REFRESHER COURSE FOR GENERAL PRACTITIONERS

CHEMOTHERAPY—I. ADMINISTRATION OF PENICILLIN

BY

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In describing the therapeutic use of penicillin it is convenient to deal first with its administration and secondly with indications for it: these will be the subject of a succeeding article.

Therapeutic Action

Two theoretical aspects must be considered briefly: one of these is the nature of the action of penicillin. This is exerted exclusively on the bacteria causing the infection, and varies in nature and degree with the concentration to which they are exposed. Low concentrations do little more than inhibit bacterial growth, but one only 5 or 10 times greater than this is actively, though not very rapidly, bactericidal: 99% or more of a fully exposed bacterial population may be killed within a few hours. If the concentration is increased beyond this point no further acceleration of bacterial death occurs, and with certain organisms the rate may even be substantially decreased. Penicillin is unique in this behaviour. It has an optimum concentration for antibacterial effect beyond which an increase will certainly be useless and may be positively detrimental, whereas with other bactericidal substances increased concentration accelerates effect indefinitely. The optimum concentration for a sensitive organism is quite low—for a staphylococcus about 0.1 unit per ml., and for a haemolytic streptococcus even less. It might appear from this that the object of treatment should be to maintain this concentration in the tissues until the infection is eliminated. In the first place this is impossible except by the use of a continuous drip. It further overlooks the fact that penicillin has to diffuse into infected areas, where the concentration is likely to be lower than that attained in the blood. The view is widely held that the intermittent production of relatively very high blood levels is useful in promoting this diffusion into undrained abscesses, areas of necrosis, cardiac vegetations, etc.

How long should this action be maintained, and should it be continuous or intermittent? There are grounds for believing that the necessary duration of treatment depends on two principal factors. One is the sensitivity of the organism: the gonococcus, the most sensitive of all, can usually be eliminated in a few hours. The other is the total number of bacteria to be disposed of, which is tantamount to saying the stage or extent of the infection. At a very early stage the dose required may be only a small fraction of that necessary later. The relative merits of continuous and intermittent effect have been much debated and are still unsettled. Penicillin acts only on multiplying bacteria, and since any given dose leaves a number of semi-dormant bacterial cells alive (Bigger's "persisters") it is argued that these should be allowed to begin multiplying before another is given. It would obviously be dangerous to carry this policy too far. It is known that bacteria exposed to but not killed by penicillin resume growth in a period averaging three to four hours, and it seems reasonable not to allow the concentration in the blood between doses to fall below an effective level for much longer than this. Recent extensive therapeutic tests in animals support this view.

Absorption and Excretion

The ordinary salts of penicillin (the sodium salt being that commonly used) are freely soluble and highly diffusible. Injected in watery solution into the tissues, penicillin is quickly absorbed, reaching maximum concentration in the blood within less than 15 minutes if the dose is not very large. This rise to a high level is followed by a fall at first almost as steep, due to rapid renal elimination. Penicillin leaves the body as fast as it reaches the kidneys, and the enormous quantities which have to be given are due to the fact that on the average each molecule spends only a few minutes in the circulation between absorption from the injection site and excretion by the kidney. Comparatively few ever reach and still fewer remain at the site of a local infection. That the doses given are enormous will be conceded when it is remembered that in a patient of average weight with total anuria the dose required to produce an adequate concentration in the blood for treating a fully sensitive infection would be only 350 units. It is advisable to bear in mind that patients with impaired renal function require smaller doses at longer intervals.

The rate of fall in the blood level, although steep at first, progressively diminishes. During the latter part of this phase traces are probably still being absorbed from the site of injection, and some which has passed into the tissues is returning to the circulation via the lymph. The relation of duration of effect to dose, and means of obtaining more prolonged effect, are discussed later.

Treatment by Intramuscular Injection

Penicillin may be given either by continuous infusion—now an uncommon practice, and feasible only in a hospital—or by spaced single injections. It is usual to make these intramuscularly, but this route was originally adopted because the crude penicillin of early days was more painful given subcutaneously. This objection to the subcutaneous route no longer holds, and it has some slight advantage in being followed by rather slower absorption. The site of injection is theoretically indifferent, and practically so in a well-nourished patient requiring few injections. In an emaciated patient having a long course, rotation of the main sites is essential. In either, skill and a really sharp needle affect his reaction considerably.

