

Procaine Penicillin Reactions

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Introduction

Procaine penicillin is listed as a treatment for a number of clinical conditions common in the remote-area health practice. It is a drug frequently administered. The adverse reactions to procaine penicillin are well documented in the literature. It is important that practitioners to be aware of these potential reactions, be able to differentiate between the types of reaction and offer appropriate treatment.

What is procaine penicillin?

Trade name: Cilicaine. An antibiotic

Presentation: 1.0 gram (1 million units) and 1.5 gram (1.5 million units).

What are the adverse procaine penicillin reactions?

There are three types of adverse reaction to procaine penicillin: severe allergic (anaphylaxis); faint (vaso-vagal); and non-allergic (pseudoanaphylactic). Similarities between these reactions can make diagnosis difficult. The clinical imperative is to exclude the life threatening anaphylactic reaction. A person who collapses from shock (low blood pressure and rapid weak pulse) or respiratory failure (from bronchospasm causing wheeze or angioedema causing respiratory obstruction)¹ following an injection of procaine penicillin should be treated for anaphylaxis. These severe allergic reactions are rare.

In this protocol, non-allergic reactions include those reactions which are predominantly psychotic in nature. In the previous protocol these were considered separate reactions. The literature suggests that these reactions are essentially the same.^{2,3,10,12,21} In some of these non-allergic reactions transient psychotic symptoms predominate. In others, symptoms may resemble an anxiety attack or mimic anaphylaxis. The variation in clinical manifestation can be confusing, however the clinical imperative remains one of excluding anaphylaxis.

Anaphylaxis

This is a potentially life threatening systemic allergic reaction, often explosive in onset, affecting primarily respiratory and cardiovascular systems but capable of affecting virtually any organ system.^{4,5,6} Anaphylaxis is a medical emergency and requires immediate treatment. The symptoms of anaphylaxis result from the action upon one or more target organs, of chemical mediators released by mast cells. The dramatic and potentially lethal consequences of systemic anaphylaxis may include upper respiratory tract obstruction (laryngeal oedema), wheezing (bronchospasm) and shock (vascular collapse).⁴

Recommendations

- Those administering medications have knowledge of anaphylaxis and its management.
- All clinics have anaphylaxis kits available, including appropriate drugs and information on management of anaphylaxis. Oxygen and resuscitation equipment should be readily available.
- Expiry dates of drugs in these kits checked regularly.

- Information regarding management of anaphylaxis displayed in clinic treatment areas and pharmacy.

Faint

This is the most common mimic of anaphylaxis. It is also known as a vaso-vagal reaction, which is a transient vascular and neurogenic reaction characterized by pallor, nausea, sweating, and a rapid fall in arterial blood pressure. These can result in a loss of consciousness. Vaso-vagal reactions are usually associated with bradycardia as opposed to tachycardia seen in anaphylaxis. Upper respiratory obstruction and bronchospasm are not usually seen in vaso-vagal reactions. This reaction is most often evoked by emotional stress associated with fear or pain.⁴

Non-allergic reactions

These encompass a number of signs and symptoms. Anxiety, fear of imminent death, visual and auditory disturbances, aggression, confusion, disorientation and restlessness, disturbances in taste, cardio-vascular changes and partial or generalized epileptiform seizures are the principle manifestations.^{2,7,10,21,18} These signs and symptoms are rapid in onset and short in duration. They usually appear immediately after intramuscular injection and resolve within 15–30 minutes.⁸

Since being first reported in 1948, this non-allergic reaction has been described frequently in the literature and referred to variously as Hoigne's Syndrome, Procaine Psychosis and Pseudoanaphylactic reaction.^{2,9,13} No other preparation of penicillin is known to produce such effects.²

Incidence of non-allergic reactions to procaine penicillin

The incidence of non-allergic reactions to procaine penicillin has been variously reported from 1:1000 to 3:1000 injections.^{10,11,12}

The cause of non-allergic reactions to procaine penicillin

At present there are two theories regarding the cause of non-allergic procaine penicillin reactions. The vascular theory was first proposed by Batchelor et al. in 1951¹¹, reporting on eight cases of procaine penicillin reaction. The rapidity of onset and the report of metallic taste suggested partial inadvertent intravenous injection. Hoigne, after whom this syndrome has been named, proposed micro-embolisation of small vessels in the lungs and brain by micro-crystals of procaine penicillin as the causative mechanism. Hoigne suggested that at the site of injection the crystals of procaine penicillin penetrate venous circulation, which then lodged in pulmonary and cerebral vessels. However, both autopsy and animal studies have failed to demonstrate micro-emboli in the brain, although this absence may in part be due to the rapid solubility of procaine crystals.¹³

