

FOR DEEP INTRAMUSCULAR INJECTION ONLY.

Indications: In treatment of infections due to penicillin G-sensitive microorganisms susceptible to the low and very prolonged serum levels common to this dosage form. Therapy should be guided by bacteriological studies (including sensitivity tests) and clinical response.

The following infections usually respond to adequate dosage of IM penicillin G benzathine.

Streptococcal infections (Group A—without bacteremia). Mild to moderate upper respiratory infections (e.g., pharyngitis).

Venereal infections—Syphilis, yaws, bejel, and pinta.

Medical conditions in which penicillin G benzathine therapy is indicated as prophylaxis:

Rheumatic fever and/or chorea—Prophylaxis with penicillin G benzathine has proven effective in preventing recurrence of these conditions. It has also been used as followup prophylactic therapy for rheumatic heart disease and acute glomerulonephritis.

Contraindications: Previous hypersensitivity reaction to any penicillin.

Warnings: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported. Anaphylaxis is more frequent following parenteral therapy but has occurred with oral penicillins. These reactions are more apt to occur in individuals with history of sensitivity to multiple allergens. Severe hypersensitivity reactions with cephalosporins have been well documented in patients with history of penicillin hypersensitivity. Before penicillin therapy, carefully inquire into previous hypersensitivity to penicillins, cephalosporins and other allergens. If allergic reaction occurs, discontinue drug and treat with usual agents, e.g., pressor amines, antihistamines and corticosteroids.

Precautions: Use cautiously in individuals with histories of significant allergies and/or asthma.

Carefully avoid intravenous or intraarterial use, or injection into or near major peripheral nerves or blood vessels, since such injection may produce neurovascular damage.

In streptococcal infections, therapy must be sufficient to eliminate the organism, otherwise the sequelae of streptococcal disease may occur. Take cultures following completion of treatment to determine whether streptococci have been eradicated.

Prolonged use of antibiotics may promote overgrowth of non-susceptible organisms including fungi. Take appropriate measures if superinfection occurs.

Adverse Reactions: Hypersensitivity reactions reported are skin eruptions (maculopapular to exfoliative dermatitis), urticaria and other serum sickness-like reactions, laryngeal edema and anaphylaxis. Fever and eosinophilia may frequently be only reaction observed. Hemolytic anemia, leucopenia, thrombocytopenia, neuropathy and nephropathy are infrequent and usually associated with high parenteral doses.

As with other antisyphilitics, Jarisch-Herxheimer reaction has been reported.

Composition: (units penicillin G benzathine as active ingredient in aqueous suspension): 300,000 units per ml—10-ml multi-dose vial. Each ml also contains sodium citrate buffer approximately 6 mg lecithin, 3 mg povidone, 1 mg carboxymethylcellulose, 0.5 mg sorbitan monopalmitate, 0.5 mg polyoxyethylene sorbitan monopalmitate, 1.2 mg methylparaben and 0.14 mg propylparaben.

600,000 units in 1-ml TUBEX® (sterile cartridge-needle unit) Wyeth, packages of 10.

900,000 units, 1.5-ml fill in 2-ml TUBEX, packages of 10.

1,200,000 units in 2-ml TUBEX, packages of 10, and in 2-ml single-dose disposable syringe, packages of 10.

2,400,000 units in 4-ml single-dose disposable syringe, packages of 10.

Each TUBEX or disposable syringe also contains sodium citrate buffer and, as w/v, approximately 0.5% lecithin, 0.6% carboxymethylcellulose, 0.6% povidone, 0.1% methylparaben and 0.01% propylparaben.

INJECTION

BICILLIN® LA

(STERILE PENICILLIN G BENZATHINE SUSPENSION)

Wyeth Laboratories Philadelphia, Pa. 19101

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Letters to the Editor

The Journal welcomes Letters to the Editor; if found suitable, they will be published as space allows. Letters should be typed double-spaced, should not exceed 400 words, and are subject to abridgment and other editorial changes in accordance with journal style.