It was originally the practice to give small doses at intervals of three or at the most four hours in order to maintain the effect. With the free availability of penicillin the practice has grown up of giving large doses at long intervals, and this has been carried to greater lengths in this country than in any other. It is important to know how far this is justified, and in considering this it must be remembered that duration of effect is by no means directly proportional to the dose given. The larger this is, the greater the rate of elimination, and doubling the dose actually prolongs effect by only about one-third. The following are the approximate times during which a detectable and thus—for a sensitive infection—therapeutically useful concentration persists in the blood.

After 25,000 units	..	..	..	..	2½ hours
" 50,000 "	..	..	..	..	3 "
" 100,000 "	..	..	..	..	4 "
" 250,000 "	..	..	..	..	5 "
" 500,000 "	..	..	..	..	7½ "

These figures are only approximate, because the rate of elimination varies inexplicably in different apparently normal subjects. They conflict in the higher range with other published figures, but the last of them is based on recent observations by a colleague and myself made by an accurate technique in a series of 31 individuals, and we have no hesitation in asserting that for a dose of 500,000 units to produce a detectable blood level after the eighth hour is exceptional.

It has already been mentioned that bacteria are known to take some hours to recover from exposure to penicillin and to resume growth, the length of this period varying with species, length of exposure, and concentration. Allowing for this factor, the following intervals are appropriate between different doses for patients in whom it is necessary that the drug should exert a full and uninterrupted effect.

Dose	Interval
25,000 units	3 hours
50,000 "	4 "
100,000 "	6 "
250,000 "	8 "
500,000 "	12 "

In less serious cases, and when frequent administration is impracticable, these intervals may be lengthened, probably with some retardation of the therapeutic effect, but it seems inadvisable in any circumstances to give penicillin in this form only once daily: the interval for bacterial recovery is then too long. It is true that penicillin persists in exudates after it has disappeared from the blood, and this may add a few hours to the period of efficacy of each dose, but it is not known how far this persistence depends on the nature of the lesion and the rate of exudation into it, and there are some conditions, notably bacterial endocarditis, in which this factor is not operative at all.

Slowly Absorbed Preparations

The effect of a single dose can be prolonged either by delaying absorption or by blocking excretion. Various substances have been used which interfere with the renal excretion of penicillin. Of these the most useful is caronamide, since it can be given by the mouth. The dose required is large, and apt to cause nausea and other disturbances. This method should be used only under hospital conditions for sustaining very high blood levels in unusually resistant infections.

Delayed absorption was first secured by suspending calcium penicillin in an oil base also containing beeswax. Beeswax is essential for the full delaying effect, and it is this ingredient which causes local reactions, sometimes going on to suppuration. These preparations are now almost entirely superseded by oily suspensions (containing no beeswax) or powders, suspended in water before injection, containing procaine penicillin. This compound of the two substances has a low solubility to which its slow absorption is mainly due, and an antibacterial action equivalent to that of penicillin itself. The rate of absorption—and, it may be added, the facility with which the material will pass through a small needle—depend on the size and shape of the procaine penicillin crystals: it is possible, although not all manufacturers have yet succeeded in doing this, to produce crystals large enough (50 μ in diameter) to dissolve slowly, but so compact as not to cause needle blockage.

The rate of absorption of a good preparation of this kind is contrasted with that of an ordinary solution of sodium penicillin in the accompanying figure. After a

dose of 250,000 units or thereabouts the blood level rises to a maximum of about 1 unit per ml. in four hours, then diminishing very slowly so that an effective or at least detectable amount is still present after 24 hours. If the preparation also contains aluminium stearate, a water-repellent substance which delays absorption further, this shallow curve is even more flattened, and penicillin may be detected in the blood after two days or even considerably longer if a large dose (one million units or more) is given. Some of these preparations also contain sodium penicillin, which will also give a high initial level lasting only a short time.

