was 53 mg/dL. Results of culture and bacterial antigen studies were negative. A CT scan of the head showed opacification of the frontal sinuses and a right frontal subdural fluid collection. She was started on a regimen of cefuroxime (1.5 g IV q6h) and metronidazole (500 mg IV q6h).

The patient underwent placement of right frontal bur holes with drainage of thick, yellow material. This was sterile on aerobic culture but grew *P micros* and *Eu-*

bacterium species. Simultaneous blood cultures grew *P micros*, *Eubacterium* species, and an unidentified, anaerobic gram-negative rod. The patient never regained consciousness postoperatively and neurologic function progressively declined. She died on the 16th hospital day.

Discussion

Subdural empyema is more common than epidural abscess and, as a result, the body of clinical literature concerning this infection is larger.^{5,7,9,16-23} Table 2 shows the incidence of subdural empyema that has been reported in several series. Each of these studies was done at a large university center where, in most instance, approximately one case per year was seen during the indicated time periods. Two reports from a regional neurosurgery center in Great Britain, overlapping each other by several years, recount two to three cases per year.^{16,20}

In the series of the past 20 years, most cases are described as being secondary to frontal sinusitis,^{7,16,18-21} though many patients do not give a history of chronic sinusitis symptoms.^{19,21} A significant number of cases still are related to otogenic foci.^{4,5,10,16,20,22} However, the latter are probably less common in the antibiotic era since appropriate therapy has greatly reduced the progression of middle ear disease to mastoiditis.²⁴ Subdural empyema also is recognized as a postoperative complication of cranial neurosurgical procedures,^{5,7,10,17,19} and occasionally is seen after trauma.^{15,17} Hematogenous seeding of the subdural space^{5,7,19,20} and a preexisting subdural hematoma¹⁷ have been suggested in several studies. However, it is difficult to know whether sinusitis, otitis, and mastoiditis were adequately ruled out.

The pathogenesis of subdural empyema is analogous to that of epidural abscess. An existing epidural abscess may erode through the dura to infect the subdural space, though the most likely route of spread appears to be by way of the valveless venous network as previously described.¹ Once organisms are introduced into the subdural space, the infection expands rapidly and may spread along the convexity of the cerebral hemisphere to the parafalcial areas and beneath the falx to the opposite cortical surface.^{1,16,18,19} The purulent material may also spread to the posterior fossa.²²

The bacteriologic profile of subdural empyema is outlined in Table 1. Aerobic streptococci and anaerobes account for 50% to 75% of infections in recent series. Infections due to *Staphylococcus aureus* and coagulase-negative staphylococci may be more common in patients with subdural empyema than those with epidural abscess.^{10,16,19} It is difficult to determine the significance of this latter ob-

Table 2
Incidence of Subdural Empyema (SDE) at Large University Centers

Author and reference	Years included	No. of cases	Comments
Kiser and Kendig (1963) ⁵	1942-1961	11	Includes 5 cases with both SDE and epidural abscess
Smith and Hendrick (1983) ⁷	1954-1981	22	Includes 3 cases with both SDE and epidural abscess
Bhandari and Sarkari (1970) ¹⁶	1954-1968	37	Regional neurosurgical center
Bannister et al (1981) ²⁰	1954-1979	66	Regional neurosurgical center (overlaps cases reported by Bhandari and Sarkari ¹⁶)
Kaufman et al (1975) ¹⁹	1967-1974	17	All underlying diseases
Kaufman et al (1983) ²¹	1967-1982	17	Sinusitis-related cases
Ariza et al (1986) ¹⁰	1975-1984	9	Includes 5 cases with both SDE and epidural abscess
Brook et al (1980) ⁹	1977-1980	4	Sinusitis-related cases

servation since all of the cited studies are retrospective and the number of reports of epidural abscess is small. Ariza and coauthors¹⁰ documented associated bacteremia in four of their patients, which they suggested was due to septic thrombophlebitis of the lateral sinus. In all four instances, bacteremia was due to multiple anaerobic organisms that were also grown from the purulent intracranial material.

Early clinical features of subdural empyema may be similar to those of sinusitis, mastoiditis, or epidural abscess. However, a high incidence of significant neurologic findings, such as papilledema, hemiparesis, seizures, and alterations in consciousness, has been reported.^{16,18-20} These findings are secondary to cerebral cortical irritation or increased intracranial pressure.⁸ Since the subdural space does not limit the spread of infection, cortical compression and increased intracranial pressure develop rapidly. Death ensues from transtentorial herniation of the brain or uncontrolled infection.¹⁹

In subdural empyema as in epidural abscess, CT scanning has replaced cerebral angiography as the most important diagnostic tool. Subdural empyema typically is visualized as a hypodense crescentic or elliptic area along the skull or the falx.^{12,23} Weisberg²³ suggests that the reasons for possible failure of CT to delineate subdural empyema in some prior reports^{20,21,25} are as follows: (1) use of older scanners with low resolution; (2) slow scan times producing motion artifact; (3) scan produced without contrast; (4) interpretative errors; (5) no coronal scans included; and (6) performance of scan before development of empyema.

