Today's Treatment

Use of antibiotics

Penicillins

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Penicillins are among the most frequently prescribed drugs, and the 15 different members are marketed in many forms and combinations. I will try to place the use of both the older ones and also the more recent additions.

In both clinical usage and antibacterial activity there are four main divisions of the penicillin family—benzylpenicillin (and other closely related antibiotics), the penicillinase-stable penicillins, the broad-spectrum penicillins, and the anti-pseudomonal penicillins. All are bactericidal agents. They act by interfering with the final stages of peptidoglycan synthesis, the substance that is found in the bacterial cell wall and is responsible for maintaining its shape.

Benzylpenicillin

Against certain pathogenic bacteria, benzylpenicillin is extremely active, and resistance is rare or even unknown. This drug must be considered the treatment of choice in infections caused by the β -haemolytic streptococcus; *Streptococcus viridans*; the pneumococcus, other than the rare penicillin-resistant South African strains¹; meningococci; *Treponema pallidum*; and *Clostridia* spp. Strains of *Neisseria gonorrhoea* which show high levels of resistance to benzylpenicillin are still rare in Britain. Originally, most strains of *Staphylococcus aureus* were sensitive, but now from 60 to 90% of isolates in hospital and general practice are resistant because these bacteria produce an enzyme that destroys the antibiotic—a penicillinase (the term β -lactamase is more generally used to describe an enzyme that destroys one or several β -lactam drugs—penicillins or cephalosporins).

Benzylpenicillin is poorly absorbed, being broken down by gastric acid, and it should be injected. The dose should be tailored to the condition treated, but as the drug is safe it is fair to say that the usual dosages clinicians use are much greater than needed. As benzylpenicillin is rapidly excreted its action can be prolonged by the concomitant use of probenecid (1-2 g a day). Another approach is to use a penicillin of lower solubility, and a single dose of procaine penicillin, 2.4 or 4.8 megaunits, remains the treatment of choice for gonorrhoea.

Penicillin V (phenoxymethylpenicillin) is more stable to gastric acid and may be given by mouth. Its absorption is at best variable, and only in the mildest of infections due to penicillin-sensitive pathogens should penicillin V be relied on. For instance, the moderately to severely ill child with pharyngitis,

when a β -haemolytic streptococcus is implicated, should receive at least one to two doses of a long-acting penicillin, such as procaine penicillin, before changing to penicillin V. In such instances broad-spectrum penicillins such as ampicillin should be avoided as these drugs are (a) less active and (b) more prone to result in rashes particularly if, instead of a β -haemolytic streptococcus, a virus is the cause of the illness. Another treatment regimen is a single injection of a triple penicillin—a mixture of benzylpenicillin, procaine penicillin, and the ultra-long-acting benzethamine penicillin.

Penicillinase-stable penicillins

As mentioned, most strains of *Staph aureus* are now resistant, because of penicillinase production, to benzylpenicillin. There are three penicillins available in Britain that are resistant to this bacterial enzyme—methicillin, cloxacillin, and flucloxacillin.

These drugs vary in their stability to penicillinase, but the clinical importance of such differences is difficult to assess. Methicillin is the most stable but least active of the three.

It must be remembered that these drugs, although active against those bacteria that are sensitive to benzylpenicillin, are far less potent—for instance, a gonococcus may be inhibited by 0.01 mg/l of benzylpenicillin, but 0.5 mg/l of cloxacillin is necessary to achieve the same effect. These drugs should be reserved for treating staphylococcal infections.

Methicillin, which can be given only by injection, is rarely used nowadays. The antibacterial activities of cloxacillin and flucloxacillin are almost identical. They differ in their absorption after oral administration. Flucloxacillin is twice as well absorbed as cloxacillin, so that only one half of the dose of flucloxacillin (usually 250 mg six-hourly) need be used to achieve the same effect as cloxacillin (500 mg six-hourly), and if used in this way the former is cheaper.

The protein-binding of both of these drugs is extremely high, only about 5% being unbound in serum. Despite this, these agents give good clinical results. In severe staphylococcal sepsis one might be cautious of relying on these drugs alone and consider using an agent such as fusidic acid or clindamycin as well.