Treatment of Pit Viper Snakebite

To the Editor:

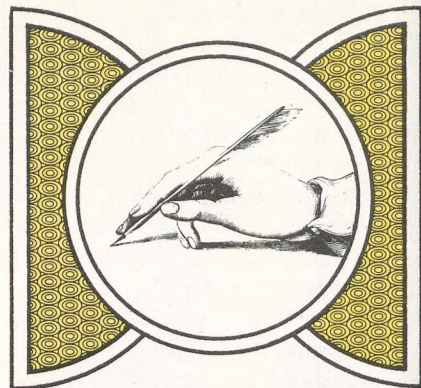
The article by Clement and Pietrusko, "Pit Viper Snakebite in the United States" (*J Fam Pract* 6:269, 1978), though a rather long and scholarly review of the literature, did not clear up much of the "confusion" about the treatment of snakebite nor did it describe what is really confusing about "snakebite."

There should be no confusion about how snakebite should be treated. The venom should be removed:

1. mechanically by suction, surgical excision, and/or thorough irrigation, or
2. by neutralization with specific or polyvalent antivenin, or
3. by a combination of both, and
4. as soon as possible after the bite, within the first six hours.

Other methods of treatment such as cryotherapy, destruction of venom by caustic chemicals (KMNO₄), and direct cauterization with heat have no place in the modern treatment of snakebite.

The "confusion of snakebite" is very simple. Within the first one to six hours after a poisonous (pit viper) bite, it is difficult for even the most experienced snakebite expert to determine the amount of venom injected, the depth of venom injection, and the organs



into which the venom has been injected.

Simply looking at the skin at the site of the bite does not necessarily give the physician enough information to adequately treat the bite.

It is easy to grade a bite properly after 24 hours, but within the first two to three hours this is extremely difficult. An incorrect guess within the first six hours post-bite results in crippling, amputations, and, occasionally, death.

Contrary to what Dr. Clement says in his article, *I do not* recommend the substitution of cortisone for antivenin. In the first paper I published on the treatment of snakebite in *Texas Medicine*, 1969, I recommended early or *immediate* surgical inspection of the snakebite site, debridement, opening of the fascia, fasciotomy, and debridement of the muscles when indicated. When toxic symptoms (nausea, vomiting, pressure changes) developed, I recommended large intravenous doses of hydrocortisone sodium succinate (Solu-Cortef) to suppress them.

I use antivenin when the bite is potentially lethal, when the patient or the parent of the victim requests it, or when there may be a legal problem if it is not used, and in the occasional case in which defibrination of the plasma occurs.

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In no event do I wait until the vascular supply to an extremity is embarrassed before doing a fasciotomy. I have seen the entire anterior muscle compartment of the leg necrotic with a palpable pulse in the anterior and posterior tibial arteries in the foot.

Dr. Clement mentions the use of vasopressors for shock. I now have in the hospital a 19-year-old patient sent to me after 36 hours of treatment with antivenin and vasopressors. This patient has lost all of the anterior compartment muscles of the right leg, has a ruptured esophagus due to extensive necrosis of the mucosa and submucosa, has acute renal failure and no urine output now for two weeks post-rattlesnake bite. The last two problems are most probably caused by the vasopressors metaraminol bitartrate (Aramine) and levarterenol bitartrate (Levophed).

Most physicians who have treated shock would agree with me that there is no place for vasopressors in the management of these cases.

In the past 24 years I have seen and cared for over 250 snakebites and I have, since 1966, operated over 160 pit viper bites, most of which were by the western diamondback rattlesnake. From this experience, my advice to a physician who is presented with a pit viper bite and who is not completely familiar with antivenin therapy, horse serum reaction, and surgery for these bites is that he/she should obtain consultation with or send the patient to someone who can be termed an expert in the field within the first two to three hours after the bite.

The most dangerous thing that can happen to the victim of a se-


vere rattlesnake bite with massive intramuscular injection of the venom is to fall into the hands of a physician who has treated 10 to 15 minor to moderate bites successfully and who thinks he is an expert in the treatment of snakebite.