With the use of newer generation scanners and by using contrast enhancement, CT should be highly accurate, except possibly when done early in the course of infection, prior to the development of a fluid collection.²³ Lumbar puncture is hazardous in this situation because of the increased intracranial pressure,¹⁹ but, if it is performed, the CSF has an elevated WBC count and protein level, normal glucose level, and negative Gram's stain and culture.^{5,19} One report of nine cases indicated that electroencephalography occasionally may be more sensitive than CT.²⁶ Abnormalities reported in essentially all cases were focal zeta waves, unilateral depression of cortical activity, and diffuse slowing of background activity. Other reports have not shown electroencephalography to be reliable.¹⁹

Subdural empyema has been considered a true "neurosurgical emergency," since without surgical intervention the disease has a high mortality.^{5,7,16-22} In a collective review, Bannister and co-workers²⁰ compared craniotomy versus bur holes for the drainage of subdural empyema. They strongly suggested that open surgical drainage had a significant benefit; however, the data were collected in an uncontrolled manner and there were many potential areas for bias. Therefore, no definite recommendations can be made in regard to the best form of surgical therapy. Likewise, the role of indwelling drains and antibiotic irrigation is not defined.⁸

Successful nonsurgical therapy for subdural empyema has been reported,^{15,27} including several patients who had large collections or depressed levels of consciousness.²⁷ Essential to this approach

is close clinical follow-up of the patients, serial CT scans of the head, and high-dose parenteral antibiotics.²⁷ The desire to avoid surgery should be tempered with the weight of experience and understanding of the aggressive nature of this infection.

Antimicrobial therapy should be started as soon as the diagnosis is made. Empiric therapy should be directed toward the aerobic streptococci and anaerobes, with the same therapy that was recommended before. Antistaphylococcal coverage should also be added until Gram's staining and culture results are obtained. In children, coverage for *Haemophilus* should be included. The mortality rate for subdural empyema with early and adequate therapy is approximately 20%.¹⁹⁻²¹ Unfortunately, some survivors may be left with permanent neurologic sequelae, primarily seizures, hemiparesis, and dysphasia.^{19,28} Patients who have a depressed level of consciousness when first seen have mortality rates that are two to three times higher than patients who are responsive.²⁰

These two cases illustrate important points concerning subdural empyema. Case 2 is an instance in which we lacked information regarding prodromal illness, other than a history of subdural hematoma. The patient's obvious focal neurologic findings and positive CT scan dictated the necessity for surgical intervention. Combined epidural abscess and subdural empyema were found at surgery, and drainage was accomplished successfully. Although some reports suggest hematogenous seeding of an existing chronic subdural hematoma as the cause, this patient had documented, untreated middle ear and mastoid disease, which was the likely source of infection.

In Case 3, the patient had nonspecific prodromal symptoms and no past history of sinusitis. Unfortunately, the unexplained periorbital edema did not prompt CT scanning. The diagnosis was not made until the patient had undergone significant change in mental status. It is not known whether the lumbar puncture contributed to her death. She had polymicrobial anaerobic bacteremia as well.

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Neutropenia/Agranulocytosis: Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Foreign marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril could not be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Precautions: General: Impaired Renal Function: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including VASOTEC, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20% of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Some patients with hypertension or heart failure with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when VASOTEC has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or VASOTEC may be required.

Evaluation of patients with hypertension or heart failure should always include assessment of renal function. (See DOSAGE AND ADMINISTRATION.)

Hyperkalemia: Elevated serum potassium (> 5.7 mEq/L) was observed in approximately 1% of hypertensive patients in clinical trials. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in 0.28% of hypertensive patients. In clinical trials in heart failure, hyperkalemia was observed in 3.8% of patients, but was not a cause for discontinuation.

Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with VASOTEC. (See Drug Interactions.)

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Information for Patients:

Angioedema: Angioedema, including laryngeal edema, may occur especially following the first dose of enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypotension: Patients should be cautioned to report lightheadedness especially during the first few days of therapy. If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia: Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

NOTE: As with many other drugs, certain advice to patients being treated with enalapril is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions:

Hypotension: Patients on Diuretic Therapy: Patients on diuretics and especially those in whom diuretic therapy was recently instituted may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril. If it is necessary to continue the diuretic, provide close medical supervision after the initial dose for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and DOSAGE AND ADMINISTRATION.)