Staphylococci resistant to these penicillins (the so-called methicillin-resistant strains) are fairly rare—being only 2% or less (there is considerable geographic variation) of isolates. Usually such organisms are resistant to other antibiotics as well, and patients harbouring these strains should be kept apart from other patients in hospitals.

Broad-spectrum penicillins

The penicillins discussed so far have little activity against most Gram-negative bacteria other than *Neisseria* spp. Ampicillin, like the other members of this group, is active against

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many strains of *Escherichia coli*, *Proteus mirabilis*, *Klebsiella pneumoniae*, *Salmonella* and *Shigella* spp, and *Haemophilus influenzae*. It is also active against those bacteria that are susceptible to benzylpenicillin, but to a lesser extent. Ampicillin is also destroyed by the β -lactamases that many bacteria produce; therefore penicillinase-producing staphylococci are not susceptible. About one-third of all *E coli* also produce a β -lactamase that will inactivate this drug as will about one in eight strains of *P mirabilis*.

Other Gram-negative organisms, such as *K aerogenes*, *Enterobacter* spp, and *Pseudomonas aeruginosa*, are not sensitive to this drug. Ampicillin is also one of the more active drugs against *H influenzae*. Up to 4% of strains of this organism produce a β -lactamase,² and this is of considerable interest as it implies that ampicillin, alone, cannot be relied on in treating pyogenic meningitis before the causative organism is known.

Ampicillin is only moderately well absorbed when given by mouth, whereas the very closely related amoxycillin is more efficiently absorbed. Food interferes less with the absorption of amoxycillin than ampicillin. In antibacterial activity there is little difference between these two drugs. There is some in-vitro and animal work to show that amoxycillin is more rapidly bactericidal, but there is no evidence to confirm this in man. As amoxycillin is about twice as well absorbed, the dose should be one-half that of ampicillin, 250 mg being the usual dose. There is now a parenteral preparation of amoxycillin.

Talampicillin, which has no microbiological activity, is the phthalidyl ester of ampicillin. The ubiquitous esterases of the gastrointestinal mucosa and portal system hydrolyse the compound to free ampicillin and the ester moiety (which is metabolised and excreted). In other parts of the world other esters are available, such as pivampicillin and bacampicillin. The only advantage any of these compounds has over ampicillin is that of improved absorption. Talampicillin is twice as well absorbed as the parent compound and so, like amoxycillin, can be used at half the dosage of ampicillin. There is little to choose between the three compounds, and if used in the doses suggested there is little cost difference. The clinician should use the compound with which he has most experience.

Ampicillin and its close relatives are extraordinarily widely used in hospital and general practice. There is a tendency to choose these drugs as a panacea for all infectious ills. From what has been mentioned already there are many gaps in the antibacterial spectrum, and these antibiotics should not be used to treat severely ill patients unless the infecting organism is known to be sensitive. They still have a part to play in treating the exacerbations of chronic bronchitis and lower urinary tract infections (when other antibiotics may be just as effective) and in otitis media in children. As the drugs are excreted quite well in the bile they have been used to treat infections of the biliary tree.

Mezlocillin is a new broad-spectrum penicillin,³ at present under trial, and likely to be marketed fairly soon. Its spectrum is broadly similar to ampicillin, but it is particularly active against *H influenzae*, gonococci, and many strains of the *Proteus* spp as well as having a useful degree of activity against *Ps aeruginosa*, but it is unstable to β -lactamases.

Antipseudomonal penicillins

Although antipseudomonal penicillins share many properties with the ampicillin group it is more convenient to consider them apart, as the way in which they are used and the clinical conditions for which they should be reserved are rather different.

Carbenicillin was the first penicillin available that had useful activity against *Ps aeruginosa*. This drug is also active against those bacteria that are sensitive to ampicillin and the less common strains of *Proteus* spp, such as *Pr morgani*, *Pr vulgaris*, and *Pr rettgeri*, which are resistant to ampicillin. Carbenicillin is inactivated by many β -lactamases so that, for instance, ampicillin-resistant *E coli* will also be resistant to carbenicillin. As may be

FIG 1—Comparison of activities and serum concentrations of commonly used penicillins.

seen in the figure the amount of carbenicillin necessary to inhibit *Ps aeruginosa* is considerably greater than, say, the amount of ampicillin to inhibit an *E coli*. This means that the dose has to be increased.