At the present time we are taking plasma from rattlesnake bite victims who have had significant envenomation but have received no antivenin. The immune globulins are being removed and given to patients with the defibrination problem. Contrary to what Dr. Clement says, the defibrination of the plasma can be a very serious problem. It occurs in about 15 percent of the rattlesnake bites that I see and is caused by bites inflicted by small snakes on the hand or foot where intramuscular envenomation has not occurred and where little fat necrosis is present. I seldom see defibrination of the plasma in bites which result in muscle necrosis. There is reason to believe that the myoglobins released into the plasma inactivate the fibrinolytic enzymes in the snake venom. Defibrination of the plasma is not a reliable indicator of the severity of a bite, but massive subcutaneous hematomas with severe anemia may occur from bites by small rattlesnakes and appear horrendous. Residual problems from this type of reaction are minimal.

It is a shame that so many articles regarding the management of poisonous snakebite are written by individuals or groups who have never had an opportunity to treat firsthand a three-year-old child bitten by a six-foot western or eastern diamondback rattlesnake in which maximum envenomation has occurred and obtain a live child with

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no amputation or crippling as a result.

Thomas G. Glass, Jr, MD,
FACS
San Antonio, Texas

The preceding letter was referred to Drs. Clement and Pietrusko who respond as follows:

We would like to offer a reply to several issues raised by Dr. Glass in his recent letter. The article "Pit Viper Snakebite in the United States" is a comprehensive review of the literature primarily intended to apprise the family physician of current medical knowledge on the subject. This is particularly important because the family physician occasionally may be confronted with the initial care of a snakebite victim. Under some circumstances, he may be required to initiate definitive therapy prior to consultation and transfer, as delay might lead to serious consequences. There is not complete agreement among authors on the proper management for snakebite. Consequently, where controversy exists, divergent medical views have been presented to allow for further study by the reader.

Dr. Glass stated that he does not recommend the substitution of cortisone for antivenin. This is perplexing. Previously, he wrote "Eighty-four victims of pit viper envenomation were treated early by debridement, and fasciotomy if indicated, as well as large dosages of intravenously administered hydrocortisone sodium succinate. This method of treatment is safe and beneficial. It can be used as the definitive treatment of a snakebite or as an alternative to other methods."¹ In his series of 140 cases of significant envenomation

which were treated with surgery and hydrocortisone, only eight were treated with antivenin.² In that article he states, "After 1962, I used the corticosteroids in place of the antivenin," and also, "Antivenin is a life-saving 'drug' that should be reserved for the most serious bites."

The statement, "hypotension or shock can usually be managed with intravenous electrolyte solution, plasma, or plasma expanders, although whole blood and vasopressors may occasionally be indicated" accurately reflects authoritative medical opinion on the subject.³⁻⁷

As discussed at length, defibrillation following snakebite is potentially serious due to the multiple actions of pit viper venom. However, as outlined in discussion of mechanism of action, when defibrillation is present as an isolated entity, it is a relatively benign condition in which hemorrhage develops infrequently.⁸⁻¹¹

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Robert G. Pietrusko, PharmD
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Before the Drug Problem Starts

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Transcutaneous Electrical Nerve Stimulation constitutes a means of delivering electrical stimuli to the body noninvasively for the purpose of stimulating different components of the nervous system, for the symptomatic relief and management of acute and chronic intractable pain, and as an adjunctive or alternative treatment in the management of post-surgical pain syndromes.

Contraindications

- Transcutaneous Electrical Nerve Stimulators should not be used on patients with implanted cardiac-demand pacemakers.

Safety Precautions

- Transcutaneous Electrical Nerve Stimulators should be kept out of the reach of children.
- In patients with known heart disease, Transcutaneous Electrical Nerve Stimulation should be used only after careful physician evaluation and patient instruction.
- During periods of stimulation, do not operate potentially hazardous machinery or vehicles, unless specifically approved by your physician.
- Turn Transcutaneous Electrical Nerve Stimulators off before removing or reapplying electrodes.
- Do not apply electrodes directly over the eyes, or internally.
- Transcutaneous Electrical Nerve Stimulators should only be used for the pain problem prescribed for you by your physician.
- Transcutaneous Electrical Nerve Stimulators should not be used in areas of the carotid sinus nerves or anywhere else in the area in the front of the neck or in the mouth.
- The safety of Transcutaneous Electrical Nerve Stimulation has not been established for use during pregnancy. Therefore, its use should be limited to those situations when, in the judgment of the physician, the benefits outweigh the potential risks.
- For post-operative use of Transcutaneous Electrical Nerve Stimulators use only those electrodes specifically designed for post-operative pain control.