The toxic theory proposes that the reaction is caused by the toxic action of procaine on the central nervous system.^{11,14} The body's enzymatic system is capable of liberating procaine from the procaine penicillin molecule. Procaine is metabolized by procainesterase to non-toxic metabolites. Systemic toxic reactions may occur from the release of procaine after the administration of procaine penicillin. Reduced plasma procainesterase activity may increase the likelihood of a reaction by delaying hydrolysis of procaine with subsequent accumulation of toxic levels in the systemic circulation.^{7,21}

The toxic theory has been further developed by the hypothesis of **limbic kindling**. The phenomenon of kindling has been described as the appearance of physiological and behavioral responses to a repetitive stimulus that initially has no effect.²⁴ The cumulative effect of this stimulation is to lower the convulsive threshold and produce secondary stimulation of other cerebral sites. The limbic system sometimes referred to as the 'emotional brain' is an interrelated group of structures that are involved in regulation of the emotional state with accompanying behavioral, physiological and psychological responses.¹³ Among the pharmacological agents, local anaesthetics such as lignocaine, cocaine and procaine have been shown to induce behavioral

kindling in experimental animal studies.¹⁶ The same neuromuscular-central nervous system syndrome noted in procaine reactions has been observed in patients receiving intravenous lignocaine for the treatment of cardiac arrhythmias and in cocaine abuse.¹⁷ Specifically, procaine has been shown to elicit a kindling-like pattern of seizure activity.¹³

Management

It is important to distinguish **anaphylactic shock** from the **acute non-allergic** reaction by determining the absence of such clinical signs as angioedema, urticaria, bronchospasm, and vascular collapse.¹⁸

Severe allergic reaction (anaphylaxis) is a medical emergency. The outcome is related to the promptness of intervention. Resuscitation involves establishing an airway, ensuring that the patient is breathing, and cardiopulmonary support as required. The cornerstone of anaphylaxis management is adrenaline 1:1000. Adrenaline is a powerful cardiac stimulant which increases systolic blood pressure, reduces diastolic pressure and increases heart rate. Adrenaline also has antihistamine and broncho-dilating properties.¹⁹ Adrenaline has a rapid onset of action but short duration. Adrenaline 1:1000 is given as a deep intramuscular injection using a 1 ml syringe. This is to ensure accuracy of dose when giving small volumes of Adrenaline.

A vaso-vagal reaction or faint is treated by laying the patient flat and elevating their legs. By doing this we are helping to correct the drop in blood pressure. Offer reassurance to allay anxiety.

Non-allergic reactions (no signs of circulatory collapse or respiratory distress) are treated with oxygen only. Stimulation of cerebral cells by local anaesthetic agents will increase the metabolic rate within these cells leading to greater oxygen demands. If oxygen demands are not met, hypoxia of the cerebral cells will lead to increased carbon dioxide concentrations, which can cause convulsions and cardiovascular collapse.²⁰

Treatment may be initially difficult if the patient is extremely anxious. Agitation, restlessness and aggression can be features of this reaction. Because of the potential for collapse and seizure it is important to minimize the risk of injury. Getting the patient to sit or lay down may minimize this risk.

It is very important to discuss these reactions with the patient, their relatives and health staff. These reactions are frightening for all concerned. The patient or relatives may believe that the needle was given incorrectly or that the wrong medicine was administered. These beliefs can be quite destructive. It is important people are aware that these reactions sometimes occur, that the exact cause is still being debated in the medical literature, and that the person who gave the needle was not at fault.

Recommendations

- Correct storage. Procaine penicillin should be refrigerated. Storage at room temperature has been shown to liberate additional free procaine.²¹ Check expiry date of drug prior administration. Protect from light. Do not freeze. Discard solution if it appears discoloured.
- Lay the patient down to administer the procaine injection. This serves two purposes. Firstly, it may reduce the chance of patient injury in the event of a reaction. Secondly, having the patient lying down for procaine injection may reduce the chance of inadvertent intravascular injection.¹¹
- Correct administration involves remixing components of procaine penicillin syringe, which can separate with storage. Procaine penicillin is only administered by deep intra-muscular injection. The needle is inserted in the upper outer quadrant of the buttock. The plunger must be withdrawn and if any blood appears in the syringe immediately withdraw the needle and discard the syringe.

- Discard any unused solution.
- Given the potential for adverse reactions to procaine penicillin, this drug should only be administered within a clinic setting or where access to resuscitation equipment and drugs is readily available.
- Report to pharmacy batch number of Cilicaine syringes which become occluded during administration. Expelling air from the syringe and needle just prior to inserting the needle may overcome this problem.

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