Except when treating a urinary tract infection (the drug being concentrated in the urine), when 1 g intramuscularly can be used, carbenicillin must be given in high dosage, and 5 g intravenously every six hours is commonly used. There are certain problems associated with this high dose (see below).

The intensive use of carbenicillin in, say, a burns unit, has been associated with the emergence of carbenicillin-resistant strains of *Ps aeruginosa* due to the acquisition by these bacteria of resistance (R) factor.

As there are other antibiotics available for treating pseudomonas infections (the aminoglycosides, gentamicin and tobramycin), when should carbenicillin be used? I find that it is rarely needed. Any infection caused by a proved sensitive strain of *Ps aeruginosa* or the more resistant *Proteus* spp can be treated with this agent. It is only relatively few patients, from whom a pseudomonas has been isolated, who need antibiotics, as often this organism is just a superficial contaminant of ulcers, tracheostomy sites, etc. Carbenicillin has a role in prolonged or recurrent treatment when it is not desirable to use an aminoglycoside, such as in treating pseudomonal osteomyelitis or the pseudomonal infections of cystic fibrosis. On the other hand, in a severely ill patient (possibly with neutropenia), a combination of an aminoglycoside with carbenicillin to obtain antibacterial synergy would be desirable.

Ticarcillin is not available in Britain but is elsewhere. It is similar to carbenicillin but about twice as active. Another compound that is under trial here is azlocillin, a potent antipseudomonal penicillin, being eight times as active as carbenicillin.

Carfecillin (Uticillin) is the phenol ester of carbenicillin and unlike carbenicillin it can be swallowed. Esterases liberate carbenicillin in the blood, which is then excreted in the urine. The blood concentrations of carbenicillin are too low to treat a systemic infection, but the amounts in the urine should be sufficient to treat a pseudomonal infection of the bladder. As carbenicillin has a wide range of antibacterial activity including pseudomonas, this compound is being promoted for treating all urinary tract infections. Many consider that carfecillin should be reserved for only the rare (less than 1% in general practice) urinary tract infections caused by *Ps aeruginosa*. This antibiotic is expensive.

Amidinopenicillins—mecillinam

Unlike the other penicillins, which are aminopenicillanic acid derivatives, mecillinam is an amidinopenicillanic acid compound.

This seemingly minor modification is accompanied by several novel features. Although it is without useful activity against Gram-positive organisms, it is extremely active against a wide range of common Gram-negative organisms.⁴ Many strains of *E coli* and klebsiellae resistant to ampicillin are sensitive. Salmonellae, including *S typhi*, are also highly susceptible. The mode of action is also different, this compound being active against only one of the penicillin-binding proteins, causing the bacterial cells to round-up rather than lyse.

A parenteral preparation of mecillinam should be available soon, and the oral form, the pivaloyl ester (Selexid), is marketed. Mecillinam is useful against urinary tract infections, particularly pathogens resistant to other agents, but it is relatively expensive. Although there is some information showing that it is efficacious against typhoid fever⁵ its position in treating this condition has yet to be fully evaluated.

Combinations of penicillins

Some preparations are available that contain fixed amounts of different penicillins, such as cloxacillin or flucloxacillin plus ampicillin (Ampiclox and Magnapen). Such preparations aim to provide a broad antibacterial spectrum. By and large this leads to rather sloppy prescribing, and it can lead to a false sense of security as the amount of the necessary antibiotic may well be too low.

Using two drugs when only one is needed may also increase the risk of toxicity. Combinations of penicillins can be used if one is treating an infection caused by more than one pathogen or where specific antibacterial synergistic effect is the aim. The commercial claims made for fixed combinations are usually exaggerated, and these compounds should be avoided.

Problems associated with penicillin usage

The penicillins must be among the safest drugs a doctor prescribes. Their high usage and infrequency of severe toxicity are evidence of this.