The object of these preparations is to secure a continuous effect from a single daily dose, from doses given at intervals of two or more days, or even to cure an infection by a single dose which need not be repeated. They provide much the simplest means of treating patients efficiently in their own homes, where only infrequent injections are feasible. They may be used in a patient under nursing care either because a continuous fairly low blood level is thought desirable, or simply in order to obviate frequent injections. What they will not do is to produce a high blood level. If the infection is a relatively resistant one, or if for any other reason it is thought desirable to achieve a blood level of much over 1 unit per ml., then large doses of sodium penicillin should be given.

Oral Administration

Penicillin is destroyed by acid in the stomach and by bacterial enzymic action in the lower bowel. There is also some loss, not wholly explained, in the upper part of the intestine, since, even in patients with total achlorhydria or given penicillin through a duodenal tube, only a fraction of the dose is absorbed. It is therefore necessary to give from 5 to 10 times the intramuscular dose in order to achieve the same effect; even so the effect is not altogether dependable, since the proportion absorbed varies inexplicably in different subjects, and even in the same subject at different times. Absorption is better when the stomach is empty: oral penicillin should therefore be given before meals. Antacids and various capsules designed to overcome the acid gastric barrier have not been found helpful. Absorption is rather more constant in infants, and penicillin may be added to feeds. Here there is the double advantage of avoiding injections in patients to whom they are most disturbing, and of reasonable economy, since the dose required is comparatively small on a body-weight basis.

It is difficult to say what place this form of treatment should have, but even its more enthusiastic advocates are reluctant to employ it in serious cases owing to the uncertainty of its effects.

Local Administration

There are many ways in which penicillin may usefully be applied to the actual site of infection. Besides being a chemotherapeutic agent, it has all the properties of the ideal antiseptic, killing or preventing the growth of susceptible bacteria without doing the slightest harm to tissue. Local application may be indicated for its simplicity and economy, because the area concerned can be reached in no other way, or in order to attain a high concentration there which will persist for some time. The following are the more important examples.

Intrathecal Injection.—Only traces of penicillin reach the cerebrospinal fluid from the blood unless enormous doses are given intramuscularly. Meningitis should therefore be treated by intrathecal injection as well as intramuscular. Pure ("white") sodium penicillin should be used, and the solution should be prepared freshly with the strictest aseptic precautions and with no preservative such as phenol. A dose of 10,000 units will maintain an adequate level for 24 hours. Unless there is a block, remarkably uniform diffusion occurs throughout the central nervous system from an injection given by the lumbar route.

Serous Sacs, Joints, and Abscesses.—Penicillin solution may with advantage be injected into an empyema cavity, a joint affected by suppurative arthritis, or abscess cavities elsewhere, the dose depending on the size of the cavity: as much as 100,000 units may be indicated for a large empyema. Absorption from such an area is slow, and penetration into it from the blood equally or more so; this is therefore not only a convenient but the only way of keeping up a high concentration in such a collection of fluid for a whole day or more. If the dose is large, slow absorption will also maintain a systemic effect, to some extent taking the place of intramuscular injections. This is not the place (nor am I the person) to discuss the surgical treatment of these conditions further than to say that penicillin does not necessarily remove the need for it.

Carbuncle can be treated very successfully by injecting penicillin into and around it. Even though the solution also contains procaine, this is a painful proceeding, but may be well worth while to accelerate resolution.

Wounds.—One way of preventing infection in a recent wound is to dust it with a powder containing penicillin. The usual diluent is a sulphonamide (preferably sulphathiazole), and the procedure has been objected to on account of the risk of causing sensitization. Established sepsis in superficial wounds and burns, if due to a demonstrably sensitive organism, may be treated similarly, or by the spraying of a solution or the application of a cream. These last two methods are applicable, under the same condition, to the treatment of infections of the skin. Among other superficial infections, conjunctivitis may be treated by drops frequently applied or by lamellae.

