Special Communication

SEMISYNTHETIC — BROAD SPECTRUM ORAL PENICILLINS

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The Penicillins are a group of antimicrobial substances produced in whole or in part by the growth of various species of the mould penicillium in suitable culture-media. Examination of the structure of the penicillin molecule shows it to contain a fused ring system of unusual design, the B-lactam and thiazolidine structure. The 5-membered thiazolidine ring appears in other natural compound, but the 4-membered B-lactam ring is quite unique. The nature of this ring delayed the elucidation of the structure of penicillin, but its determination was reached as a result of a collaborative research programme involving research groups in Great Britain and the United States during the year 1943-1945 (Clark et al., 1949).

A group of British Scientists (Bachelor et al., 1959) reported the isolation of 6-aminopenicillanic acid from the culture of p. Chrysogenum. This compound can be converted to penicillin by acylation of the 6-amino group. A fuller scope for variation in the nature of the penicillin side chain was achieved by Batchelor et al. (1959) with the development of fermentation methods to produce 6-aminopenicillinic acid. This intermediate, isolated initially from cultures of p. Chrysogenum grown on a medium free from side chain precursors has since been obtained by enzymatic deacylation of penicillin-G (Rolinson et al., 1960). 6-Aminopenicillinic acid is readily acylated and, as this method of synthesis does not carry the limitation inherent in the "biosynthetic approach" a much greater variety of analogues can be prepared.

The discovery of 6-APA made possible a vast extension on modified penicillins, and three main groups of semisynthetic penicillins of clinical interest emerged as the result of acylation of 6-APA. These groups are:

1. *The acid stable penicillins* which can be administered e.g. phenoxymethyl-penicillin, phenoxyethyl-penicillin and phenoxy propylpenicillin as well as several others.

2. *The penicillinase resistant penicillins*, e.g. methicillin, oxacillin, cloxacillin and dicloxacillin. These penicillins are not attacked by the staphylococcal penicillinase, because they have a very slow affinity to the enzyme. For this reason they are active against the organism in vitro, and in vitro activity is fully paralleled by the efficacy in clinical infections with benzyl penicillin resistant staphylococci. Their introduction has, in fact brought the penicillinase producing benzyl penicillin resistant staphylococcus under full therapeutic control — a noticeable advance in bacterial chemotherapy. Methicillin is unstable towards acids and must be given by injection. Oxacillin and cloxacillin are acid stable and can, therefore be administered orally. Methicillin is only about one-sixth as active in vitro as oxacillin and cloxacillin in the absence of serum. This advantage is however offset to some extent by the fact that the anti-bacterial activity of the latter two is considerably reduced in the presence of serum, much more so than the antibacterial activity of methicillin.

3. *Penicillins exhibiting broad antibacterial spectrum.* This group includes: Ampicillin, Hectacillin, Metampicillin, Pivampicillin, Epicillin, Cyclocillin, Carbenicillin and Amoxycillin.

Ampicillin

Ampicillin, a semisynthetic antibacterial obtained by interaction of 6-aminopenicillinic acid and D(—) aminophenyllacetic acid, was first prepared by Doyle et al. and made available in 1961. The introduction of the amino group in the position of the side-chain conferred activity against selected gram-negative microorganisms as well as acid stability. Unfortunately these modifications of the structure did not confer resistance to hydrolysis by B-lactamase (Penicillinase) and thus has been a prominent defect of this otherwise excellent compound. This is a disadvantage shared by all of the new aminopenicillins.

Ampicillin is similar to benzyl-penicillin in its bactericidal action against sensitive organisms during the stage of active multiplication. It acts through the inhibition of biosynthesis of cell wall mucopeptide.

Ampicillin is absorbed well when administered orally, and absorption is not seriously affected by time of administration with respect

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to meals, although plasma levels are somewhat reduced when food is ingested prior to administration. Whether the drug is given orally or intramuscularly, peak levels usually occur later than when phenoxymethylpenicillin (Penicillin V) is administered by mouth, but significant levels persist for a longer time. Following an oral dose of 0.5 or 1 Gm ampicillin usually achieves a maximum concentration of about 3 or 6 microgram per ml respectively, in the plasma in about 2 to 3 hours and is detectable for about 4 hours. Intramuscular injection (of sodium salt) produces higher peak level in the plasma — approximately 7 or 10 microgram per ml after injection of 0.5 or 1 Gm respectively, and the antibiotic is usually detectable for at least 6 hours (The United State Dispensatory, 1975).

Ampicillin diffuses readily into all body tissues and fluids with the exception of brain and spinal fluid except when mininges are inflamed. Higher serum levels are obtained following I/M injection. Most of the ampicillin is excreted unchanged in the urine and this excretion can be delayed by concurrent administration of probencid. The active form appears in the bile in higher concentration than found in the serum. Ampicillin is one of the least serum bound of all the penicillins, averaging almost 20% compared to approximately 60% — 90% for other penicillins.