The usual side effects are those related to immunity, a rash associated with treatment being the commonest. Ampicillin is the penicillin with the highest incidence of rashes—in up to 8% of courses of the drug as against 2-3% of other penicillins. Most ampicillin rashes are macular rather than urticarial and are extremely common if the drug is given in viral illnesses, especially glandular fever (when the incidence can approach 100%). The common ampicillin rash is therefore somewhat different to other penicillin rashes and does not necessarily mean that all penicillins are contraindicated in that patient. A generalised urticaria can be seen after any penicillin, and this is more serious.

A patient who has been labelled as allergic to penicillin because of an associated simple rash should not be denied a penicillin if this is the treatment of choice for a severe illness, such as endocarditis, but otherwise another drug should be chosen. In such cases the penicillin should be given with caution, with a small test dose first and adrenaline at hand. Anaphylaxis is rare and is a medical emergency. There is cross-allergenicity between the penicillins and about one in eight patients allergic to these drugs will also be allergic to the cephalosporins.

In renal failure it should be remembered that when taking high doses of benzylpenicillin or carbenicillin, the patient is also receiving considerable amounts of potassium, or more usually sodium (about 4.7 mEq sodium/g carbenicillin) and this could be important. Patients with severe renal failure are also at risk from neurotoxicity (usually manifested as convulsions) if large doses of either of these two drugs are used.

Haematological side effects are a haemolytic anaemia of immunological origin associated with massive penicillin treatment. High dose carbenicillin has been associated with a coagulopathy, platelet aggregation being affected by prevention of release of adenosine diphosphate from the platelet. This appears to be dose dependent and hence can occur with drug accumulation in renal failure.

Gastrointestinal side effects are not uncommon. By altering the body's flora, any of the broad-spectrum agents may cause overgrowth with resistant organisms. Oral candidiasis (thrush) is common. Diarrhoea is seen with any agent, especially the oral compounds. Talampicillin, while possibly causing less diarrhoea, is associated more with nausea and indigestion and has an unpleasant taste. A nephropathy has been described caused by penicillin or methicillin treatment. This appears to be an interstitial nephritis and reversible on stopping the antibiotic.

Conclusions

The penicillins are among the safest and most widely used drugs. The choice of which to use in a given condition is not difficult. They are all, including benzylpenicillin, extremely valuable agents. This usefulness can be preserved only by careful prescribing habits.

References

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How often are acute alcohol poisoning and alcohol withdrawal convulsions associated with acute hypoglycaemia? What is the mechanism of the hypoglycaemia that follows the consumption of a small amount of alcohol with a moderate amount of carbohydrate? Does hypoglycaemia always take place with alcohol withdrawal symptoms and if so, how many hours after the last ingestion of alcohol does the hypoglycaemia reach its maximum?

"Hypoglycaemia induced by alcohol may sometimes be a significant precipitating factor" in the production of withdrawal fits,¹ and although experience suggests that hypoglycaemia is uncommon in acute alcoholic withdrawal I have been unable to find any exact figures. In chronic alcoholism hypoglycaemia usually follows a period of low food intake and heavy alcohol consumption. Alcohol inhibits gluconeogenesis and hypoglycaemia ensues when hepatic glycogen stores are exhausted. Plasma insulin concentrations are suppressed, and plasma concentrations of glucagon, growth hormone, and cortisol are raised. Recently, O'Keefe and Marks² have shown that hypoglycaemia

can follow a modest intake of alcohol accompanied by glucose. Four of their ten non-alcoholic subjects developed minimum blood glucose values below 45 mg/100 ml (2.5 mmol/l), and three developed symptoms consistent with neuroglycopenia. Alcohol potentiates the plasma insulin response to glucose, and O'Keefe and Marks suggested that this might increase the tendency to reactive hypoglycaemia; however, the plasma insulin concentrations were not raised at the time of maximum hypoglycaemia. The effect of alcohol on plasma concentrations of "diabetogenic" hormones such as glucagon has not been fully investigated.

Dobrzanski and Pieschl³ measured blood glucose concentrations in patients with delirium tremens. Most had normal fasting levels on the first and seventh days of admission, but it is not clear from their report whether these patients had alcohol withdrawal symptoms when the blood was taken.

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² O'Keefe, S J O, and Marks, V, *Lancet*, 1977, **1**, 1286.

³ Dobrzanski, T, and Pieschl, D, *Journal of Studies on Alcohol*, 1976, **37**, 327.