Penicillin Sodium Salt.

Contributors

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Wellcome Collection
183 Euston Road
London NW1 2BE UK
T +44 (0)20 7611 8722
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PENICILLIN

Sodium Salt

DESCRIPTION

Penicillin is a potent antibacterial substance which is obtained from the culture liquor of the mold *Penicillium notatum.*

The sodium salt of penicillin is the preparation which has been most widely used clinically. In its present form it is an amorphous yellowish brown powder, which is very soluble in distilled water, physiological saline solution, and 5 per cent dextrose solution. Penicillin is rapidly inactivated by high temperatures and may undergo slow deterioration even at room temperature. It should be stored below 10°C. (50° F.).

At present penicillin is assayed in terms of the Oxford (Florey) unit. The Oxford (Florey) unit is defined as "that amount of penicillin which when dissolved in 50 ml. of meat extract broth, just inhibits completely the growth of the test strain of *Staph. aureus.*"

ACTION

Penicillin exerts a powerful antibacterial action against the Staphylococcus, the pneumococcus, the hemolytic streptococcus, the gonococcus, and the meningococcus. Increasing experience will undoubtedly prove it to be an effective therapeutic agent in infections caused by several other gram-positive bacteria. Except for its action on the gonococcus and the meningococcus, penicillin

appears to be without effect against gram-negative bacteria.

In the clinical treatment of infections, the mode of action of penicillin has been shown to be bacteriostatic rather than bactericidal. From this it follows that the duration of treatment is an important consideration in the use of penicillin. Therapy should not be discontinued until recovery appears to be well established. In addition, it would seem essential that careful attention be given to general supportive measures such as the use of transfusions, plasma, parenteral fluids, oxygen, vitamins, and any other measures which might enhance the activity of the patient's normal defense mechanisms by improving his general condition.

PHARMACOLOGY

Penicillin is rapidly inactivated by the hydrochloric acid of the gastric juice, and very little, if any, is absorbed following rectal instillation. Therefore, to secure adequate absorption, penicillin must be given parenterally, either by intravenous or intramuscular injection. Higher blood levels are obtained following intravenous injection, but more evenly sustained levels result from intramuscular administration.

Following either intravenous or intramuscular injection, penicillin is rapidly excreted by the kidney. An average of 58 per cent of the amount injected is found in the urine at the end of one hour. Even when relatively large amounts of penicillin are given in a single injection, the blood will be practically cleared of penicillin after 2 to 3 hours.

After intravenous or intramuscular injection, very little, if any, penicillin passes into the cerebrospinal fluid or into any of the various serous spaces of the body.

ADMINISTRATION

In the treatment of infections, penicillin can be administered intravenously, intramuscularly, or locally. For the treatment of systemic infections, a continuous intravenous drip or multiple intravenous or intramuscular injections may be used. All 3 methods have proved successful in practice. In particular cases the exact method of administration may be selected by the attending physician on a basis of which method will be most convenient and practical.

When a continuous intravenous drip is used, the penicillin may be dissolved in either 5 per cent dextrose solution or in physiological salt solution. The concentration should be adjusted so that the rate of flow, usually 50 or 100 cc. per hour, will provide the amount of penicillin which it is desired to administer hourly.

When penicillin is administered by multiple injections, either intravenously or intramuscularly, the interval between injections should not exceed 3 hours. Even when large doses are given, almost all the penicillin injected will have disappeared from the blood at the end of 3 hours. Studies on the excretion of penicillin suggest that when it is necessary to administer very large daily doses of penicillin, the drug will be utilized more efficiently if the interval between doses is shortened rather than if the size of the individual injections is increased.

For multiple intravenous injections a concentration of 1,000 units of penicillin per cc. of physiological saline is usually employed, while for intramuscular injections the concentration should be increased to 5,000 units per cc. Distilled water should not be used, since the resulting solution will not be isotonic and will be irritating.

Because significant amounts of penicillin do not enter the cerebrospinal fluid or the various serous spaces of the body after intravenous or intramuscular injection, the physician when treating an infection of the meninges, of the body cavities or of the joints, should introduce penicillin directly into the infected cavity. For this purpose a concentration of 1,000 units per cc. in physiological salt solution is satisfactory. Since the absorption of penicillin from the body cavities is slow, local administration need be performed only once or twice every 24 hours.

Penicillin should not be used as an irrigating solution since it must remain in contact with the infecting organisms for at least 6 to 8 hours before it exerts its maximum antibacterial effect.

In the treatment of infected wounds, systemic therapy is generally far superior to local therapy except in selected cases where the infection is extremely superficial. In such cases penicillin can be applied in a solution of 250 units per cc. of physiological salt solution or in a suitable ointment base containing 250 units of penicillin per gram.