Ampicillin is indicated in the treatment of infections due to susceptible strains of the following:

Gram-negative: Shigellae, Salmonellae (including S. Typhosae). M-influenzae, E. coli, P. mirablilis, N. gonorrhoeae and N-mengitidis.

Gram-positive: Streptococci, D. Pneumoniae and non- penicillinase producing staphylococci.

Adverse Reactions: As with other penicillins, it may be expected that reactions will be essentially limited to sensitivity phenomenon. They are more likely to occur in individuals who have previously demonstrated hypersensitivity to penicillins and in these with a history of allergy, asthma, hay fever, or urticaria. The following adverse reactions have been reported as associated with the use of ampicillin (Martindale 1973).

1. *Agranulocytosis*: Agranulocytosis occurred in an elderly patient with nephrolithiasis and urinary tract infection after administration of ampicillin but resolved on withdrawal of drug.

2. *Allergy and hypersensitivity*: (i) middle-aged woman with Addison's disease developed an allergic reaction within 10 minutes of the administration by mouth of 500 mg of ampicillin. She recovered completely after injection of adrenaline and hydrocortisone.

(ii) Of the antibiotics, ampicillin was most likely to cause skin rashes. These usually appeared 5 to 14 days after starting treatment and consisted of a maculopapular, bright, red mauve rash on the extension aspects of the limbs and trunk, particularly over the knees and elbow.

(iii) of 13,638 patients treated with ampicillin, 383 (2.8%) were reported to have experienced skin reactions. Patients with salmonella infections often developed rashes after treatment with ampicillin.

(iv) A rash was reported in 9.5% of 422 patients treated with ampicillin, in 4.5% of 622 patients treated with other penicillins and in 1.8% of 2941 patients not receiving these drugs. The risk of a rash occurring after ampicillin and other penicillins was 7.7% and 2.7% respectively. The occurrence of a rash after ampicillin was unaffected by the route of administration, but with other penicillins, a rash appeared more frequently after injection than after administration by mouth. There was no association between the mean daily dose of ampicillin and the frequency of drug rash, nor was a rash associated with duration of treatment.

Supra-infection: In 25 patients with urinary tract infection who were given ampicillin 2 Gm daily for 10 days, Candida albicans was absent from the faces of 2 patients, persisted and increased through treatment in 2 and appeared during treatment in 21. The intestinal candidiasis was symptomless, but 1 patient developed severe candidal vaginitis.

Two patients with infections mononucleosis developed generalised morbilliform eruptions after treatment with ampicillin. Patients with infectious mononucleosis should not receive ampicillin.

Hectacillin

Hectacillin is the condensation product of ampicillin and acetone. The compound is hydrolysed in the body to ampicillin within 15 minutes of administration so that all of its activity is due to ampicillin. Careful studies

(Sutherland and Rolinson, 1967) have not shown that this agent has any pharmacological advantage over ampicillin. Blood level are not higher than with ampicillin and only minimal prolongation of serum levels has been achieved. This compound has no advantage over ampicillin.

Metampicillin

Metampicillin is a compound obtained as the reaction of ampicillin and formaldehyde. It also is converted to ampicillin following absorption. Blood level studies have failed to show any advantage (Sutherland et al., 1972).

Pivampicillin

Pivampicillin is the pivaloyloxymethyl ester of ampicillin which is stable in aqueous acid but undergoes rapid hydrolysis in serum, blood and tissue to yield ampicillin. At no time does the concentration of ester in the blood exceeds 2% and within 15 minutes more than 99% of the compound has been converted to ampicillin. Human volunteers studies as well as studies of patients, have demonstrated that pivampicillin is absorbed more rapidly and completely than ampicillin producing blood levels three times those after equimolar doses of ampicillin (Dachne et al., 1970).

Epicillin

Epicillin (D-amino-1, 4-cyclohexadienlyl methyl penicillin) is a compound in which the benzene ring has been replaced by a cyclohexadienyl ring. The compound is active in its own right and is not converted in the body to ampicillin. The oral absorption and serum binding of epicillin is similar to ampicillin. Epicillin has been shown to be effective in ottis media, bronchitis, diarrhoael diseases, and urinary tract infections (Brogden and Avery, 1973).

Cyclacillin

Cyclacillin is another aminopenicillin that is not converted to ampicillin, but has intrinsic activity. Cyclacillin has been used in comparative studies with ampicillin to treat ottis media and urinary tract infections (Hertz, 1973).

Carbenicillin

It is a semi-synthetic injectable penicillin derived from the penicillin nucleas 6-aminopenicillinic acid (Carboxybenzyl penicillin). It is bacterial and demonstrates activity against both gram-positive and gram-negative organism.

Carbenicillin sodium is contraindicated in patients known to be sensitive to penicillin and it should be given with caution to patients with known histories of allergy. Because of its sodium contents it should be given cautiously to patients on a restricted sodium diet.

Adverse Reactions: The following adverse reactions have been reported (Martindale 1973).

