

# "Pseudoanaphylactic" Reactions from Inadvertent Infusion of Procaine Penicillin G

JEFFREY E. GALPIN, M.D., ANTHONY W. CHOW, M.D., F.R.C.P.(C),  
THOMAS T. YOSHIKAWA, M.D., and LUCIEN B. GUZE, M.D., F.A.C.P.,  
Torrance and Los Angeles, California

Acute, nonallergic reactions simulating anaphylaxis have been reported after intramuscular injections of aqueous procaine penicillin G, and it has been assumed that the antibiotic inadvertently reaches the intravascular space during the injection. We report three patients in whom the classical "pseudoanaphylactic" reactions occurred after inadvertent administration of aqueous procaine penicillin G by intravenous infusion. Cardiorespiratory arrest with slow idioventricular rhythm and acute anxiety reactions with tinnitus and dizziness were observed within 15 minutes of the infusion in these patients. Microembolization to the lungs and brain, as well as direct toxicity from the procaine component of aqueous procaine penicillin G, are probably the pathogenetic mechanisms. Our experience with three patients within 12 months suggests that this complication may be more frequent than might be surmised from the literature, and medical personnel should be alerted to this potentially lethal reaction.

**ACUTE, NONALLERGIC** reactions simulating anaphylaxis have been well recognized as a potential complication of aqueous procaine penicillin G therapy (1-11). In all reported cases reactions occurred after intramuscular administration of aqueous procaine penicillin G, and it was assumed that the antibiotic inadvertently reached the intravascular space during the injection. Between 1973 and 1974, however, three patients admitted to Harbor General Hospital, Torrance, California, inadvertently received aqueous procaine penicillin G by the intravenous route. An immediate reaction occurred in each instance, but different manifestations were observed. Inadvertent intravenous administration of aqueous procaine penicillin G may be potentially lethal, and medical personnel should be alerted to this complication, which may be more frequent than is supposed.

## Case Reports

### CASE 1

A 61-year-old man with chronic obstructive lung disease

► From the Department of Medicine, Harbor General Hospital, Torrance; the Department of Medicine, UCLA School of Medicine, and the Research and Medical Services, Veterans Administration Hospital, Los Angeles, California.

was admitted to hospital because of pneumonia and cor pulmonale. A tracheostomy was done, and he gradually improved with intravenous ampicillin, bronchodilators, postural drainage, and intermittent positive pressure breathing. A purulent cellulitis, however, developed around the tracheostomy site, and therapy with aqueous penicillin G 600,000 units intravenously every 6 hours by Volurol<sup>®</sup> was ordered. On the fourth day of therapy, 15 minutes after the antibiotic infusion had begun, the patient became tachycardic, anxious, and unresponsive. A generalized seizure and cardiorespiratory arrest rapidly ensued. An electrocardiogram showed a slow idioventricular rhythm. Resuscitation measures were immediately begun. He developed ventricular tachycardia and eventually reverted to a sinus rhythm. Blood gases on 100% inspired oxygen during resuscitation were  $P_{O_2}$  144 mm Hg,  $P_{CO_2}$  62 mm Hg, and the pH was 7.22. Serum electrolytes at the time of arrest were sodium, 144 meq/litre; potassium, 5.4 meq/litre; and chloride, 91 meq/litre. During the arrest, it was noted that the intravenous Volurol chamber contained 50 ml of milky solution, which was immediately withdrawn. It was subsequently learned that a nurse had inadvertently added 600,000 units of procaine penicillin to the Volurol chamber of the aqueous penicillin prescribed. After resuscitation, the patient completely regained consciousness and reported lightheadedness but no chest pain just before his arrest. His chest X-rays remained unchanged, and a lung scan done 12 days later did not show any perfusion defects. He was subsequently discharged after a prolonged hospitalization for his underlying pulmonary disease.

### CASE 2

A 59-year-old woman with a poorly differentiated squamous cell lung carcinoma was being treated for a right pleural empyema with aqueous penicillin G 600,000 units intravenously every 6 hours by Volurol. On the fifth day of therapy, 15 minutes after the antibiotic infusion had begun, she suddenly became extremely apprehensive, tachycardic, and complained of shortness of breath, dizziness, and ringing in her ears. She denied chest pain and reported no change in sputum. Her blood pressure rose sharply from 120/70 mm Hg to 150/80 mm Hg, and her pulse rate rose to 120. An electrocardiogram showed a sinus tachycardia. At this point, the fluid being infused was noted to be cloudy, and it was learned that a nurse had inadvertently added 1,000,000 units of procaine penicillin instead of the aqueous penicillin prescribed. The infusion was immediately withdrawn. Thirty minutes later, the patient was markedly improved, although the tinnitus and dizziness persisted for another hour. She was subsequently placed on oral potassium phenoxymethyl penicillin therapy without ill effects and was later transferred to a chronic care facility.

### CASE 3

A 63-year-old man with chronic obstructive lung disease and

a cavitary pulmonary lesion was being treated with aqueous penicillin G, 600 000 units intravenously every 6 hours by volutrol, immediately after a bronchoscopy. On the next day, while a chest X ray was being obtained, he suddenly became extremely anxious, with clammy extremities and a thready pulse, and he complained of dizziness. The fluid being infused through the volutrol was noted to be milky, and its administration was immediately stopped. Within 5 minutes the patient had completely recovered. Arterial blood gases, electrocardiogram results, and chest X rays were unchanged after this episode. It was learned later that a nurse had inadvertently added 600 000 units of procaine penicillin to the volutrol instead of the aqueous penicillin prescribed. Intravenous aqueous penicillin G therapy was continued without further untoward reactions. He was subsequently found to have a squamous-cell carcinoma of the lung.