INDICATIONS

Clinical trial has established the therapeutic efficacy of penicillin in most infections caused by the

Staphylococcus, the pneumococcus, the hemolytic streptococcus, and the gonococcus. As increased production of penicillin makes more extensive clinical experience possible, penicillin will undoubtedly be found to be effective in an even wider range of diseases. At present, because of the extremely limited amount of penicillin available, its use should be restricted to patients who are seriously ill with infections caused by the above organisms and in whom adequate sulfonamide therapy has not been effective.

Preliminary experiments have indicated that penicillin therapy is rarely effective in the various forms of bacterial endocarditis. It should not be used, therefore, for the treatment of such conditions until a much larger supply of the drug becomes available.

DOSAGE

In general it has been found that in gonococcal, pneumococcal, and hemolytic streptococcal infections, relatively small dosages and short periods of treatment are usually effective. Staphylococcal infections, on the other hand, frequently require prolonged and intensive therapy. The following tentative dosage schedules have been derived from the results of clinical experience with penicillin to date. The dosages that are given are for adults. When children are being treated, the dosage can usually be reduced to one half or one quarter of the adult dose depending on the size of the patient.

Gonococcal urethritis — 15,000 units intramuscularly or intravenously every 3 hours for 8 doses.

Pneumococcal pneumonia — 10,000 to

15,000 units intramuscularly or intravenously every 3 hours for 72 to 96 hours.

Pneumococcal empyema—20,000 to 40,000 units injected directly into the pleural cavity daily for 3 days. Pus or fluid should be aspirated before the penicillin is introduced.

Pneumococcal meningitis—10,000 units intrathecally into the lumbar sac or into the cisterna magna every 12 hours for the first 48 hours and then every 24 hours for 5 to 7 days more. Intravenous or intramuscular therapy should be carried out at the same time.

Serious hemolytic streptococcal infections with or without bacteremia—10,000 to 15,000 units intramuscularly or intravenously every 3 hours until the temperature has been normal for 48 to 72 hours and definite signs of healing of the local lesion have appeared.

Hemolytic streptococcal meningitis—Same schedule as for pneumococcal meningitis.

Hemolytic streptococcal empyema—Local instillation of penicillin as for pneumococcal empyema. More prolonged treatment may be necessary. Intramuscular or intravenous therapy may be advisable as well, because underlying pneumonic process is likely to be still active.

Severe staphylococcal infections with and without bacteremia—120,000 to 240,000 units daily in continuous intravenous drip, or intramuscularly or intravenously in divided doses at 2 or 3 hour intervals. After the temperature has returned to normal, the total dose for a 24-hour period may be reduced by half, but therapy

should be continued for at least 7 days after the temperature has become normal. When there is an associated staphylococcal meningitis, empyema, or suppurative arthritis, injections of penicillin into the infected cavity should be made daily until the fluid has been sterile for 48 to 96 hours.

Chronically infected wounds, such as osteomyelitis — 10,000 to 15,000 units intramuscularly or intravenously every 3 hours. Treatment should be continued until the exudate has been sterile for several days, and, if possible, until healing of the lesion has taken place.

TOXICITY

No serious toxic reactions have been encountered following the clinical administration of penicillin. In the doses used clinically, penicillin has no harmful effect on the blood forming organs, the liver, or the kidneys. Febrile reactions have been observed in a few instances, but the material now provided has been carefully tested and is released only after it has been shown to be free of pyrogens. Care should be taken to use only pyrogen-free salt solution or dextrose solution in preparing penicillin for use.

Transient flushing of the face, tingling in the testes, and headache have been encountered on rare occasions. A syndrome resembling serum sickness, including urticaria, arthralgia, fever, sore throat, and enlarged lymph nodes and spleen has been seen occasionally during or following penicillin treatment. In several instances penicillin has been re-administered without harmful

effect to patients who have shown such reaction. Thrombophlebitis occasionally occurs at the sites where penicillin has been injected intravenously.

PREPARATION OF SOLUTIONS

The penicillin in the vials has already been sterilized and it is not necessary to re-sterilize it before using. Because penicillin is less stable in solution than it is in the dry state, it is advisable not to dissolve at any one time more penicillin than can be used within the next 24 hours. However, if solutions of penicillin are kept at a temperature of 5°C. (41° F.) or less, they will usually not lose significant activity over a period of several days. Thus if a batch of solution is not entirely used within 24 hours after being prepared, it should not be discarded but should be kept in the refrigerator and used as soon thereafter as possible.

As a general rule it has been found most convenient to dissolve penicillin in sufficient sterile physiological saline solution to make a concentration of either 5,000 units or 1,000 units per cc. This solution is then stored in a refrigerator in a rubber stoppered bottle, and the amounts needed for individual injections are then withdrawn from time to time throughout the 24-hour period.

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