The intramuscular infection of carbenicillin had resulted in a rise of SGOT values, whereas the same dose by intravenous infection had not. This indicated that muscle damage and not liver damage was responsible for the effect.

Electrolytic disturbances: Two patients who received carbenicillin sodium 30 Gm daily by intravenous infusion developed symptoms of hypokalemia which responded rapidly to therapy with potassium chloride by mouth.

Haemorrhage: Of 30 patients who received carbenicillin sodium in doses of 500 to 750 mg per kg body weight daily, purpura and bleeding from mucus membranes occurred in 6. The bleeding appeared within 12 hours of starting thereby and took from 3 to 7 days to disappear after discontinuation of the drug.

Amoxycillin

Amoxycillin is a new semi-synthetic penicillin with a broad spectrum of antibacterial activity.

Amoxycillin is highly active against Gram-positive cocci including streptococci, phenumococci and penicillin sensitive staphylococci. Against streptococcus facalis, amoxycillin is not active against penicillin resistant staphylococci owing to instability to staphylococcal penicillinase.

Amoxycillin is highly active against hemophilus influenzae, most strains being inhibited by concentrations of 0.1-0.5 microgram/ml. It also shows a level of activity similar to that of ampicillin, against the gonococcus and, like ampicillin, amoxycillin is somewhat more active than benzyl-penicillin against the penicillin resistant strains.

Among the Gram-negative bacilli most strains of Escherichia coli, proteus mirabilis, shigella-sonnei and salmonella species are inhibited by amoxycillin at a concentration of 5 microgram/ml. Against these organisms amoxycillin shows a level of activity very similar to that of ampicillin.

Amoxycillin is not active against pseudomonas aeroginosa, and most strains of Klebisiella/enterobacter, indole-positive proteus species and serratia marcescens are also resistant (Rolinson 1973).

Amoxycillin is stable in gastric acid and is readily absorbed from the gastrointestinal tract. Absorption is more complete than with ampicillin and serum levels are generally more prolonged after amoxycillin than after ampicillin and mean peak serum levels of amoxycillin are usually about twice those achieved after an equivalent dose of ampicillin. The absorption of amoxycillin is not appreciably influenced by the presence of food. As with other penicillins, mean peak serum levels of amoxycillin are attained later and persists for longer in newborns than in older children or in adults, and serum levels are enhanced by the prior administration of probencid.

In patients with renal failure, serum levels of amoxycillin are higher, attained later and persist longer than in patients with normal renal function. The serum half-life is about 60 minutes in subjects with normal renal function and about 6 hours in patients with renal failure off dialysis. Serum half-life is approximately halved by dialysis in patients with end-stage renal failure. In these respects amoxycillin resembles ampicillin (Brogden et al., 1975).

Amoxycillin, unlike pivampicillin and hectacillin is not changed to ampicillin in the body.

Studies involving many hundreds of patients have shown amoxycillin to be an effective antibactericidal agent in the treatment of infections of the genitourinary tract, or the upper and lower respiratory tract and of skin and soft tissue, and in gastro-intestinal infections except shigellosis.

Adverse Reactions

Most commonly reported side effects are nausea and diarrhoea, skin rashes, pruritis and urticaria, less commonly reported side effects have included vaginal or vular irritation, monibiasis, dizziness stomatitis, bitter taste and soreness or numbness of the tongue. Side effects from oral amoxycillin have generally been moderate to mild and have rarely necessitated withdrawal of the therapy.

The following adverse reactions have been reported.

1) *Skin rashes*: The overall incidence of skin rash and/or urticaria has been 3% although they have occurred in upto 22% of patients (Fiegel et al., 1973). These skin eruptions have generally been transient and have cleared in a few days, sometimes without discontinuing the drug. In some studies, maculopapular eruptions have been reported to be similar to those seen with ampicillin. A few reports (Dubb 1973; Mulory 1973) suggest that in patients with infections mononucleosis, amoxycillin may like ampicillin, produce a macupapular erythma.

In studies which have compared amoxycillin and ampicillin in the treatment of various diseases, the frequency of skin eruptions has been lower with amoxycillin than with ampicillin. Skin rash occurred in 1.4% of 348 patients given amoxycillin as compared with 4% of 246 patients given ampicillin (Aronovitz 1974).

2) *Diarrhoea*: Diarrhoea has been reported as a side-effect in just over 2% of all patients treated with amoxycillin at various dosage but has been reported in upto 13% of cases (Adachi et al., 1973).

3) *Nausea and Vomiting*: Nausea and/or vomiting has overall occurred in about 2% of cases but has occurred in upto 19% of patients (Momose et al., 1973).

Amoxycillin is contra-indicated in patients with a history of sensitivity to any of the penicillins. On the basis of present evidence, it would appear wise not to use amoxycillin in patients with infections mononucleosis or lymphatic leukaemia because of the high frequency of exanthemia associated in these diseases with the use of ampicillin. (Baker 1978).

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