Agents Causing Renin Release: The antihypertensive effect of VASOTEC is augmented by antihypertensive agents that cause renin release (e.g., diuretics).

Other Cardiovascular Agents: VASOTEC has been used concomitantly with beta-adrenergic-blocking agents, methyl-dopa, nitrates, calcium-blocking agents, hydralazine, prazosin, and digoxin without evidence of clinically significant adverse interactions.

Agents Increasing Serum Potassium: VASOTEC attenuates potassium loss caused by thiazide-type diuretics. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium. Potassium-sparing agents should generally not be used in patients with heart failure receiving VASOTEC.

Lithium: A low cases of lithium toxicity have been reported in patients receiving concomitant VASOTEC and lithium and were reversible upon discontinuation of both drugs. Although a causal relationship has not been established, it is recommended that caution be exercised when lithium is used concomitantly with VASOTEC and serum lithium levels should be monitored frequently.

Pregnancy—Category C: There was no fetotoxicity or teratogenicity in rats treated with up to 200 mg/kg/day of enalapril (333 times the maximum human dose). Fetotoxicity, expressed as a decrease in average fetal weight, occurred given 1200 mg/kg/day of enalapril but did not occur when these animals were supplemented with saline. Enalapril was not teratogenic in rabbits. However, maternal and fetal toxicity occurred in some rabbits at doses of 1 mg/kg/day or more. Saline supplementation prevented the maternal and fetal toxicity seen at doses of 3 and 10 mg/kg/day, but 30 mg/kg/day (50 times the maximum human dose).

Radioactivity was found to cross the placenta following administration of labeled enalapril to pregnant hamsters. There are no adequate and well-controlled studies in pregnant women. VASOTEC® (Enalapril Maleate, MSD) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Milk in lactating rats contains radioactivity following administration of ¹⁴C enalapril maleate. It is known whether this drug is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when VASOTEC is given to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Adverse Reactions: VASOTEC has been evaluated for safety in more than 10,000 patients, including over 2987 patients treated for one year or more. VASOTEC has been found to be generally well tolerated in controlled clinical trials.

Hypertension: The most frequent clinical adverse experiences in controlled trials were: headache (5.2%), dizziness (4.3%), and fatigue (3%).

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in controlled clinical trials were: diarrhea (1.4%), nausea (1.4%), rash (1.4%), cough (1.3%), orthostatic effects (1.2%), and asthenia (1.1%).

Heart Failure: The most frequent clinical adverse experiences in both controlled and uncontrolled trials were: dizziness (7.9%), hypotension (6.7%), orthostatic effects (2.2%), syncope (2.2%), cough (2.2%), chest pain (2.1%), and diarrhea (2.1%).

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in both controlled and uncontrolled clinical trials were: fatigue (1.8%), headache (1.8%), abdominal pain (1.6%), asthenia (1.6%), orthostatic hypotension (1.6%), vertigo (1.6%), angina pectoris (1.5%), nausea (1.3%), vomiting (1.3%), bronchitis (1.3%), dyspepsia (1.3%), urinary tract infection (1.3%), rash (1.3%), and myocardial infarction (1.2%).

Other serious clinical adverse experiences occurring since the drug was marketed or adverse experiences occurring in 0.5% to 1% of patients with hypertension or heart failure in clinical trials in order of decreasing severity within category:

Cardiovascular: Myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension; high-risk patients (see WARNINGS, Hypotension); cardiac arrest; pulmonary embolism and infarction; rhythm disturbances; atrial fibrillation; palpitation.

Digestive: Ileus, pancreatitis, hepatitis or cholestatic jaundice, melena, anorexia, dyspepsia, constipation, glossitis.

Nervous/Psychiatric: Depression, confusion, ataxia, somnolence, insomnia, nervousness, paresthesia.

Urogenital: Renal failure, oliguria, renal dysfunction (see PRECAUTIONS and DOSAGE AND ADMINISTRATION), ureteral hypotrophy.

Respiratory: Bronchospasm, rhinorrhea, asthma, upper respiratory infection.

Skin: Herpes zoster, pruritus, alopecia, flushing, photosensitivity.

Other: Muscle cramps, hyperhidrosis, impotence, blurred vision, taste alteration, tinnitus.

A symptom complex has been reported which may include fever, myalgia, and arthralgia; an elevated erythrocyte sedimentation rate may be present. Rash or other dermatologic manifestations may occur. These symptoms have disappeared after discontinuation of therapy.