## Discussion

In 1951 Batchelor, Horne, and Rogerson (1) first described an acute, nonallergic reaction to aqueous procaine penicillin G, when it was administered intramuscularly in doses of between 600 000 and 1 000 000 units. Characteristically, symptoms begin within a minute of injection, and consist of vertigo, tinnitus, feelings of marked anxiety and impending doom (angor animi), violent behavior, hyperventilation, visual and auditory hallucinations, and elevated blood pressure and pulse rate. Syncope, grand mal seizures, and sudden death have also been described (2-6). The incidence has been estimated to be from 1 to 3 per 1000 injections (1). Allergic manifestations, such as urticaria, wheezing, or laryngospasm are not part of the syndrome, and patients tolerate subsequent injections or other penicillin preparations without complication. The reaction is usually short-lived, subsiding within 15 minutes. In these cases it has been generally assumed that aqueous procaine penicillin G inadvertently reaches the intravascular space during the injection, with subsequent microembolization to the lungs and brain (6). Procaine penicillin G is an aqueous suspension with a solubility in water of only 1:250 (wt/wt). After intravascular injection, insoluble aggregates varying from 5  $\mu$  to 100  $\mu$  in size are formed, producing embolization. Bell, Rannie, and Wynne (10) noted similar reactions to aqueous procaine penicillin G when it was administered intravenously to cats. Manifestations of hyperventilation, dilation of pupils, violent behavior, grand mal seizures, or coma developed within seconds of injection. Death was dose-related, and sublethal doses were associated with complete recovery. At necropsy, multiple small emboli were found in pulmonary vessels; most were found in the dilated precapillary arterioles. The number of emboli found was directly related to the dose of aqueous procaine penicillin G administered.

Although microembolization is the most popular explanation for this "pseudoanaphylactic" reaction of aqueous procaine penicillin G, some of the manifestations may be owing to the direct toxic effects of the procaine component of the antibiotic. About 6% of procaine penicillin is unconjugated, so that in 2 400 000 units of the anti-

biotic 60 mg would be free procaine (6). It is estimated that from 2 mg to 7 mg of free procaine was received by our patients during the antibiotic infusion. Procaine causes depression of the reticular activating system and cortical stimulation, which may progress to seizures (12). Early manifestations of procaine toxicity are marked anxiety, feelings of impending doom, fever, tachycardia, blood pressure elevation, vomiting, pupillary dilation, and audiovisual hallucinations, all of which have been noted in the "pseudoanaphylactic" reaction to aqueous procaine penicillin G. Sudden death has been associated with as little as 10 mg of procaine administered intravenously (11). Thus the acute nonallergic reactions of aqueous procaine penicillin G might best be described as a combination of toxic and embolic phenomena.

To our knowledge, the three cases reported here document for the first time that intravenous administration of aqueous procaine penicillin G produces the classic reactions previously described after intramuscular injection. We suspect that this potentially lethal complication is much more frequent than might be surmised from the literature and suggest that medical and nursing personnel should be warned of this adverse reaction to the erroneous intravenous administration of aqueous procaine penicillin G.

ACKNOWLEDGMENTS: Received 7 March 1974; revision accepted 14 May 1974.

► Requests for reprints should be addressed to Lucien B. Guze, M.D., Chief of Staff, Research and Education, Veterans Administration Hospital, Wadsworth Hospital Center, Wilshire and Sawtelle Blvd., Los Angeles, CA 90073.

## References

- BATCHELOR RCL, HORNE GO, ROGERSON HL: An unusual reaction to procaine penicillin in aqueous suspension. *Lancet* 2:195-198, 1951
- BELL RC: Sudden death following injection of procaine penicillin. *Lancet* 1:13-17, 1954
- SORVAL AR: Severe immediate constitutional reactions to penicillin. *JAMA* 152:1430-1431, 1953
- TOMPSETT R: Pseudoanaphylactic reactions to procaine penicillin G. *Arch Intern Med* 120:565-567, 1967
- UTLEY PM, LUCAS JB, BILLINGS TE: Acute psychotic reactions to aqueous procaine penicillin. *South Med J* 59:1346-1348, 1966
- DOWNHAM TF, RAMOS DP: Non-allergic adverse reactions to aqueous procaine penicillin. *Mich Med J* 68:23-25, 1973
- HOIGNE VR, SCHUCH K: Anaphylaktische Schock und akute nichtallergische Reaktionen nach Procain-Penicillin. *Schweiz Med Wochenschr* 89:1350-1356, 1959
- HOIGNE VR: [Acute side-reactions to penicillin preparations.] (Ger.) *Acta Med Scand* 171:201-206, 1962
- DENNIG H, SCHWÖRER W: [Acute procaine poisoning following the use of depot penicillin.] (Ger.) *Dtsch Med Wochenschr* 88:532-537, 1963
- BELL RC, RANNIE I, WYNNE NA: Adverse reactions to procaine penicillin in cats and man. *Lancet* 2:62-66, 1954
- GROUNDS MD: Immediate reactions to procaine penicillin injection with a report of 3 cases. *Med J Aust* 112:167-168, 1967
- MOORE DC, BRIDENBOUGH LD: Oxygen and antidote for systemic toxic reactions from local anesthetic drugs. *JAMA* 174:842-847, 1960