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PENICILLIN REACTIONS

REVISED

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INTRODUCTION

1. Penicillin is a Beta–lactam group of antibiotic. Cephalosporin is the other member of this group with which Penicillin shares cross reactivity for allergic reaction.

2. Penicillin was the first antibiotic to be used in 1941 and remains one of the least toxic antibiotic to be available even today. However, it is known commonly to produce drug allergies, the fear of which, specially anaphylaxis, has seen a decline in its usage.

3. Benzylpenicillins (PnG) is a naturally occurring penicillin made commercially from P. chrysogenum though it was originally obtained form P. notatum Procaine penicillin and benzathine penicillin are salts of PnG. The shortcoming of PnG are its poor oral efficacy (acid labile), narrow antibacterial spectrum and susceptability to penicillinase.

4. Semi- synthetic penicillins have overcome these problems to a large extent . These include:

a) Acid resistant : phenoxymethyl penicillin .

b) Penicillinase resistant penicilin: methicillin ,oxacillin, cloxacillin and nafcillin.

c) Extended spectrum penicillins
   (i) Aminopenicillin : ampicillin and amoxicillin.
   (ii) Carboxypenicillin : carbenicillin and tricarcillin.
   (iii) Ureidopenicillin : piperacillin and mezlocillin.

d) Beta-lactamase inhibitors with only mild antibacterial action : Clavulanic acid and sulbactam. These agents augment the action of amoxicillin, ampicillin and ticarcillin when combined with them.

5. All the above members of the Penicillin family produce an array of allergic or hypersensitivity reactions . They cross react with each other and also with cephalosporins. Hence if a patient is allergic to one member then avoid using the other member of this group.

6. Allergic reactions can vary in severity from innocuous skin rashes to explosive anaphylactic reaction which can be fatal . Allergy can follow trivial doses (even intradermal test dose or topical ophthalmic and dermatological use) of PnG through any route, though commonest is following parenteral use . Topical use of this drug is not recommended because of the risk of sensitization, except may be in gonococcal ophthalmitis.

7. A patient can develop Penicillin allergy with no previous history of allergy to the drug or even prior exposure to this drug . The latter is explained by environmental exposure to fungal moulds elaborating penicillin like substances or inadvertent skin sensitization in medical and paramedical staff when they prepare and administer penicillin to patient .

8. Penicillin reaction can be classified into the following types.

(a) Allergic or due to hypersensitivity reaction

(i) Immediate reaction

- Occurs within 20 minutes
- Most often after parentental administration
- Incidence 0.004 to 0.4 percent
- Anaphylaxis and angioedema are the life endangering immediate reaction necessitating prompt institution of treatment.

(ii) Accelerated reaction

- Occurs within 1 to 72 hrs after drugs administration
- Urticaria is the commonest manifestation
- Angioedema is infrequently seen and mortality is rare

(iii) Late reaction

- Occurs from 72 hrs to several weeks after therapy
- Characterised by skin rashes which can be maculopapular, itchy vesiculo –bullous, urticarial and rarely exfoliative.
- Occasionally serum sickness can develop with fever, lymphadenopathy, arthalgia, myalgia and splenomegaly
- Skin rashes are commoner following use of semisynthetic pencillins specially ampicillin (9 percent). When the latter is used in patients with infectitous mono nucleous and lymphatic leukaemias the incidence of the skin rashes sharply rises to 90 to 100 percent.
- Interstitial nephritis, oliguric renal failure and generalized allergic vasculitis secondary to methicillin use.
- Coombs positive haemolytic anaemia.

(b) OTHERS

(I) Penicillin has minimal direct toxicity. It can cause hepatitis with oxacillin and nafcillin; platelet aggregation defects and bleeding tendency with use of carbenicillin, PnG and ticarcillin When used in high doses it can rarely cause bone marrow suppression with granulocytopenia.

(ii) Neurological dysfunction in form of myoclonus , lethargy , confusion and seizures can occur when PnG is given in doses higher than 20 million units daily or even lower doses when there is renal insufficiency.

(iii) Procaine penicillin G which is to be given only through the intra muscular route can cause dizziness, tinnitus, headache , hallucinations and seizures if it is accidentally given intravenously . 1 in 200 patients receiving more than 4.8 million units of this drugs for venereal disease can also have similar side effects despite being used by the intramuscular route.

(iv) Local irritation

- Muscle necrosis and pain at site of injection
- Thrombophlebitis at intravenous site

- Arachnoiditis and encephalopathy when used intrathecally. Presently this route is not recommended for use.
- Nausea, vomiting and diarrhoea when given orally

(v) Super infection by C difficile and C.albicaus in the gut .The former can rarely cause pseudomembranous colitis.

(vi) Severe and at times fatal hyperkalemia can result especially when there is renal dysfunction as 20 million units of the potassium salt of PnG releases 34 m Eq of potassium. Similarly the sodium salt can lead to fluid retention which can be troublesome in cardiac failure patients

(vii) Contact dermatitis follows local application or occupational exposure to penicillin in doctors and nurses.

(viii) Rarely acute psychotic syndromes, myocarditis , pericarditis, deranged liver function (raised ALT & AST) and eosinophilia can occur.

(ix) Jarisch -Herxheimer reaction follows the first injection of PnG in majority of patients with secondary syphilis. The skin lesions flare up and there is fever with chills, myalgia, arthralgia and headache. It occurs due to release of spirochaetal antigens and resolves with symptomatic treatment with aspirin. PnG is not discontinued. Less frequently it can occur in other forms of syphilis when treated with PnG.