Angioedema: Angioedema has been reported in patients receiving VASOTEC (0.2%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with VASOTEC should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Hypotension: In the hypertensive patients, hypotension occurred in 0.9% and syncope occurred in 0.5% of patients following the initial dose or during extended therapy. Hypotension or syncope was a cause for discontinuation of the drug in 0.1% of hypertensive patients. In heart failure patients, hypotension occurred in 6.7% and syncope occurred in 2.1% of patients. Hypotension or syncope was a cause for discontinuation of therapy in 1.9% of patients with heart failure. (See WARNINGS.)

Clinical Laboratory Test Findings:

Serum Electrolytes: Hyperkalemia (see PRECAUTIONS), hyponatremia.

Creatinine, Blood Urea Nitrogen: In controlled clinical trials, minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.2% of patients with essential hypertension treated with VASOTEC alone. Increases are more likely to occur in patients receiving concomitant diuretics or in patients with renal artery stenosis. (See PRECAUTIONS.) In patients with heart failure who were also receiving diuretics without digitalis, increases in blood urea nitrogen or serum creatinine, usually reversible upon discontinuation of VASOTEC and/or other concomitant diuretic therapy, were observed in about 11% of patients. Increases in blood urea nitrogen or creatinine were a cause for discontinuation in 1.2% of patients.

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 and 1.0 vol %, respectively) occur frequently in either hypertension or heart failure patients treated with VASOTEC but rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia.

Other (Causal Relationship Unknown): In marketing experience, rare cases of neutropenia, thrombocytopenia, and bone marrow depression have been reported.

Liver Function Tests: Elevations of liver enzymes and/or serum bilirubin have occurred.

Dosage and Administration: Hypertension: In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally may occur following the initial dose of VASOTEC. The diuretic should, if possible, be discontinued for two to three days before beginning therapy with VASOTEC to reduce the likelihood of hypotension.

WARNINGS: If the patient's blood pressure is not controlled with VASOTEC alone, diuretic therapy may be resumed. If the diuretic cannot be discontinued, an initial dose of 2.5 mg should be used under medical supervision for at least an hour and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS, Drug Interactions.)

The recommended initial dose in patients not on diuretics is 5 mg once a day. Dosage should be adjusted according to blood pressure response. The usual dosage range is 10 to 40 mg per day administered in a single dose or in two divided doses. In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval. In such patients, an increase in dosage or twice-daily administration should be considered. If blood pressure is not controlled with VASOTEC alone, a diuretic may be added.

Concomitant administration of VASOTEC with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics may lead to increases of serum potassium (see PRECAUTIONS).

Dosage Adjustment in Hypertensive Patients with Renal Impairment: The usual dose of enalapril is recommended for patients with a creatinine clearance >30 mL/min (serum creatinine of up to approximately 3 mg/dL). For patients with a creatinine clearance <30 mL/min (serum creatinine >3 mg/dL), the first dose is 2.5 mg once daily. The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily.

Heart Failure: VASOTEC is indicated as adjunctive therapy with diuretics and digitalis. The recommended starting dose is 2.5 mg once or twice daily. After the initial dose of VASOTEC, the patient should be observed under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS, Drug Interactions.) If possible, the dose of the diuretic should be reduced, which may diminish the likelihood of hypotension. The appearance of hypotension after the initial dose of VASOTEC does not preclude subsequent close dose titration with the drug, following effective management of the hypotension. The usual therapeutic dosing range for the treatment of heart failure is 5 to 20 mg daily given in two divided doses. The maximum daily dose is 40 mg. Once-daily dosing has been effective in a controlled study, but nearly all patients in this study were given 40 mg, the maximum recommended daily dose, and there has been much more experience with twice-daily dosing. In addition, in a placebo-controlled study which demonstrated reduced mortality in patients with severe heart failure (NYHA Class IV), patients treated with 2.5 to 40 mg per day of VASOTEC, almost always administered in two divided doses. (See CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects.) Dosage may be adjusted depending upon clinical or hemodynamic response. (See WARNINGS.)

Dosage Adjustment in Heart Failure Patients with Renal Impairment or Hyponatremia: In heart failure patients with hyponatremia (serum sodium <130 mEq/L) or with serum creatinine >1.6 mg/dL, therapy should be initiated at 2.5 mg daily under close medical supervision. (See DOSAGE AND ADMINISTRATION, Heart Failure, WARNINGS, and PRECAUTIONS, Drug Interactions.) The dose may be increased to 2.5 mg b.i.d., then 5 mg b.i.d. and higher as needed, usually at intervals of four days or more, if at the time of dosage adjustment there is not excessive hypotension or significant deterioration of renal function. The maximum daily dose is 40 mg.

For more detailed information, consult your MSD representative or see Prescribing Information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19386. J8V336(815)

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