Upper Air Passages.—Infections of the main nasal cavity (it being remembered that the sinuses are generally inaccessible to such measures) can be treated either with a spray or, probably better, by the frequent use of a snuff containing 5,000 units of calcium penicillin per gramme of sulphathiazole. This has been particularly successful in clearing up nasal carrier conditions; and, owing to the backward flow of mucus in the nose, it has also an effect on the nasopharynx and even the throat.

Local treatment of the throat and mouth is best carried out with gelatin pastilles, one of which should be kept in the buccal sulcus throughout the day. Solution is slow, and replacement necessary at intervals of not less than an hour. The official trochiscus penicillinae of the B.P., a tablet with a lactose base, is less satisfactory. The choice of this product was dictated by the greater stability of penicillin in a dry form, but gelatin pastilles are now obtainable which retain the greater part of their activity for months; alternatively, they can easily be made fresh by a pharmacist. Penicillin chewing-gums are also suitable for this type of use if the patient will persist with them.

Infections of the bronchi and lungs may be treated by inhalation, a small volume of concentrated solution containing, say, 100,000 units being administered by a Collison or other inhaler several times a day. There is some absorption by this route: thus a large enough dose will also exert a systemic effect. The inhalation of a fine powder of penicillin, recently advocated in the U.S.A., has not apparently been adopted in this country, and seems likely to be more disagreeable to the patient than a liquid spray.

PHARMACY AND POISONS ACT, 1933

The Poisons List Order, 1950 (S.I. 1950, No. 1213) and the Poisons Rules, 1950 (S.I. 1950, No. 1214), which were made by the Secretary of State on July 21, come into operation on September 1. These Statutory Instruments make the following changes in the Poisons List and the Poisons Rules, 1949, hereafter called the Principal Rules.

Part I of the Poisons List and the First Schedule to the Principal Rules.—The following substances are added: Alphaprodine; its salts. The following antihistamine substances and their salts: antazoline, diphenhydramine, 3-di-*n*-butylaminomethyl-4:5:6-trihydroxyphthalide, phenindamine, substances being tetra-substituted N derivatives of ethylenediamine or propylenediamine. Betaprodine; its salts. Di-isopropyl fluorophosphonate. Hydroxypethidine; its salts. Iso-amidone; its salts. Ketobemidone; its salts. Methadol; its salts. Methadyl acetate; its salts. Polymethylenebistrimethylammonium salts. The following items are amended: Amidone (DL-2-dimethylamino-4:4-diphenylheptane-5-one); its salts. The chemical description is omitted and the entry now reads: "Amidone; its salts." The item "6-morpholino-4:4-diphenylheptane-3-one; its salts," which describes the poison now known as phenadoxone is omitted, and after the item "Pethidine; its salts;" there is inserted "Phenadoxone; its salts."

The Third Schedule to the Principal Rules.—Antihistamine substances and their salts are added to Group II of this Schedule and are thereby exempted from the requirements of the Pharmacy and Poisons Act and the Principal Rules when in the form of "preparations intended for external application only."

The Fourth Schedule to the Principal Rules.—Antihistamine substances and their salts, other than the preparations exempted by inclusion in Group II of the Third Schedule, and polymethylenebistrimethylammonium salts are added to this Schedule. The item "6-morpholino-4:4-diphenylheptane-3-one; its salts" is deleted from this Schedule. This poison (under the name phenadoxone) is now subject to control under the Dangerous Drugs law.

The Seventh Schedule to the Principal Rules.—At the end of this Schedule the following paragraph is added: To be labelled with the words "Caution. This preparation should be administered only under medical supervision. The vapour is dangerous": Medicines made up ready for the internal or external treatment of human ailments and containing di-isopropyl fluorophosphonate.

Rules 7 and 12 of the Principal Rules.—These Rules are amended to provide that when a poison is supplied in ampoules the "signed order" or prescription may state either the total amount to be supplied (as at present) or the total amount intended for administration or injection.

Rule 16 and the Thirteenth Schedule to the Principal Rules.—In paragraph (e) of the proviso to this Rule and in the Schedule the description "executive officer" is replaced by the description "county agricultural officer or assistant county agricultural officer."

Copies of the Poisons List Order and of the Poisons Rules may be obtained from H.M. Stationery Office or through any bookseller.