Side Effects

- If skin irritation develops consult with your physician.

Transcutaneous Electrical Nerve Stimulation is intended to be used only with a physician's prescription or order. U.S. Federal law restricts this device to sale by or on the order of a physician.

Duration of Treatment

Pain relief will vary substantially from one patient to another. Stimulation for only a few minutes a day will relieve the pain of some patients; others may need longer or more frequent periods of stimulation. Some do not achieve complete pain relief, while others may require stimulation combined with other types of treatment for relief. NOTE: If you are not able to sustain the pain relief produced initially during the treatments, report this information to the treating physician immediately.



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Agranulocytosis and Antipsychotic Drugs

To the Editor:

We read with interest the article in a recent issue of *The Journal of Family Practice* (6:993, 1978) by Charalampous and Keepers entitled "Major Side Effects of Anti-psychotic Drugs." In studying their review, one could be misled regarding side effects of loxapine.

The sentence on page 1000, midway down the left column, is misleading due to unfortunate structure. It describes the incidence of agranulocytosis and it reads, "It appears more frequently with aliphatic phenothiazine derivatives and perhaps more with clozapine than with other drugs, but has been reported with all phenothiazines, thioxanthenes, butyrophenones, and dibenzoxazepines." I believe that the "all" in this sentence refers only to phenothiazines, but it could be interpreted to refer to all members of all the drug classes named. In the case of the dibenzoxazepines, of which loxapine is the only member current-

ly available, agranulocytosis has not been reported. The authors are correct in noting that agranulocytosis has been reported frequently with clozapine. However, clozapine is not a dibenzoxazepine, rather it is a dibenzodiazepine.

May we suggest an erratum message in a future issue in order to correct the record and to report the lack of agranulocytosis with the only commercially available dibenzoxazepine, loxapine.

Frederick P. Funk
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The preceding letter was referred to Dr. Charalampous who responds as follows:

Upon closer scrutiny of the sentence to which Mr. Funk refers, I am inclined to agree that the inclusion of "all" is misleading since up to this point no cases of agranulocytosis have been reported with loxapine.

In view of the fact that this drug has been recently introduced to wider use, one may not be in a position to predict if agranulocytosis may have any connection with loxapine administration. Nevertheless, one needs to be precise and I would accept the modification of the sentence to read something like "though not with the dibenzoxazepine, loxapine."

Many thanks.

K. D. Charalampous, MD
Professor and Chairman
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Lubbock, Texas

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DESCRIPTION Each tablet of PERCOCET[®]-5 contains 5 mg oxycodone hydrochloride (WARNING: May be habit forming), 325 mg acetaminophen (APAP).

INDICATIONS For the relief of moderate to moderately severe pain.

CONTRAINDICATIONS Hypersensitivity to oxycodone or acetaminophen.

WARNINGS Drug Dependence Oxycodone can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of PERCOCET[®]-5, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications. Like other narcotic-containing medications, PERCOCET[®]-5 is subject to the Federal Controlled Substances Act.

Usage in ambulatory patients Oxycodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using PERCOCET[®]-5 should be cautioned accordingly.

Interaction with other central nervous system depressants Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with PERCOCET[®]-5 may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Usage in pregnancy Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, PERCOCET[®]-5 should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in children PERCOCET[®]-5 should not be administered to children.

PRECAUTIONS Head injury and increased intracranial pressure The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal conditions The administration of PERCOCET[®]-5 or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Special risk patients PERCOCET[®]-5 should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

ADVERSE REACTIONS The most frequently observed adverse reactions include light-headedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include euphoria, dysphoria, constipation, skin rash and pruritus.

DOSAGE AND ADMINISTRATION Dosage should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of narcotics. PERCOCET[®]-5 is given orally. The usual adult dose is one tablet every 6 hours as needed for pain.

DRUG INTERACTIONS The CNS depressant effects of PERCOCET[®]-5 may be additive with that of other CNS depressants. See WARNINGS. 6085 BS

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