9. A detailed history of prior penicillin allergy is of paramount importance and in such cases the drug should not be administered. Overall incidence of allergic reactions to penicillin group of drugs is 0.7 to 10 percent. Anaphylaxis is the most dreaded reaction and is seen in 0.004 to 0.04 percent of the patients. Approximately 0.001 percent patients die following anaphylaxis and interestingly more than two third of these have history of prior exposure to penicillin with one third of these having documented some form of allergic reaction following exposure to penicillin. Also in patients with history of Atopic Bronchial asthma or other allergies , great caution should be exercised in administering penicillin as a higher

incidence of allergic reactions is seen in this group following penicillin administration.

10. Anaphylaxis most often follows penicillin injections, though it can occur even following oral intake or intradermal test dose of the drug. Clinical picture varies in severity. It can be explosive with hypotension , circulatory collapse and death within minutes. It can be less dramatic with abdominal symptoms (pain nausea , vomiting and diarrhoea), respiratory symptoms (bronchospasm) , skin eruptions and extreme weakness

11. Angioneurotic edema is charactersed by marked swelling of lips, tongue, face and periorbital tissues accompanised by respiratory distress and giant hives. In addition to anti-anaphylactic therapy securing a patent airway is of vital importance (intubation ; tracheostomy if required)

MECHANISM OF DRUG ALLERGY

12. This is a immunologically mediated reaction. Antibodies are formed to the penicillin molecule and also to its break down products which act as haptens and combine covalently with penicillin binding proteins (PBP). Hapten –PBP combine is the antigen to which antibodies are formed. The penicilloyl moiety which is a breakdown product of penicillin acts as the major determinant for penicillin allergy while the intact molecule of PnG and some of in break down product like penicilloate act as the minor determinant. Major and minor determinant refers to the frequency with which antibodies are formed and not to severity of reactions they elicit , as is evident by anaphylaxis, which is caused by the minor determinant. On the contrary accelerated and late penicillin reactions are mediated by the major determinant.

13. Penicillin antibodies develop in all patients who receive the drug not necessarily causing any drug allergy . Anaphylaxis and angioedema are IgE mediated ; serum sickness is IgG mediated and haemolytic anaemia, IgM mediated.

PREVENTION

14. Certain guidelines if adhered to can minimize the incidence of penicillin allergy

(a) A detailed history to be taken about prior exposure to penicillin and penicillin allergy . Also enquire about any underlying allergic diathesis (eg Bronchial Asthma). It is best to avoid this drug in such situations.

(b) awareness of the possible allergic reaction to penicillin and a high index of suspicion to enable an early diagnosis.

(c) Topical use of penicillin should be discontinued to avoid sensitisation.

(d) PnG and the semisynthetic penicillin to be used only for specific indications.

(e) Testing for penicillin sensitivity

Skin Scratch Test : A drop of acqueous solution of PnG containing 5 units/ ml is placed on the volar aspect of the forearm and a scratch made in the skin using a disposable, sterile 26 G hypodermic needle. Wait for 15 minutes. If no local erythema , itching or edema appears, repeat the test using 10,000 units PnG per ml concentration. If this is also negative for a allergic reaction proceed to do the intradermal test.

(ii) **Intradermal test** employs a dose of 0.02 ml of 1000 units per ml PnG, given intradermal on the volar aspect of the forearm on the opposite side to the one used for the skin scratch test. Wait for 20 minutes and observe for a local reaction as in skin scratch test. If no reaction is noted , proceed to give the therapeutic dose of PnG. A control using normal saline is also injected which should not elicit any reaction.

CAUTION :- A syringe loaded with 2 ml of 1: 1000 adrenaline B.P is to be kept ready at hand whenever any of the above tests are conducted. Concomitant use of antihistaminics

may interfere with the sensitivity tests, hence should be avoided.

TREATMENT OF IMMEDIATE PENICILLIN REACTION

15. On diagnosis of penicillin anaphylaxis and angioneurotic edema, an emergency call should be sounded by the attending medical and nursing staff.

(a) Patient made to lie down in head low position . Reassure the patient.

(b) Start an intravenous line and oxygen using mask or nasal prongs at 5 to 6 litres per minute .

(c) Make a record of TPR , BP and level of consciousness.

(d) The first drug to be administrated should always be **Adrenaline** (Epinephrine)1:1000 .

(i) If onset is explosive with hypotension administer 0.5 ml of adrenaline diluted in 10 ml normal saline by slow intravenous route . Dose to be repeated every 5 minutes till a response is attained

(ii) If onset is less dramatic with no hypotension , 0.5 ml of adrenaline is to be given subcutaneously. Repeat every 5 minutes till a response is obtained,

(iii) Injection adrenaline 1:10,000 dilution could be delivered as an aerosol through an endotracheal tube when no venous access is available in peripheral cirulatory collapse. The durg is readily absorbed from the capillary bed of the lung.

(iv) Injection chlorpheniramine maleate 25-50 mg slow intravenous.

(v) Bronchospasm is treated with salbutamol nebulisation and intravenous deriphylline (220 mg diluted in 20 ml of 5 % dextrose over 10 minutes).

(vi) Injection hydrocortisone hemisuccinate 200 mg intravenously followed by 100 mg six hourly for one to two days.

TREATMENT OF SERUM SICKNESS

16. Serum sickness with severe arthralgia, arthritis and myalgia can be incapacitating and myocarditis though rare is life endangering . This is treated with oral prednisolone in a dose of 1 mg / kg body weight given in three divided dose for 5 –7 days . Serum sickness is a self limiting reaction and resolves in 6 – 12 days

17. All patients who have suffered any form of PnG allergy should be explained in detail about this problem and the same should be documented in I.A.B-64, in health record card of the patient and in the hospital records (AFMSF-7A).